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NUCLEAR REGULATORY COMMISSION

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ADVISORY COMMITTEE ON THE MEDICAL USES OF ISOTOPES

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OPEN SESSION MEETING

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THURSDAY,

SEPTEMBER 20, 2012

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The Open Session portion of the meeting was convened in Room T-2B3 of Two White Flint North, 11545 Rockville Pike, Rockville, Maryland, at 8:30 a.m., Leon S. Malmud, M.D., ACMUI Chairman, presiding.

MEMBERS PRESENT:

LEON MALMUD, M.D., Chairman

BRUCE THOMADSEN, Ph.D., Vice Chairman

DARICE BAILEY, Agreement State Representative

MILTON GUIBERTEAU, M.D., Diagnostic Radiologist

SUSAN LANGHORST, Ph.D., Radiation Safety Officer

STEVE MATTMULLER, Nuclear Pharmacist

CHRISTOPHER PALESTRO, M.D., Nuclear Medicine Physician

JOHN SUH, M.D., Radiation Oncologist

ORHAN SULEIMAN, Ph.D., FDA Representative
WILLIAM VAN DECKER, M.D., Nuclear Cardiologist
LAURA M. WEIL, Patients' Rights Advocate
JAMES WELSH, M.D., Radiation Oncologist
PAT ZANZONICO, Ph.D., Nuclear Medicine Physicist

NRC HEADQUARTERS STAFF PRESENT:

BRIAN McDERMOTT, Director, Division of Materials Safety and State Agreements
PAMELA HENDERSON, Deputy Director, Division of Materials Safety and State Agreements
CHRISTIAN EINBERG, Chief, Radioactive Materials Safety Branch
MICHAEL FULLER, Alternate Designated Federal Official, Team Leader, Medical Radiation Safety Team
ASHLEY COCKERHAM, Alternate Designated Federal Official, ACMUI Coordinator
SOPHIE HOLIDAY, Alternate ACMUI Coordinator
NEELAM BHALLA, FSME/DILR/RB-B
SUSAN CHIKADEL, OGC/GCLR/RMR
JACKIE COOK (via webcast), RIV/DNMS/NMSB-B
SAID DAIBES, Ph.D., FSME/DMSSA/LISD/RMSB
SARA FORSTER, RIII/DNMS/MLB

SANDRA GABRIEL, Ph.D., FSME/DMSSA/LISD/RMSB

ANDREA KOCK, OCM/WO

JEFF KOWALCZIK, FSME/DMSSA/LISD/RMSB

LATISCHA HANSON (via webcast), RIV/DNMS/NMSB-A

ANGELA McINTOSH, FSME/DMSSA/LISD/RMSB

LIZETTE ROLDAN (via webcast), RIV/DNMS/NMSB-B

MOHAMMAD SABA, RES/DSA/RPB

RONALD ZELAC, Ph.D., FSME/DMSSA/LISD/RMSB

PUBLIC PARTICIPANTS:

SCOTT BERTETTI, Bayer

JEFFREY BOVA, Bayer

UWE BUDDE, Bayer

ROBERT DANSEREAU, NYS Department of Health

WILLIAM DAVIDSON, University of Pennsylvania

LYNNE FAIROBENT, AAPM

MARIA FAVORITO, Cohn & Wolfe

MARIA GARRIGAN, Bayer

JUERGEN GAY, Bayer

JOSEPH GERMINO, Bayer

DEEPIKA JALOTA, Bayer

KAREN LANGLEY, University of Utah

RALPH LIETO, Trinity Health

PETER LUEHRS, Bayer

ANDREW McKINLEY, American Society of Nuclear Cardiology

JANETTE MERRILL, Society of Nuclear Medicine and Molecular Imaging

JATINDER PALIA, Veterans' Health Administration

DENNIS PHILLIPS, U.S. Department of Energy

JOE RODGERS, Theragenics

GLORIA ROMANELLI, American College of Radiology

RUTH SCHUKMAN-DAKOTAS, University of Kansas Hospital

MICHAEL SHEETZ, University of Pittsburgh

JEFFRY A. SIEGEL, Nuclear Physics Enterprises

CINDY TOMLINSON, American Society for Radiation Oncology

MONA WAHBA, Bayer

GARY E. WILLIAMS, Department of Veterans Affairs/National Health Physics Program

NANCY YOUNG, Xcenda

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

(11:17 a.m.)

CHAIRMAN MALMUD: We will begin with the open session, which was to have started at 11:15, with opening statements from Mr. Einberg and Mr. McDermott. Who will be starting first?

MR. EINBERG: I'll go ahead and start. This is Chris Einberg.

CHAIRMAN MALMUD: Thank you.

MR. EINBERG: Okay. As the designated federal officer for this meeting, I am pleased to welcome you to this public meeting of the Advisory Committee on the Medical Uses of Isotopes.

My name is Chris Einberg. I am the Chief of the Radioactive Materials Safety Branch, and I have been designated as the federal officer for this Advisory Committee in accordance with 10 CFR Part 7.11.

Present today as the alternate and designated federal officers are Mike Fuller, team leader for the medical radiation safety team, and Ashley Cockerham, who is the ACMUI coordinator.

This is an announced meeting of the Committee. It is being held in accordance with the rules and regulations of the Federal Advisory Committee Act and the Nuclear Regulatory Commission. The meeting was

announced in the June 21, 2012, edition of the Federal Register, Volume 77, page 37446.

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 their opinions. I request that, whenever possible, we try to reach a consensus on the issues that we will discuss today. But I also recognize that there may be minority dissenting opinions. If you have such opinions, please allow them to be read into the record.

At this point, I would like perform a roll call of ACMUI members. Dr. Leon Malmud, ACMUI Chairman and hospital administrator.

CHAIRMAN MALMUD: Here.

MR. EINBERG: Dr. Bruce Thomadsen, Vice Chairman, therapy medical physicist.

VICE CHAIRMAN THOMADSEN: Here.

MR. EINBERG: Ms. Darice Bailey, agreement state representative.

MEMBER BAILEY: Here.

MR. EINBERG: Dr. Mickey Guiberteau,

diagnostic radiologist.

MEMBER GUIBERTEAU: Present.

MR. EINBERG: Dr. Sue Langhorst, radiation safety officer.

MEMBER LANGHORST: Here.

MR. EINBERG: Mr. Steve Mattmuller, nuclear pharmacist.

MEMBER MATTMULLER: Present.

MR. EINBERG: Dr. Christopher Palestro, nuclear medicine physician.

MEMBER PALESTRO: Present.

MR. EINBERG: Dr. John Suh, radiation oncologist.

MEMBER SUH: Here.

MR. EINBERG: Dr. Orhan Suleiman, FDA representative.

MEMBER SULEIMAN: Here.

MR. EINBERG: Dr. William Van Decker, nuclear cardiologist.

MEMBER VAN DECKER: Present.

MR. EINBERG: Ms. Laura Weil, patients rights advocate.

MEMBER WELSH: Here.

MR. EINBERG: Dr. James Welsh, radiation oncologist.

MEMBER WELSH: Present.

MR. EINBERG: Dr. Pat Zanzonico, nuclear medicine physicist.

MEMBER ZANZONICO: Here.

MR. EINBERG: Okay. Thank you. We do have a quorum. We have at least seven members, and actually we have perfect attendance.

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

MR. FULLER: This is Mike Fuller. I'm the team leader of the Medical Radiation Safety Team.

DR. ZELAC: Ronald Zelac, senior health physicist, Medical Radiation Safety Team.

DR. GABRIEL: Sandy Gabriel, health physicist, Medical Radiation Safety Team.

MS. COCKERHAM: Ashley Cockerham, health physicist, ACMUI coordinator on the Medical Radiation Safety Team.

MS. HOLIDAY: Sophie Holiday, on the Medical Radiation Safety Team, alternate ACMUI coordinator.

DR. DAIBES: Said Daibes with the medical team.

MS. McINTOSH: Angela McIntosh in the branch of radioactive materials safety.

MR. EINBERG: Thank you. Is there anybody in the regions who is online?

(No response.)

Ashley, can they respond from the regions right now, or are they muted?

MS. COCKERHAM: They should be able to respond.

MR. EINBERG: I will note also that Jeff Kowalczik is a member of the NRC staff from the Radioactive Materials Safety Branch as well.

Okay. And I would also like to add that this meeting is being webcast, so other individuals may be watching online. We have a bridge line available, and that phone number is 888-864-0940. Once again, 888-864-0940. The pass code is 71341 pound. 71341 pound.

Following the discussion of each agenda item, the ACMUI Chairman, Dr. Leon Malmud, at his option, may entertain comments or questions from members of the public who are participating with us today. We ask that only one person speak at a time, that this meeting is also closed-captioned.

At this point, I would like to turn the meeting over to Mr. McDermott, who is the Director of the Division of Materials Safety and State Agreements.

MR. McDERMOTT: Okay. Thanks, Chris. Again,

Brian McDermott. I appreciate having the opportunity to spend today with the ACMUI. After taking over my position about a year ago -- I know I missed your last meeting due to other travel and work commitments, so I am pleased to be able to be here with you today.

I see on your agenda you've got a wide range of topics, and I'd just like to reflect that in the NRC -- in the minutes, that staff, as well as the Commission, certainly appreciate the views and insights of the ACMUI.

The ACMUI brings insights and perspectives -- the ACMUI brings perspectives and views to the staff and to the Commission that we would otherwise not have, and I think for that reason it is so valuable. We have rulemakers, we have engineers, we have health physicists, but we don't necessarily have your background and experience.

So I think it is essential in our work that we have the insights of the practitioners, the folks that can bring the perspective at the other end of those regulations as they really affect the care of patients and public health and safety.

I see a couple of issues on here. I just wanted to mention that the staff is actively working regarding the permanent implant brachytherapy. As you

know, we have received direction from the Commission to move forward with some interim steps regarding policy relative to medical event reporting.

The staff is working on both a regulatory information summary to help clarify the interpretation of the regulations, and at the same time we are looking at enforcement guidance that would offer discretion for an alternative look at how to assess the potential for a medical event based on activity rather than dose.

So I think that's a positive move. As you know, our rulemaking process is not always the swiftest, but it's a collaborative process that gives a lot of perspective into the regulations before they become permanent.

In this case, I think the -- between the ACMUI views, other stakeholder views, and the staff opinions that were all provided to the Commission, it gave them I think a pretty clear picture and driver for the reason to move forward with, as much as we could, pending that permanent rule change.

And so I want to assure you that folks are actively working on that, and we hope to have that out --

MR. EINBERG: In the next few months.

MR. McDERMOTT: -- in the next few months. So the rulemaking process, when we talk about the Part 35

broader rulemaking, the final rule is due to the Commission there in the December of '14 timeframe. So it will hopefully make a difference to everyone in the community if we are able to get that information out sooner rather than later.

Some other things that have been going on within NRC, we recently at the end of August rolled out a component of the integrated source management portfolio. This is one more step towards enabling the suppliers of radioactive materials to be able to ensure that the people requesting the radioactive materials in Category 1 and Category 2 quantities have a valid license. This goes back to the GAO audit from a few years ago. This is a major milestone.

Over the last 20 years, I have heard rumors of projects working on a web-based licensing tool that would make the staff more efficient and make greater access available to some of the end users. And today it is one step closer to that being a reality.

We have the National Source Tracking System that is tracking those sources, but that is going to combine ultimately with web-based licensing and something called the license verification system, which is really that final piece that will allow those suppliers to match up their requests for material and do

that efficiently and securely over the internet. So a major milestone in our rolling out of technology.

I did want to mention we will be doing calls for nominations for the hospital administrator and nuclear cardiologist positions on the ACMUI. We will be seeking nominations this fall. Dr. Malmud's term ends in May of 2013, so we need to get ahead of that process and seek nominations.

And then, Dr. Van Decker's term ends in October of 2013. So we need to have those activities ramping up here before too long.

I see you've got a good range of topics on the agenda, including radium-223, the abnormal occurrence report, some potential changes that the staff is looking at to make sure that as the agency, under its responsibilities reports to Congress abnormal events across the whole spectrum of NRC activities, that items related to medical events are properly screened, and that we are not either over- or under-informing Congress of events that deal with medical issues.

And then, finally, I know you are going to have an update that -- from Don Cool, on what is going on relative to potential changes to Part 20 on radiation protection standards, and I think that should be an interesting discussion. I spent some time with Don

yesterday, and it was rather enlightening for me I guess, you know.

As the process slowly moves along and he is doing more and more outreach with different segments of the community, whether it's professional groups or different committees, the discussion is being refined, you know, that this -- the same basic issues are there, but the ability to articulate it I think is improving on our part. And I think you should find that to be an interesting discussion, and certainly I'm sure Don will walk away from your questions and inquiries even better prepared to tackle that going forward.

We are still waiting on Commission direction of what to do in that regard. The staff advocated for further investigation, and we are waiting on the final votes from the Commission to give us authorization to do that. In the meantime, we are continuing with some of these outreach activities.

And that's about all I had to offer. I say thank you for being here. We appreciate your service. It is extremely valuable to the NRC, and I hope you have a very good meeting.

CHAIRMAN MALMUD: Thank you, Mr. McDermott.

MR. EINBERG: Dr. Malmud, if I may? Because we did have technical difficulties with the telephone

when I did roll call -- the phone line was not on -- so if I may, I'd like to do roll call of the members on the phone call.

CHAIRMAN MALMUD: Please do.

MR. EINBERG: Are there any regional staff on the call right now? Regional NRC staff.

MS. FORSTER: This is Sara Forster. I'm in the Region III office.

MR. EINBERG: Okay. Thank you, Sara. Anybody from Region I or IV?

(No response.)

Okay. Are there any members of the public that are on the line?

(No response.)

Okay. Thank you, Dr. Malmud.

CHAIRMAN MALMUD: Thank you.

The next item on the agenda, therefore, is old business, which will be discussed by Ashley Cockerham.

MS. COCKERHAM: So very quickly, I will just go through all of the old outstanding recommendations from ACMUI. The first chart is from 2007, and there are actually no changes or updates here. All of these items are pending the current rulemaking that is going on right now, unless it indicates otherwise.

If you look at the 2008 charts, the only thing I noted here is for Item Number 9 that is in regard to the abnormal occurrence criteria. Nothing changed with this recommendation necessarily, but we are discussing revisions to that AO criteria. And so if we need to refer back to this particular recommendation to see where the Committee was in 2008, we can easily find this and reference it.

If you go to 2009, there are no changes there, and those items are also pending rulemaking. And for 2010, every single item on this list is closed from 2010. So this chart will go away.

2011, Item Number 6 says ACMUI created an action item to reevaluate its satisfaction with the reporting structure annually. So this is something that was talked about in January of 2011. So this is the first time in 2012 that we are going to visit this, and it's an agenda item that Sophie will be talking to you about later today.

Also, for 2011, on the second page, Item Number 21, we closed out an item where Dr. Malmud created a subcommittee to address the electronic signatures. That subcommittee report was sent to us, so the subcommittee is finished.

Item Number 23, Dr. Malmud added several

members to the Permanent Implant Brachytherapy Committee. So we went ahead and closed that out. That's still -- you have submitted your final report, hopefully that's the final report for permanent implant brachytherapy, but at least we know the individuals that are serving on that subcommittee.

And on the third page for 2011, this also deals with the abnormal occurrence criteria. So we can see that ACMUI has made recommendations in 2008, also in 2011, and then we expect there may be more to come tomorrow morning.

For the 2012 recommendations, for Item Number 2, ACMUI approved the Electronic Signatures Subcommittee report, so we have closed that out. It is published on the public website.

For Item Number 3, Dr. Thomadsen created a subcommittee to provide recommendations on the licensing for alpha emitters, including radium-223. And this subcommittee is still currently active, and we will be discussing that topic very soon today.

And Item 5 is also in regard to radium-223, and this is the subcommittee report that was revised, and we will have discussions on it today.

Any questions about any old recommendations?

CHAIRMAN MALMUD: Are there any questions for Ms. Cockerham?

(No response.)

There being none, thank you for the report.

MS. COCKERHAM: Thank you, Dr. Malmud.

CHAIRMAN MALMUD: The next item on the agenda is an ACMUI group photo, which is scheduled at 11:45. And we are about nine minutes early for that. Where will that occur?

MS. COCKERHAM: I'm sorry, Dr. Malmud. This is Ashley. What was the question?

CHAIRMAN MALMUD: Where will the ACMUI group photo be taken?

MS. COCKERHAM: The individual is actually already here. He is meeting us at this room, and we are just going to walk outside and go ahead and take the photo, and you can go straight to lunch from there.

CHAIRMAN MALMUD: Thank you. Are we just awaiting his arrival, or he is here?

MS. COCKERHAM: He is here right now.

CHAIRMAN MALMUD: So we're set. Thank you. Then we will follow --

MR. EINBERG: So, Dr. Malmud, just so everybody is clear, we will go directly to lunch, and then we will reconvene here at 1:00.

CHAIRMAN MALMUD: Yes. We will reconvene at 1:00. And the 1:00 item on the agenda is the use of dose calibrators in medicine, and Dr. Suleiman will present that.

Thank you.

(Whereupon, at 11:36 a.m., the proceedings in the foregoing matter went off the record.)

CHAIRMAN MALMUD: The first topic is the Use of Dose Calibrators in Medicine presented by Dr. Suleiman.

MR. McDERMOTT: This is usually where the witnesses sit.

(Laughter.)

MEMBER SULEIMAN: Thank you. I'm coming from a residual cough so I'm going to try to make sure it doesn't recur, so I'll try to speak slowly and clearly.

The subject of this topic came up because of the events of the last couple of years, so I decided maybe this is a good time to sort of raise some issues because it's relevant for a lot of other things.

As I was getting this reviewed, one of our radiation oncologists said you know, Orhan, it's really not a dose calibrator, it's an activity calibrator. And I think -- so, I decided to edit my slide and actually add that in the title here because what he said was, in

fact, pretty much on.

This is my disclaimer. Clearly, I'll be reflecting policies and regulations of the FDA, but if I happen to mention a commercial product or I express something that may be more my opinion than official policy I want you to be aware that it is my opinion.

So, why do we need dose calibrators? A lot of time I try to explain this with people with all sorts of backgrounds, very smart people who don't necessarily understand radiation, lay people who don't understand some of the technology, that basically we need to know the amount of radioactivity patients are being administered. So, so what? What's the purpose of that?

Well, we need to know the activity so we can actually estimate the radiation dose to the organs and the whole body. The community has a very -- dose and activity -- dose is used for many, many, many things, and I think there's an awful lot of confusion out there. So, I think I'd like to clarify right from the beginning you need to know activity so you can calculate the radiation dose, but that's not all you need. You need to know the patient's size; you need to know the bio distribution of the specific radiolabeled drug which may, in fact, depend on different metabolic rates in individuals, their size,

and so on. So, activity is just one of several factors that need to be addressed.

And how you calculate organ dose coefficients or derive them in tables, how they generated is beyond the scope of this presentation. I'm not going to be discussing that. I'm just going to be focusing on radioactivity. But if you know the amount of activity for a specific nuclide that's given to a patient in a certain route, and some other information you can calculate or estimate the radiation dose to a variety of organs.

Now, the point I want to make here, and maybe I'm going to be comparing diagnostic doses with therapy doses. I'm going to be comparing external beam radiation or gamma radiation -- external beam radiation with drugs or unsealed sources. And we're going to talk about current practice of medicine in some of these areas.

In radiation therapy, and to a lesser degree brachytherapy, deviations of more than 20 percent, and I know you can get much better precision and accuracy than that, but when you start to deviate from the actual absorbed dose calculations of more than 20 percent, patient outcomes start to be impacted.

Radiation therapy, in my opinion, is the most science-based of the cancer treatments because we know the dose, we know how we -- we know it's actually

calibrated and we know the accuracy of what that dose is, and the physicists, the health care team makes a lot of effort to make sure the equipment is operating properly, reproducibly so that the same dose can be delivered often.

To insure such precision and accuracy, radiation dose, equipment testing, and calibration are all done with I consider surprisingly consistent accuracy, notwithstanding the fact that we're -- mistakes happen with qualified personnel.

Now, in contrast of that when you talk about calculating radiation dose from unsealed sources or from drugs, essentially, it's much more challenging. Not only do you need to know the amount of administered activity, again, as I said earlier you need to know the biodistribution, and you need to know patient dimensions. So, calculating radiation dose doesn't have 20 percent precision or accuracy by anybody's stretch of the imagination.

And just so I don't ignore diagnostic imaging because a colleague once said, "You know, in therapy if you're off -- in diagnostic if you're off by a factor of 10 the patient is not going to drop dead, but in therapy you really can't afford that level of error."

Well, in imaging it's becoming much more

critical. I think accuracy is essential for imaging based standardization, such as calculating standard uptake values, or monitoring cancer treatment over a period of time. And you need to make sure that the variability in your metric, be it activity, that you administer FDG several different times over the course of time, that that is very stable, and precise, and reproducible, and that that change is, in fact, less than the change you're trying to observe. Whereas, in cancer treatment basically you'll see 20, 30, 50 percent change in dimension. It's sort of a subjective evaluation; yet, I suspect that a lot -- one of the main reasons why imaging-based cancer trials -- the imaging metrics don't always do very well. And I think it's because there's a tremendous lack of standardization. I think you're starting to see some efforts in this area, but even in imaging you need to standardize, and it gets back to the activity.

Dose calibrators are designed to verify clinically administered activity, and are just one type of a radiation detector. It's a shielded column and you -- it measures ionization, and you put the vial with the radioactivity in there. And it's pretty straightforward, but dose calibrators are really designed for gamma emitters.

They not only measure the ionization, but you assume that it's traceable to a reference standard preferably the same radionuclide, or at least a nuclide that has very, very similar energy so you can compare the ionization.

You couldn't determine if there were contaminants in a sample because you're just looking at the ionization coming from that measurement. So, a dose calibrator, you're assuming that what you're counting is pure, and you're assuming that what is traceable is very similar. There are alternative detector technologies and protocols to the detect radiation at different levels and different types.

Now, let's get away from gamma or photon-type radiation. Calibration of particulate radiation is even more challenging. I think this Committee is aware of micro spheres, be they glass or resin-encased yttrium-90 beta emitter for hepatic cancer, and monoclonal antibodies for the CD-20 antigen in non-Hodgkins lymphoma, Bexxar, which is basically I-131, and Zevalin which uses yttrium-90, for its imaging agent it uses indium-111.

Now, I want you to note here that the maximum dose, or the maximum activity for Zevalin as listed on the label is 32 millicuries, or 1.1 gigabecquerels of

yttrium-90.

Now, why is that -- why would you limit activity when dose depends on the mass it's being divided by? The activity is limited for patient safety. The inherent uncertainties in measuring activity and estimating the absorbed dose for unsealed sources is so large that to protect against a serious overdose administered activity is limited.

This is not radiation dose in the classical sense, so when you hear that dosing is limited what they're saying we don't have the level of precision and accuracy, and we may give a dose that may be too much for an individual just because of all the uncertainty, all the other -- the biodistribution and the different patient dimensions.

And I want to make a point here. I've stated this before, but I feel that dosing for a radiolabeled therapeutic is much more similar to chemotherapy where systemic toxicity is limiting, not analogous to radiation therapy where a specific target dose is calculated. So, comparing unsealed doses with external beam radiation doses is really comparing apples and oranges. I think there would be more similarity if you compared radiolabeled doses with other chemotherapy doses.

So, the first step in approving radiolabeled therapy is really to accurately assay the administered activity, which sort of brings us back to the dose calibrator. So, you're saying why did he sort of digress? Well, I wanted to point out the limitations of unsealed sources versus external beam, particulate versus gamma emitters. And how can you calculate absorbed dose when, in fact, you're not sure because of the uncertainty in measuring activity what you're actually administering the patient?

I'm going to refer to two of the regs for the NRC [CFR] 10 [Part]35.6, which really says you've got to have instrumentation that's calibrated according to nationally recognized standards or the manufacturer's instructions.

I point this out because in one of the incidents we had this last year the first part of Part (b) says "in accordance with nationally recognized standards, or the manufacturer's instructions." Well, we had one situation where one of the companies said the label is the manufacturer's instructions, so we're not responsible for having it traceable to a national standard. And the label instructions in this case weren't as accurate as maybe it could have been.

And the other regulation is in terms of

dose, 35.63, where basically we're concerned that if the doses from the -- patients shouldn't be receiving more than 20 percent. If they're receiving more than 20 percent, the activity shouldn't be administered. And they talk about direct measurement of radioactivity, but they talk about calculational and other methods, as well.

Now, what really prompted me aside from this being an ongoing saga was that AAPM came out with a report, 181, in June. The Chair of that, James Carey and Ralph Lieto, who used to serve on this Committee were authors on that. And it's a really nice report. It covers an awful lot of things, and it sort of gives an overview. But just kind of a summary here, we talk about accuracy; the NRC says if it's more than 20 percent don't administer. IAEA says 5 percent, ANSI says 10 percent, U.S. Pharmacopeia, which has a really, really nice section on 821, talks about using authentic reference sources, so there's some interesting and useful information out there.

One of the states says thou shalt follow the FDA requirements, which are basically the label. Well, I'll share with you the fact that our labels are generated on a product by product case, and sometimes they're not consistent in terms of some of the radioactivity measurements because FDA defers a lot to the NRC for how

the radiation is used.

So, the state requires the licensee to comply with the label. And although the intent is to insure good practice, this sometimes has the potential to cause both regulatory and practice of medicine conflicts. Because I am aware of one therapeutic where the manufacturer says you can't deviate from the label; yet, maybe there's an opportunity to improve on the treatment but it sort of restricts it.

So, just a quick summary here in this slide. Report number -- the AAPM report identifies a number of important things that should be tested that people sometimes take for granted, the electronics, the clock accuracy. That comes into play really critically for rapidly decaying nuclides, and a lot of other standard things, voltage, zero background, reference check, source and so on.

And, as I said, I like the USP document, and that covers in detail a lot of other specifics that one should consider. But as somebody had commented to me earlier, none of these tell you exactly what to do. It's sort of like you've got the encyclopedia on your shelves but what tests do different sites have to do?

This is probably near and dear to my heart more so because I think if you have a reference standard

traceable to a national lab, and in the U.S. we're talking about NIST, or some other well established laboratory, you have primary standards that are basically traceable to NIST, so you have what we call a reference source that gives you a measurement that the national lab certifies is, in fact, accurate, and you just compare it to your detector. My secondary standards are just one step further away but at least they're traceable back to the primary standard to the national lab.

So, the question I was asking, with all of this information and technology, and all these qualified professionals, why do we truly not know what patients are administered when using unsealed radioactive sources? Nowhere near the accuracy we get with radiation therapy.

And I guess these are more questions, how we insure the patient's administered activity is correct? Now, these are based on observations I've seen over the last few years, some going further back. But simply measuring activity in a dose calibrator doesn't constitute a calibrated measurement. There has to be documentation that shows that that dose calibrator, in fact, works, is functioning properly, has some sort of reference standard, what's the nuclide that you're looking at? So, there are a lot of things that are taken for granted.

Some therapeutics are only calibrated by the manufacturer, and most of the time that's a legitimate requirement. Why? Because sometimes it's difficult for sites to have the type of instrumentation necessary to do that, so you see some radionuclides that can only be calibrated by the manufacturer. And I think the NRC regs address that, too, where you'll take the manufacturer's claim and then do some calculations, volumetric or otherwise, to come up with a dose. But the question I ask, are sites capable of either accurately performing calibration or verifying the activity of a known radionuclide?

Again, we've seen a host of sites and what I always tell people is most people in this room are representing the top quartile, or top 10 percentile. What you need to do is see what's going on out there, and are sites capable of doing this?

And the other thing that's really bothered me because, to me, I think I understand what calibration means, but a lot of people out there are doing these tests, pushing buttons sometimes not even aware of what they are, and assuming that everything is fine. So, things are not under as good control I think as they could be.

So, one question I think that may come up

later this afternoon, also, should every dose be verified on site? Of course, what do we mean by verification? Is the manufacturer certification sufficient? Is the nuclear pharmacy certification sufficient? And what's the responsibility of the site? And I think some of the challenges that really were critical in prompting me to put this presentation together was radium-223, an alpha emitter currently undergoing clinical trials in the U.S. will present some very interesting challenges to both validation and therapeutic dosimetry.

There are some FDA approval beta emitters such as I-131 and yttrium-90, both approved as drugs or devices that have continued to raise dosimetry challenges in terms of the distribution, how do you calculate the penetration of the beta through the glass or the resin, and so on.

And even, as I said, let's not forget diagnostic, but even for diagnostic radiolabeled drugs activity calibration standards need to be standardized and addressed in a much more rigorous way because the field is going to move forward. And, again, from my personal observation, I think a number of the imaging-based trials don't succeed on their imaging metrics because I think there's a fundamental lack of standardization, nothing more complicated than that.

So, in closing I think the two questions I raise is sort of does the definition of a dose calibrator need to be updated? We had a situation where I think it was a state regulator said well, why don't -- you know, you can't use a dose calibrator for measuring this low level of activity. Why don't you use a well counter? And they said well, the label says use a dose calibrator. Well, then maybe FDA needs to clean up how we label and say or alternative technology. The key thing is we need to measure the activity at the level you're dealing with. We don't intend to restrict better technology but somebody shouldn't be using that as an excuse to prevent somebody from using a better technology.

I think traceability to a national standard is almost essential in one way, shape, or form. And I've seen correction factors misused, people don't understand them. There are correction factors for energy, for geometry, for absorption, vial attenuation, and so on, so you can't just throw correction factors out there. And stating that a detector, that a given make and model is sufficient just is not, because there are all sorts of things that change.

And the second question, which I think is valid is should site verification via some sort of measurement always be performed prior to a radionuclide

administration? That's it. Thank you.

CHAIRMAN MALMUD: Thank you, Dr. Suleiman. Are there questions or comments for Dr. Suleiman? Dr. Zanzonico.

DR. ZANZONICO: Well, thank you, Orhan, for that review. I guess the question comes, what would you personally recommend? I mean, should every dose whether it's diagnostic or especially therapeutic be assayed on site, or what should sites do differently or in addition in terms of verifying that activity assays are accurate, et cetera?

MEMBER SULEIMAN: You know, it always depends. Just like when we look at drugs, each one is individual, so making general statements. But I think for therapeutics where overdosing can kill a patient, obviously, you want some discipline in doing the measurement. And that's the case in radiation therapy. And I think that's the case with the radiolabeled therapeutics. But, again, my opinion is that I don't think the state of the practice is so precise and so accurate that people can get the dose up as high as it ought to be because when the variability is going to exceed the dose that could kill a patient, you're going to err on the lower side.

I think the radiolabled therapeutics are,

on an S curve, they're still down here at the tote. So, I'd like to see the field move forward, but how do you do that? I mean, the Research Institute, they're doing state of the practice. They're trying to move things forward, but do you want to -- if you approve a drug and then people aren't administering properly, they're going to say this isn't working, or it's not working as good as it could. So, I guess my point is if the dosimetry for some of the therapeutics is better, it will show up in better efficacy.

And for the diagnostics, again, it depends on the test. I mean, clearly, there needs to be some standard -- yes, the SUVs, most standard uptake values are done on a site basis. They're relative metrics because you can't translate -- there isn't a true standardization traceable to some sort of national number.

CHAIRMAN MALMUD: Dr. Welsh.

MEMBER WELSH: James Welsh. Are there any specific examples, or is there any evidence that the current state of the practice has led to patient harm or diagnostic studies that were grossly inadequate that are directly because of what you're talking about here today?

MEMBER SULEIMAN: Not that I'm directly familiar with, but I -- some of the trials that I've

observed I think didn't succeed because some of this lack of standardization. But I think -- and what I guess I'm implying is with the radiolabeled therapeutics the doses probably are not as high as they could be because the whole process is not as precise as it -- and maybe we're not there yet. Maybe we'll need some more sophisticated imaging or standardization in the future.

I mean, so let's get back to the dose calibrator. I mean, the first thing, forget about the standard imaging. If you're giving a patient twice as much activity between measurements you can have the most standard imaging you want, but you're going to see twice as much activity, but that's because maybe the dose calibrator wasn't used right. Maybe there wasn't some standardization there.

CHAIRMAN MALMUD: Next question.

MEMBER BAILEY: I just had an add-on to Dr. Welsh.

CHAIRMAN MALMUD: Yes, please.

MEMBER BAILEY: We had noticed one of our, in Texas, radiopharmacies have upgraded some of their internet capabilities, and they're watching more things, and they're able to see things that they weren't able to see before. So, we felt there was a great increase in some mislabeled -- this is all diagnostic, that mislabeled

wrong isotopes arriving, wrong quantities arriving. So, yes, I think we do know that not patient harm, it's diagnostic levels. But having to redo tests, doses that shouldn't have been received have been received as a result of the not checking on site. And they are not required to, and many diagnostic places don't have dose calibrators, don't even have them on site.

CHAIRMAN MALMUD: Dr. Thomadsen.

VICE CHAIRMAN THOMADSEN: And as I recall from Dr. Welsh's presentation on medical events last time, there were several events where the patient received an injection of the wrong material which would have been detected had the dose been checked in a dose calibrator before administration.

CHAIRMAN MALMUD: Dr. Guiberteau.

MEMBER GUIBERTEAU: It's not a direct question about calibrators, but one of your slides brings up a related point, and that is if the regulation is 20 percent variation from the measured dose. And, of course, in the case of particulates you don't necessarily know exactly what you're measuring but you're close. And if you look at the slide that you had from the IAEA, and the AAPM, and ANSI that their recommendations were 5 to 10 percent, some divided between therapeutic and diagnostic doses.

And I'm just wondering if you or someone here could remind me where the 20 percent came from. Not that it's a huge difference. It certainly isn't an order of magnitude or anywhere close, but it is -- it does seem out of line with what the other recommendations are. And I realize a larger number is better for practice because many times if you get too close, then you can't treat patients and you limit their access to it, or they're inconvenienced, or everyone is inconvenienced. But I'm just wondering where the 20 percent -- that figure comes from.

MEMBER SULEIMAN: I don't know where it came. I defer to the NRC. From my experience in other regulatory activities, when you set a regulatory limit you allow -- you cut the community some slack. Whereas, the other documents, some of them are addressing the state of the practice. You can get it as good as this, so the regulatory limit being higher doesn't necessarily surprise me, but I don't know exactly the reasoning that went into the NRC adoption of 20 percent.

MEMBER GUIBERTEAU: Well, I think if you're going to cut some slack you probably had an idea of what ideally it should be, and then you cut the slack. But I'm just wondering what data this came from, or how it was derived. I'm just curious of that. I know Donna Beth is

not here.

CHAIRMAN MALMUD: Dr. Guiberteau, are you referring to radiation oncology or nuclear medicine?

MEMBER GUIBERTEAU: Well, I think it's the same, is it not?

MEMBER SULEIMAN: Well, the reg --

CHAIRMAN MALMUD: They differ.

MEMBER SULEIMAN: Yes, the reg -- I don't know.

MEMBER GUIBERTEAU: I'm talking about for unsealed.

CHAIRMAN MALMUD: Unsealed sources. For example, for I-131 the dose is, must be within 10 percent above or below the ordered dose on the physician's prescription, which is referred to as the written directive. I always block on the term "written directive" because it sounds like something else which is much more lethal. So, the written directive for I-131 administered for hyperthyroidism or thyroid cancer allows plus or minus 10 percent. And that, I believe, is based upon a very old figure which in part was determined because when the I-131 dose was prepared it may not be given at the precise time that it was supposed to be given, and that gave some leeway plus or minus 10 percent for the decay of the pharmaceutical.

With radiation oncology there was very lengthy discussion in the Committee among the radiation oncologists with respect to the 20 percent being a fair estimate because of the nature of the -- for example, with prostate cancer, the nature of the swelling of the prostate after the implantation of the seeds. And, therefore, even if the seeds were placed totally correctly, the radiation burden would not be the burden that was calculated in advance, but would be the radiation burden borne by the prostate and the adjacent organs based upon the swelling of the prostate following the insertion of the seeds, so that gave some leeway there.

With respect to radiation oncology, I am totally ignorant of how the limit is set for a radiation oncology dose using a sealed source. Perhaps one of the radiation physicists can tell us where that number came from.

VICE CHAIRMAN THOMADSEN: I have no idea.

MEMBER SULEIMAN: But, Dr. Thomadsen, what is it in external beam; 20 percent is way, way too high. What sort of level?

VICE CHAIRMAN THOMADSEN: Well, it depends what you're asking. I mean, if you're asking what is the target precision is 5 percent. And that actually does

-- that goes back a long way to just casual recommendations in chapters that have just been perpetuated. Has been adopted by the IAEA, and then it was in ICRU reports as a target goal. So, it's just been perpetuated for decades on end, plus or minus 5 percent in the dose in radiotherapy.

CHAIRMAN MALMUD: But isn't the question whether or not we should be using dose calibrators for routine practice? Is that the question before the Committee?

MEMBER SULEIMAN: That's one of the questions.

CHAIRMAN MALMUD: May I offer an opinion?

MEMBER SULEIMAN: Yes, yes.

CHAIRMAN MALMUD: I have never worked in a department that did not have a dose calibrator. And I personally would be very anxious receiving a radiopharmaceutical whether it's for diagnostic or therapeutic purposes that has not been reconfirmed prior to administration to me as a patient. And I speak from a number of years of experience, because errors occur with the use of the dose calibrator independent of the dose calibrator.

For example, two patients came in both named Jones that day, one to receive technetium-99m HIDA for

hepatobiliary imaging, another one to receive technetium sulfur colloid for marrow or liver imaging, and the two doses are reversed. They're both technetium-99m. They're both going to look identical in the dose calibrator.

The dose calibrator will not take care of that error. That's a misadministration, if the two doses were reversed. But the dose calibrator will affirm that it's a 5 millicurie dose as shipped by the radiopharmacy and labeled as such. So, yes, eliminating the dose calibrator will not solve the problem, but its absence will create a new level of problem that we have not experienced until now.

What I'm interested in knowing is, are there many nuclear medicine sections that do not have dose calibrators?

MEMBER BAILEY: Yes, sir.

CHAIRMAN MALMUD: They rely totally upon the radiopharmacy?

MEMBER BAILEY: Yes, sir.

CHAIRMAN MALMUD: Very interesting.

MEMBER SULEIMAN: We found out during the CardioGen investigation that a lot of the dose calibrators were being misused. I mean, there was variability enough to suggest that things weren't done in a standard way.

CHAIRMAN MALMUD: Well, the dose calibrators themselves are supposed to be recalibrated at regular intervals. Obviously, an instrument that's used for measuring that's inaccurate is not a valuable instrument, but calibration should be done on a routine basis. And I assume that it is from our own radiation safety standards within my own university. But perhaps one of the nuclear physicians can comment on that. Dr. Palestro.

MEMBER PALESTRO: Yes, Chris Palestro. I like you, Leon, have never worked in a department where there was not a dose calibrator. On the other hand, I've never worked in a department that didn't have a generator, so we made up all of our kits on site and we have to use the dose calibrator. But as far as I know there is a continuing decrease in number of sites that use generators and make up their own kits. And you have an expanding use of unit dose technology where the dose calibration is not required. And I would suspect that the majority of sites nowadays, the average hospital probably does not use a dose calibrator.

CHAIRMAN MALMUD: Dr. Guiberteau, as a nuclear physician what's your experience been?

MEMBER GUIBERTEAU: Well, I think it's similar to Chris'. I do think that the fact that when you

receive a unit dose, it doesn't require you to re-measure the dose. But I can say in my own department we re-measure every dose before it's administered just to get the technologist used to doing it, particularly for the therapeutic agents.

But, I mean, I don't -- I do appreciate the fact that there are, as Darice is shaking her head yes, in the State of Texas, there are many small nuclear medicine departments and nuclear cardiology office practices that don't have dose calibrators. And I'm not making a decision on whether or not it should be used, but my feeling is just as practice in our hospital, because we have one we use it whether we need to or not. And that's just our own policy.

CHAIRMAN MALMUD: And my observation is the same as Dr. Palestro's and yours, and that is that we used to have a generator on site which made it a necessity. However, today we sometimes will receive material which is technically not a unit dose from a dispensing pharmacy, and then we have to calculate what the remaining dose is, assuming it's not expired, for injection into the patient for which we use the dose calibrator. But I don't know that -- there may be many departments that simply don't do that. They only accept unit doses.

MEMBER BAILEY: There are many that only do unit doses, and then there are times of non-compliance when they think they're using a unit dose but they have extracted some or left some behind, and that is non-compliant, but it's done.

MEMBER SULEIMAN: The one thing that we -- I had asked of NIST, National Institute of Standards Technology, if they could come. Apparently, they weren't able to send anybody. But also, I know Ralph Lieto -- we had invited him, but it was -- they couldn't come. But I know NIST has done intercalibration study where forget the fact that you may have a dose calibrator so you have the illusion of a piece of equipment that's performing correctly. My concern is when they have the equipment, how accurate is it for the variety of nuclides that are out there? And even when NIST has done these intercomparison studies with other organizations, they find surprising -- and these are sites that are expecting to be tested. Things are not as consistent as you would expect.

So, how critical is it? Is it -- do we just be aware of this and let things go on, or are there some unsealed sources that require more rigorous calibration?

CHAIRMAN MALMUD: Dr. Langhorst.

MEMBER LANGHORST: Thank you. One thing I

want to clarify is that we're not getting dosages that are not measured. They come measured from the -- typically, a commercial radiopharmacy. So, what we're talking about here is re-measuring at site to do what Dr. Thomadsen was saying, confirm you got the right isotope, or the right dose and so on.

But I think the question comes down to, I think we all agree if you have a dose calibrator, it's prudent to do that check, but is it necessary for that to be an NRC regulation? NRC is not the only reason to be checking all this information. I mean, there's patient safety, there's your hospital policies and so on, but is it really necessary that NRC put this in their regulatory requirements?

To me, if you have problems with people understanding how to properly calibrate a dose calibrator, it seems like the focus should be on the nuclear pharmacies and making sure they have it right, and that you're getting the right measurement from there.

One question I do have for Darice is whether in Texas, do you have licensees who are doing therapeutic doses that don't have dose calibrators?

MEMBER BAILEY: I'm going to say I doubt it, but I don't know 100 percent.

MEMBER LANGHORST: Okay.

MEMBER BAILEY: And therapy is done primarily more at a large university, or hospital or something with the large --

MEMBER LANGHORST: Right.

CHAIRMAN MALMUD: May I follow-up with your question, Dr. Langhorst?

MEMBER LANGHORST: Certainly.

CHAIRMAN MALMUD: Does that mean that these departments are not even doing I-131 therapy for hyperthyroidism?

MEMBER BAILEY: I don't know for sure. I can find out, make some calls.

CHAIRMAN MALMUD: I may be overly cautious, and I'm not speaking for the Committee. I'm just giving the opinion of a nuclear physician, and that is that I believe we have as few errors as we do because we have redundancy in the methods that we use, whether it's signing a written directive, or whether it is actually providing the dose to the patient. We check more than once on what we're doing. And that is the reason I believe we have so few errors because we catch these things before they occur.

Eliminating the dose calibrator to me is a bit anxiety provoking. Now, there may be exceptions. For example, in nuclear cardiology where the only isotope

they may be using is the technetium agent, it's unlikely that there's going to be a significant misadministration unless they're using other isotopes, or may use other isotopes in the future which have greater radiation burden implications than the technetium agents being used currently. But perhaps Dr. Van Decker might care to comment on that.

MEMBER VAN DECKER: I don't disagree with what people have said. I mean, obviously, it needs to be measured at some point. It's all -- when it's unit-based, obviously, it's been measured at a radiopharmacy. And if you're talking about plus or minus 10 percent on a 9 or 10 millicurie dose, you're talking about under a millicurie of change. So, it's not usually a huge amount that's going to make a major difference.

So, the other part of this, obviously, on a delivery basis and the current pressures of the health care system is redundancy is nice but what's the cost of the redundancy to the health are system? So, I would agree with what other people have said. I think it's got to be a case by case basis as to what's the exact play and what's trying to be accomplished, and what's the absolute dose of the radiation, because then a percentage is going to make more of an absolute change. So, I think there's variable ways to look at this.

CHAIRMAN MALMUD: Please.

MEMBER WEIL: I have a question, Dr. Suleiman. Do you know how this is handled in other countries? Do we have a reference, if you will, for whether there's recalibration at the site as a standard anywhere?

MEMBER SULEIMAN: You've got physicists out there in some countries, but generally speaking we're sort of setting the standard I think I would expect. Unless there may be some developed countries that do it more rigorously, like I'd say Germany, just default, because my experience with other areas. But generally speaking, probably less so than here. They probably accept what they get. But then again, they may be dealing with simpler nuclides, they may be dealing with almost pure technetium and not mixing and matching. I think the issue becomes more relevant if you've got multiple nuclides that you're using. But then again you're assuming now you've got a more upscaled clinic that's got the equipment, we're back to the 25 percentile here, you know.

CHAIRMAN MALMUD: Mr. Einberg.

MR. EINBERG: Yes. Dr. Suleiman, would you like to comment on the use of -- the measurements of PET pharmaceuticals considering the short half lives for

radionuclides?

MEMBER SULEIMAN: It is done. I mean, the PET sites are held to a pretty rigorous standard because they're now considered -- you know, manufacturers, you just have new PET regulations go into place. I'm not specifically familiar with all of the measurements, but I was taken aback that they actually do require a radionuclidic purity, radionuclidic analysis in terms of -- so, it's a much higher standard. I mean, you have to know if there are any contaminants or whatever, so that's done probably spectrally.

MR. EINBERG: I guess -- I'm sorry.

CHAIRMAN MALMUD: May we ask Mr. Mattmuller for his opinion?

MEMBER MATTMULLER: Yes. As a budding FDA drug manufacturer, yes. We won't go there. Yes, but in some sense we do exactly what all departments do. We do have a dose calibrator for our PET dose calibrator, is that we do the tests that are on slide 19, the linear, the accuracy, the geometry, we do do those. And also, for PET we do also do a spectral analysis on an annual basis to satisfy those -- but if I may, you had a statement on Slide 23 of simply measuring activity in a dose calibrator does not constitute a calibrated measurement.

And for certain radionuclides I would agree

with that, but not in general. I would disagree, because of slide 19, because of everything we do on a periodic basis that inspectors check for, the linearity test, the constancy checks, the geometry tests. So, it's not like we have our dose calibrator sit on a shelf and never verify it or check it. It does get quite a bit additional testing on a periodic basis to make sure it is working properly.

MEMBER SULEIMAN: I agree except, again, some of the experiences of the last year or two, we had situation where sites have correction factors which they didn't know where they came from. They were not -- they were applying cobalt correction factors for a very different nuclide. They had correction factors for a dose calibrator without even knowing the make or the model. So, when you have that level of specificity you sort of wonder do they really know what they're doing. So, that's the horror side, where they've got this piece of equipment, they're putting it in, they're getting a number, and they believe it. And how critical it is? I don't think since it's a diagnostic, the safety issue is not as important as it would be in a therapeutic. So, I think basically if you're dealing with therapeutics you're aware of that, and you're paying more attention. But without some sort of survey or whatever you don't

know.

But I was just surprised at the lack of standardization. And when we looked into the dose calibrator issue more and more, the companies are on top of what they're doing. You know, they have little buttons that will -- they can calibrate it for a variety of nuclides. The sites think they're already calibrated for those variety of nuclides, but calibration -- the company's instructions tell you if you want to claim this calibration for this nuclide, you've got to get a reference standard probably traceable to NIST and do the measurements, so when you push that button for that nuclide the number you're getting is correct. Some of the sites were oblivious to that. They were not even aware of that level of civility.

CHAIRMAN MALMUD: Well, Dr. Suleiman, I understand your point, but would the solution to that be removing a current safety test completely? If they're not competent to -- I shouldn't use the term "competent." If they're not adhering to standards for managing the dose calibrator, removing the dose calibrator removes another safeguard on behalf of the patient.

MEMBER SULEIMAN: Well, I'm not advocating that. I mean, I was -- I don't know the answer to some of these questions.

CHAIRMAN MALMUD: I know you're not advocating it. I'm just trying to get it on the record that if someone doesn't know how to use an instrument, is the solution to remove the instrument? And the answer is no.

MEMBER SULEIMAN: No.

CHAIRMAN MALMUD: Obviously not.

MEMBER SULEIMAN: Is get them to use it better, or properly.

CHAIRMAN MALMUD: The other issue is, I know that errors have not occurred because a technologist will take a syringe that has let's say three millicuries of Indium-111 DTPA and confuse it with another syringe that contains three millicuries of technetium sulfur colloid. And when they put it in the dose calibrator it doesn't ring up correctly, and they realize that they've set it on the wrong radioisotope and the dose is not administered incorrectly. Without the dose calibrator there they might not have realized they had the wrong syringe in their hand. It isn't the pharmacy that made a mistake. The pharmacy delivered it correctly. It's that the tech might have made the mistake, except for the fact that there was one more level of checking.

How expensive is a dose calibrator? Is this an enormous expense for a department? Anybody know what

they cost?

MEMBER SULEIMAN: A couple of thousand dollars.

CHAIRMAN MALMUD: Just a couple of thousand? I shouldn't say just, but I had a feeling they were more expensive than that.

MEMBER SULEIMAN: They may approach five figures if you've got some spectral analytical capabilities and stuff, because I investigated how expensive some of these add-ons were. So, I think you can get a real state-of-the-art dose calibrator with a lot of bells and whistles and abilities for $120,000.

CHAIRMAN MALMUD: Well, it's an interesting question that you raise, and I think that the point that was made by the State Representative is a valid one; and that is that some departments are small, and may only use one isotope, in which case they wouldn't be facing this issue. However, I think we have to look to see how many incidents are occurring currently in those departments versus departments that are using dose calibrators.

And, of course, there's also a question of reporting, which we can't answer, and that is who's reporting these things or not. Now, misadministrations, we have the feeling are clearly reported, but variability in doses may not be reported.

MEMBER SULEIMAN: I guess one of my main messages here was the state of the practice with dose calibrators isn't as perfect as everybody may assume. You know, you've got sites out there who don't necessarily understand how to use them, and I think we should just be aware. I think with some new radionuclidic products out there that have very different characteristics, there are therapeutics, this could be more of an issue. It may not be. It may not be. Again, therapeutics may be taken more seriously. But I think if nothing more, people should not assume that everybody's measuring their activity necessarily correctly.

CHAIRMAN MALMUD: Dr. Langhorst.

MEMBER LANGHORST: I think we would all agree that it's prudent to use a dose calibrator at your site. I don't think that necessarily that has to be something regulated by the NRC.

CHAIRMAN MALMUD: I won't argue your point. The question is who would enforce the use of dose calibrators if you really feel that they are worthwhile, what agency? Would it be the FDA, would it be the Hospital Standards Committee?

MEMBER LANGHORST: I think it would be the Hospital Standards Committee.

CHAIRMAN MALMUD: What about the private

office?

MEMBER LANGHORST: They have a standard which they have to meet in order to be delivering their product to their patients.

CHAIRMAN MALMUD: Now, there is a database that is misadministrations, and we haven't seen many come before the Committee for review recently, I-131 misadministrations which would be the most frequently used isotope for therapy. And I haven't seen any come through lately, so you may be absolutely correct, there is no issue.

MEMBER LANGHORST: As far as --

CHAIRMAN MALMUD: Or there's very little issues.

MEMBER LANGHORST: -- NRC regulatory oversight goes.

CHAIRMAN MALMUD: Yes. You raised a very interesting point. I see a number of hands up. Okay.

MEMBER WEIL: You can probably say it better.

MEMBER BAILEY: Oh, I don't know -- I just had a quick -- I got a response back and we do have some I-131 therapy sites, off site, small facilities that only use unit doses probably don't have dose calibrators.

CHAIRMAN MALMUD: Thank you.

MEMBER WEIL: And my concern regarding the

private physician offices when you say they have a standard that they must meet, but that standard is their license. Correct? Which is regulated by NRC, so -- so, if -- I mean, in major medical centers where excellent medical care is provided we probably have less concern than in those less -- those sites with less oversight with less professional administrative layers that are looking at how a practice is managed. That's where I have concerns.

MEMBER LANGHORST: Can I respond?

CHAIRMAN MALMUD: Please do, doctor.

MEMBER LANGHORST: Sue Langhorst. Those clinics probably use a single isotope. It may be only tech-99 or perhaps only I-131, but I -- those dosages are measured by their radiopharmacy who are delivering that. Now, they're not perfect but that is overseen by the NRC, also. So, I mean, I would rely more on the commercial radiopharmacy than I would on those small clinics to get it right, as far as measuring the dosage. Now, confirming that you've got the right thing, I think that's good practice.

MEMBER MATTMULLER: Like the rest of this panel, I would be very, very uncomfortable for any site not to have a dose calibrator on site. And I don't -- I guess I'm concerned about the sites that get unit doses.

I don't think that should be interpreted that they don't need a dose calibrator, because I -- and I do have a lot of faith in centralized pharmacies. And I know they take great care in making sure their dose calibrators are working and are calibrated properly. And I think that works well for when patient Joan comes at the set time for the set procedure, but in a real lab there are delays, they switch patients around, they switch -- they change the procedure and then they start adjusting the dose by squirting a few drops here and there. That's when they need to have the dose calibrator, so if it works smoothly on schedule every time yes, no, they wouldn't need one. But there's probably an instance just about every day at these labs where they should have re-measured it to make sure they have what they think they're giving to the patient.

MEMBER SULEIMAN: The other question I had when I was looking at the reg, you could get a unit dose and basically by volumetric calculation measure, but if you're not measuring the activity and there's a mistake, you'd never know it. It gets back to the, we don't know what we don't know. So, I mean, I'm always concerned when people say we haven't seen anything; therefore, things are safe. And that continues to bother me, but I would think there would have to be some sort of -- I mean, even

if I was getting unit doses I'd feel comfortable they're coming in a standard way. But still, like you said, if you want to make an adjustment in the -- volumetric doesn't necessarily translate into activity used.

MEMBER BAILEY: And just response back, I'm totally in agreement with both of you. And I think for Sue, the response was when it was taken out of the diagnostic regulations that it had to be measured on site. That's when the calibrators disappeared, because it was not a regulatory requirement any more. They'll say we'll only use unit doses, but they're not always used as unit doses. And it is non-compliant, but you've got to catch that.

CHAIRMAN MALMUD: Dr. Langhorst.

MEMBER LANGHORST: Sue Langhorst. But, again, it comes back to what Orhan has been talking to us about, is whether they're maintaining their dose calibrator in the correct way. And it just may be a good check, it may not be a calibrator.

MEMBER BAILEY: Right.

MEMBER LANGHORST: So, yes. It's a --

(Simultaneous speech.)

CHAIRMAN MALMUD: Other comments? Dr. Suh.

MEMBER SUH: Does the NRC have any recommendation regarding the use of a dose calibrator?

CHAIRMAN MALMUD: You have to ask a member of the NRC staff. Mr. Einberg, Mr. McDermott?

MR. EINBERG: I'm going to turn it over to the medical team leader, Mike Fuller.

MR. FULLER: I think the question was do we have recommendations? We don't have specifically recommendations, but we do provide guidance in our -- to our licensees as far as the types of instruments that are required or need to be used in order to demonstrate compliance and things like that.

I mean, we have our volume -- it's called NUREG-1556, Volume 9, which has a great deal of information and guidance available to licensees on all these types of issues. So, yes. But there aren't recommendations as far as what make, or model, or anything like that. No, it's more along the lines of the capabilities that our licensees are expected to have.

MEMBER SUH: Is there a difference between diagnostic versus therapeutic in terms are the guidances different going to therapeutic dosing versus diagnostic?

MR. FULLER: No, there's not separate guidance. It's all contained in the same guidance, and then the guidance will address -- if there are differences with regard to what would be adequate or what would be appropriate, then that would be addressed in

that guidance, as well. But no, there's no specific differences in the guidance, whether it be -- for the types of things we're talking here today, instrumentation and so forth available. No, there wouldn't be.

CHAIRMAN MALMUD: Other questions? Dr. Zanzonico.

DR. ZANZONICO: Pat Zanzonico. This is more a comment than a question. I think in this context precision may actually be more important than accuracy. I think we would all concede that dose calibrators are fairly simple instruments. They're very geometry, energy, emission, property dependent and for other than a pure gamma or x-ray emitter in the standardized geometry the actual reading may deviate considerably from the activity. But as long as one does the most basic QC, like putting a calibrated standard, long life standard in the dose calibrator each morning and verifying you get the same reading, then for any other corresponding geometry, if you get a different reading than you've gotten before it's a different activity. So, even given all of the limitations of dose calibrators, it does have considerable value as has been pointed out in detecting misadministrations, whether it's a syringe with the wrong isotope or the incorrect amount of

activity, and so forth. So, again, given all the limitations of dose calibrators I agree, that using it has considerable value in avoiding misadministrations.

CHAIRMAN MALMUD: Thank you. Dr. Suleiman, if you raised a question, I think you have an answer, and that is the majority feels that it's more comforting to know that there is a dose calibrator being used to check the dose before it's administered. However, there does not seem to be a strong opinion with regard to mandating this as a regulation rather than a recommendation. Is that a fair summary of what the Committee has come up with? Thank you for bringing that forward.

It's being 2:00, we'll move on to the next item on the agenda, which is the licensing of radium-223 dichloride, radium-223 dichloride Subcommittee report. And that will be given by Dr. Zanzonico and Ashley Cockerham.

DR. ZANZONICO: I think Ashley is going first.

CHAIRMAN MALMUD: Ashley will be going first.

MS. COCKERHAM: My name is Ashley Cockerham, and I'm going to be talking about the licensing of radium-223 dichloride. And, specifically, I want to discuss a Subcommittee report that was already submitted

to NRC, and things that have sort of transpired since that.

So, I'm going to go over the history of where this all started, talk about the specific issues with that particular Subcommittee report, talk about a few options, and then get some options for a path forward.

So, at the last public ACMUI meeting on April 17th, Bayer provided an informational presentation to the Committee, and during that meeting the ACMUI created a Subcommittee, and their goal was to provide recommendations on how to license alpha emitters which includes radium-223 dichloride.

So, in July the Subcommittee provided their report, and their report provided recommendations for licensing radium-223 under 10 CFR 35.300 instead of 1000. Those were the two places that we were looking at. And the report also talked about requiring an appropriate radio assay system for measurement of activity before and after administration using a NIST-traceable standard. So, this sort of ties into what Orhan was just talking about and the Committee discussed.

During that Subcommittee, or during the public teleconference that was on July 9th when the Committee discussed the Subcommittee's report, there was also discussion about clarifying the current status of

the drug with the FDA. And Orhan was not able to participate on that phone call, so the Committee wanted to make those changes, consult with him, and then bring Dr. Suleiman's input back as a final report. And we didn't expect that those changes -- they were really just wording changes to be consistent throughout the document with exactly where the drug stood with the FDA.

So, a week later we got the Subcommittee report and there were substantive changes in that report. And the first thing that was important to us that we're really asking for clarification on was the removal of the word "requiring the radio assay system for direct measurement of activity before and after administration." And the second change, there was a removal of a statement that the recommendations contained in that report applied to any future alpha emitting radiopharmaceuticals. And the last change was that there was removal of the statement that radium-223 dichloride significantly prolongs survival.

For the second and the third bullets, I don't think those are really issues. I think that it just needs to be recognized during a public meeting since those things were removed in non-public space in Subcommittee space via email; we just need to acknowledge those changes in a public setting. And if that's truly

the Committee's intent they can say this is exactly what we wanted, vote on it, the Subcommittee report moves forward.

But for the first bullet on requiring radioassay systems are directly measuring activity before and after, we're going to need a little more information on that.

So, in our current regulations direct measurement is not required before and after administration. And the appropriate regulation is 10 CFR 35.63. And in 35.63 direct measurement is one of three options, so the other two options are a combination of measurement of radioactivity and mathematical calculations, so that's going to be the situation I'm assuming where the radiopharmacy does the measurement, you do math, you get your number, this is what you say you administered.

The third one is a combination of volumetric measurements and mathematical calculations based on the measurement made by a manufacturer or radiopharmacy.

So, I'm sorry, I'm thinking about a lot of things here. So, the question is, does ACMUI want to recommend, and I'm not sure that that question was answered in the last discussion, do you want to require -- is it specific to radium-223? Do you want to keep that

in your report, or if you do, and you want to require radioassay -- here I'll jump to the next slide.

So, for the -- sorry, let me back up. For this first bullet, if you want to recommend that radium-223 dichloride be regulated under 300, you can't require radioassays before and after because we can't add things to the requirements. It's not currently in the requirements. There are the three options in 35.63.

So, the next option is for the Committee to change their report to recommend licensing under 10 CFR 35.1000. Then you can say we would like the assays before and after.

The other option, again, was just discussed is should there be a revision to 10 CFR 35.300 that requires for all radiopharmaceuticals, not just radium-223, that that be required.

So, those are kind of the three options that are out there. I think there are two questions. One is just for radium-223, and then there's the bigger question of should it apply to everything else, as well.

So, for a path forward we'd like you to clarify your intent, and then acknowledge the report changes that I talked about that were bullets number two and three regarding those two things. I'm sorry, I've drawn a blank, whatever the second and third bullets

were. Dr. Malmud.

CHAIRMAN MALMUD: I think the question is before the Committee to move it into 1000 means that there's going to be a longer review, and that the use of the measure before and after could be part of that, would be part of that. To leave it as it is currently is not -- it's not possible to add the requirement that the measurements be made without it affecting the entire group of applications, not just this one. And that's what it boiled down to when we were discussing this and the emails were moving back and forth.

The basic question, though, as always is what's best for the safety of the patient? And that's what I think the Committee should be reviewing, and then coming up with a recommendation. If the recommendation doesn't fit into either of the two options then there will have to be a third recommendation. But our concern as always is, what's best for the patient, and what's best for members of the public who are involved in the treatment. Dr. Suleiman.

MEMBER SULEIMAN: I have a question. I don't know why it didn't occur to me before, but then I wasn't here for that last meeting. This is still investigational. It's not been approved by FDA. The nature of an investigation is you're still collecting

data and doing research.

I mean, I would clearly defer to the experience gained by this investigation as to some of these very issues. In other words, how good is the dosimetry, how good -- in their measurement of their activity do they feel? The company should want a good product, and so if it requires measurement, the equipment to do such measurement is not expensive, and it's a small cost over -- if you talk about just gearing up for using this product on a regular basis, the key is to require these necessary technologies at the beginning, because later on people say oh, we don't have -- we've been getting along fine. Let's not require this. But it's got to be a true answer.

In other words, if they think they're approving dosimetry by measuring the doses, the activity more rigorously because it is a therapeutic. And, also, this is the first of its kind in the United States, and this is just the way this is -- this is the chemical form of this specific radium product, but you can have some other chemical form that's going to behave very differently. So, I remember I was not supportive of extrapolating this to all alpha emitters because it's more the chemistry and the radionuclide tags along. So, do we -- for research products do we -- that still comes

under the 300/1000, or --

MS. COCKERHAM: For us, yes.

MEMBER SULEIMAN: Okay. But, in other words, I'd want to bide time to get like more data to make a final decision.

CHAIRMAN MALMUD: Ashley, I think I interrupted you. I apologize.

MS. COCKERHAM: Sue has question.

CHAIRMAN MALMUD: Dr. Langhorst.

MEMBER LANGHORST: I wanted to clarify that it is getting measured, the dosage is getting measured and very carefully. It may not get that level of careful measurement at the end use, but the radiopharmacy is measuring the dosage. And it sounded -- I just wanted to clarify to make sure -- you were saying it's not getting measured very rigorously, but it is getting measured very rigorously by the radiopharmacy.

MEMBER SULEIMAN: Okay. What I heard was it wasn't at the site versus -- not at the site.

MEMBER LANGHORST: Not at the site. But, I mean, I wanted to clarify that yes, it is getting measured very carefully but with the radiopharmacy.

MEMBER BAILEY: Or in this case the manufacturer.

MEMBER LANGHORST: Yes. Well, in our case it

was our local radiopharmacy, not at our -- under our license but our local radiopharmacy.

MEMBER SULEIMAN: So, how do you fractionate it? I mean, how do you change the dose on site?

MEMBER LANGHORST: We didn't. We were under clinical trial so we didn't.

MEMBER SULEIMAN: You just went with the dose you got.

MEMBER LANGHORST: We ordered the dosage that we needed, yes, or were given, sent the dosages that were needed.

CHAIRMAN MALMUD: Dr. Zanzonico.

MEMBER ZANZONICO: Pat Zanzonico. I think we shouldn't lose sight of the fact that in clinical trials to date, although many of them were outside the United States, there have been I think at this point nearly 1,000 patients who have been treated with radium chloride, so there's quite a body of clinical data which has demonstrated the effectiveness of this agent in its indicated setting, castrate-resistant prostate cancer.

So, one could continue to acquire data indefinitely, and try and get more and more compelling data that the agent is safe and effective. And that is -- I concede that's the jurisdiction of the FDA. But I think there's compelling data already available to

indicate that as it is planned to be marketed it has been shown to be safe. And even though it's not within the scope of what we consider really effective as well.

That's not to say I disagree with the recommendation to -- for both the pre and post radio assay, but I think as Dr. Malmud said, the ultimate charge, so to speak, is what's in the best interest of the patient. And there's two components of that, one is safety, and one is effectiveness. And if you make the safety consideration so onerous as to restrict appropriate referral patterns and clinical use, and so forth and so on, you may in effect be denying access to a very effective agent to a large number of patients. So, I think we have to consider both of those.

There's any number of additional tests we might want to include to nail down the safety even more, and more, and more compellingly, but at some point you have to quench the process and say the data we have, the algorithm in place is reasonable, it's compelling. And given the clinical evidence of effectiveness in a large patient population who would benefit from it, that's where the weight of the decision comes down.

CHAIRMAN MALMUD: Thank you.

MS. COCKERHAM: I wanted to, if I could, follow on a comment. You had mentioned, basically, if we

chose to put it in 35.1000, that that would be a longer period of time. I don't know that that would necessarily be a longer period of time. It's simply a matter of developing the guidance. And as soon as that guidance is developed, it could contain the requirement to assay before and after. That's the process for that. It's not anything very complicated. Obviously, we can see it fits in pretty nicely with 300 with an exception of a few things, so we have a model to follow. And things in 35.1000, the ultimate goal is to eventually put them back into the regulations, to either revise the regulations, or if you I guess get enough data and decide these assays are not required, the guidance is always changeable. You could take it out later. Just I'm trying to get like more of a process and procedure type thing from our perspective of how we would handle it.

CHAIRMAN MALMUD: Thank you. Dr. Welsh.

MS. COCKERHAM: We don't think it would take longer.

CHAIRMAN MALMUD: Good. That's good to hear, thank you. Dr. Welsh.

MEMBER WELSH: So, it's reassuring to hear that if it -- if our recommendation is such that this would wind up in Part 1000 it might not slow things down too much. However, if the conclusion of our

recommendations results in Option 3, recommending changes to 35.300, would that significantly slow things down?

MS. COCKERHAM: That was -- it's definitely a bigger question.

MEMBER WELSH: I just wanted to hear that for the record, and I think that's worth keeping in the back of our minds.

MS. COCKERHAM: Rulemaking takes a very long time.

CHAIRMAN MALMUD: The answer was?

MS. COCKERHAM: Yes.

CHAIRMAN MALMUD: Yes, it would slow it down. Dr. Thomadsen.

VICE CHAIRMAN THOMADSEN: Well, let me refine the question and say would that necessarily slow down the use of the radium dichloride if it were just classified under 300, and it was separated from the recommendation that for therapeutic radionuclides there should be assay before application for all applications then under 300.

MS. COCKERHAM: I don't believe so. You're essentially saying the Committee would recommend licensing under 300, no recommendation for assays before or after. And if NRC agreed with moving it into 300,

that's completely done separate.

VICE CHAIRMAN THOMADSEN: That's done.

MS. COCKERHAM: That's done.

VICE CHAIRMAN THOMADSEN: And the separate, a separate issue is an eventual --

MS. COCKERHAM: Rulemaking.

VICE CHAIRMAN THOMADSEN: -- rulemaking.

MS. COCKERHAM: Done by a different group.

VICE CHAIRMAN THOMADSEN: Correct.

MS. COCKERHAM: Handled separately. Yes.

VICE CHAIRMAN THOMADSEN: Correct.

CHAIRMAN MALMUD: This is Malmud. I think we're missing some data, and the data is, "Has there ever been a report of a radiopharmacy, a licensed radiopharmacy sending out incorrect doses?" That would only be reported by a department which had its own dose calibrator to check it, but I'm not aware that that's ever occurred. Has it ever occurred?

MEMBER BAILEY: Yes.

CHAIRMAN MALMUD: And who at NRC would know?

MEMBER BAILEY: Well, it's occurred in Texas.

CHAIRMAN MALMUD: And do we know the frequency of the occurrence?

MR. EINBERG: We can get that data.

CHAIRMAN MALMUD: I think that would be useful, because if we could say that there have been errors then we have the responsibility to see if we can reduce those errors in some fashion. And one obvious way of reducing those errors is to check the dose in the dose calibrator at the site it's being dispensed.

If on the other hand there's no significant record of errors from licensed radiopharmacies sending material to departments in error, then we're dealing with a non-issue, and we may be putting a roadblock up or slowing something down for no purpose. But I'd like to see -- I think the Committee would like to see the data on the frequency and the absolute number of instances in which radiopharmacies have dispensed incorrect amount.

I think you were first, then Dr. Thomadsen.

MEMBER BAILEY: I think there are several prongs to that one. One is not all the errors would be caught by the dose calibration. We have record of errors that put the wrong tracer in or whatever, so they got a scan of a wrong organ. We do have records of the wrong thing coming out of the pharmacy, mislabeling, whatever. And we have some that would make it to NMED and some that would not, so NMED wouldn't necessarily pick up all of -- if you just wanted a record that nuclear pharmacies make mistakes, human error, they wouldn't all be picked

up through the NRC database.

We have some that we've kept up with that wouldn't -- we have not had to report through NMED.

CHAIRMAN MALMUD: I didn't hear the last two words you said.

MEMBER BAILEY: We have not had to report them to the NRC so that they're in the big national database.

CHAIRMAN MALMUD: Thank you. Dr. Thomadsen.

VICE CHAIRMAN THOMADSEN: I think it was the consensus of the Subcommittee, and the other members of the Subcommittee can verify or dispute this, that the use of the radium dichloride shouldn't be treated any different than other therapeutic agents, which is why I was asking about it being tied to this at all, in which case moving it into 300 would have been the option of choice, disregarding now the requirement to do any type of extra checks on those doses. And could I ask, is that the consensus of the Subcommittee?

MEMBER LANGHORST: This is Sue Langhorst. I agree with you.

DR. ZANZONICO: Can I just --

CHAIRMAN MALMUD: Dr. Zanzonico.

DR. ZANZONICO: Pat Zanzonico. Could you just clarify one point, and this is an issue that had come

up in emails. Regardless of whether it's in 300 or 1000, licensees with a broad license will still have to submit an amendment application?

MS. COCKERHAM: Yes.

DR. ZANZONICO: Okay. And if it were in 1000, you could -- the Subcommittee could recommend requiring pre and post assays. And since you would have to submit an amendment in either case, 300 or 1000, it wouldn't slow things down for the end user.

MS. COCKERHAM: Yes. I didn't articulate that very clearly, but that's what I was saying, it would not take any longer.

DR. ZANZONICO: And would it involve any new rulemaking?

MS. COCKERHAM: Just development of guidance. Which like I said, we have a template. I think we have some very clear things of -- it's very close to 300, and then we would just add the extra things we need to.

CHAIRMAN MALMUD: Dr. Langhorst.

MEMBER LANGHORST: Let me ask this question. So, we would want that done for the radium therapeutic agent but not for any other therapeutic agent. And why would that be the case?

DR. ZANZONICO: That's my problem. I don't

think radium dichloride or any other specific should be a trial balloon for what we think is better medical practice. So, if you're not going to impose these requirements on every other therapeutic agent, why impose it on radium dichloride? That's my first kind of visceral objection.

The other objection is in -- whenever I think of 1000, I think of yttrium-90 SIR-spheres. And it's nothing like that. It's far more like everything else that nuclear medicine physicians use every day, so why segment it in that kind of artificial no logical basis way? But I think as Sue pointed out, the fact that we're treating it differently when it's in fact not different just doesn't seem to make sense.

CHAIRMAN MALMUD: Thank you. Dr. Palestro.

MEMBER PALESTRO: Yes, I was just going to say -- I was going to actually ask the question, is there something unique about radium-223 dichloride that sets it apart from the other therapeutic agents that we use, the other unsealed sources, other than it's an alpha emitter. If the answer is yes, well then maybe it deserves a separate regulation, a separate rule. If the answer is no, I would agree, why treat it any differently than any of the others?

CHAIRMAN MALMUD: Dr. Langhorst, then Dr.

Welsh.

MEMBER LANGHORST: I would say it's no different other than it's an alpha emitter, but it has lots of betas, it has lots of gammas. It's very easy to survey.

CHAIRMAN MALMUD: Thank you. Dr. Welsh.

MEMBER WELSH: I would agree, it is no different; and, therefore, rather than change Part 35 or put it in Part 1000, it would make sense to go along with our initial recommendation for Part 300 and keep our recommendation for good practices just that rather than change it to a requirement which would have implications that require a lot of additional action that I don't think is necessary because it is not different.

CHAIRMAN MALMUD: Thank you. Dr. Zanzonico, you chaired the Subcommittee. Am I correct?

DR. ZANZONICO: Yes.

CHAIRMAN MALMUD: Would you like to make a motion?

DR. ZANZONICO: We have -- so, should I give my presentation and then --

CHAIRMAN MALMUD: Yes.

DR. ZANZONICO: So we can then use that as a basis for the motion?

CHAIRMAN MALMUD: Absolutely.

DR. ZANZONICO: Okay.

CHAIRMAN MALMUD: The presentation will be the motion.

DR. ZANZONICO: Yes.

PARTICIPANT: Well, if we vote on it, then we don't need to hear his presentation.

(Laughter.)

DR. ZANZONICO: Good afternoon, everyone. A lot of what I'm going to present has been said in various ways. But, again, since we've reached the stage of making a motion, I think this is a convenient way of putting it on the table.

I'd first like to thank all my fellow Subcommittee members who really took this to heart, and we had a lot of spirited discussion via email and otherwise, and I really appreciate the input.

So, the Subcommittee charge as you all know is to provide recommendations on licensing of radium-223 dichloride. And this is just background which I think we're all familiar with at this point. And the only distinctive feature in terms of distinguished from other therapeutic radiopharmaceuticals is that this is a first in class alpha particle emitting therapeutic radionuclide -- radiopharmaceutical.

And as was pointed out, it's much more

similar than it is different from other therapeutic radionuclides. I mean, they're all different from one another, obviously. But there's nothing qualitatively different versus other therapeutic radiopharmaceuticals.

So, the first issue, and what I thought was the primary issue was licensure. And should there be any special credentialing requirements for authorized users to administer radium dichloride? And as has been discussed, there's a consensus that 35.300 applies, and the credentialing options, therefore, are 35.390, either Cat (3) or Cat (4); 35.396 sets the new category for alpha emitters, or 1000, which is other and might require a specific license amendment; although, as we've been told, even if it was under 390 it may require a license amendment.

So, the Subcommittee recommendation is that physicians authorized to use therapeutic radiopharmaceuticals already under 390 or 396, already have the requisite education, training, and experience to safety and effectively use radium dichloride. And, therefore, licensing under 390 or 396 is therefore recommended.

The secondary issue which has engendered a lot of discussion is that of calibration of the

administered activity. Is end user calibrations necessary; can it be done accurately? Again, I think it's worth pointing out, is it necessary, can it be done accurately for other currently approved and used therapeutic radiopharmaceuticals, or radiopharmaceuticals generally?

We know dose calibrated settings do not have radium-223 settings. It has a complex decay scheme and so forth, but NIST-traceable standards -- a NIST-traceable standard is available, so in principle it could be done. And if done properly, would be reasonably accurate.

So, the Subcommittee recommendation was to minimize the probability of a therapeutic misadministration, an appropriate radio assay system such as a dose calibrator for measurement of the radium-223 activity prior to its administration, and the residual activity following its administration is recommended.

The issue we've been discussing is should this be a recommendation or requirement? If it's a -- if we recommend it as a requirement, then that moves it from 300 to 1000. And I think based on logic, if nothing else, since it is fundamentally no different from other therapeutic radiopharmaceuticals licensed under 300,

that that's -- that this should be left as a recommendation, and that as I personally -- radium dichloride should not be a trial balloon. I mean, if we feel that all such radiopharmaceuticals require pre and post radio assay, I think that should be left for subsequent rulemaking, and not imposed arbitrarily on this particular agent given all the other considerations of safety, effectiveness, and so forth.

So, I guess I can make a motion at this point for the Subcommittee to adopt those two recommendations, the licensing recommendation and the recommendation, not requirement for pre and post radio assay of patient doses.

CHAIRMAN MALMUD: Thank you for that motion. Is there a second to the motion?

MEMBER LANGHORST: I'll second.

CHAIRMAN MALMUD: Dr. Langhorst seconds the motion. Is there any further discussion of the motion of the Chair of the Subcommittee, Dr. Zanzonico? If not, we will move forward. All in favor of the motion? Any opposed to the motion? Any abstentions from the motion? The motion carries unanimously. Your presentation was very eloquent, Dr. Zanzonico. Thank you.

DR. ZANZONICO: Thank you.

CHAIRMAN MALMUD: Yes?

MEMBER WEIL: Dr. Malmud, this is Laura Weil. So, one of the options that was put on the table clearly not for us to act on was rulemaking change for 300, and whether or not all radiopharmaceuticals should be required to be assayed before and after administration.

CHAIRMAN MALMUD: All therapeutics?

MEMBER WEIL: Yes.

CHAIRMAN MALMUD: Are you referring to all functions --

MEMBER WEIL: Well, I guess I'm --

CHAIRMAN MALMUD: Just therapeutics.

MEMBER WEIL: -- referring to therapeutics. What's the mechanism for moving in that direction?

CHAIRMAN MALMUD: Well, if I may, before we address the mechanism, I think that you would agree given your background that we ought to know what the prevalence is of the problem. And those are the data that I think we want to see.

MEMBER WEIL: Yes, but I'm concerned that the data that we may see which would be from the NRC database is not inclusive of a lot of the stuff that happens at the state level. And we may not, therefore, know the magnitude of error.

CHAIRMAN MALMUD: I see two hands.

MEMBER SULEIMAN: Orhan Suleiman. Quick

question, how difficult would it be to find out if sites that deliver therapy have dose calibrators on hand? I mean, forget whether they're using it properly. If they don't have it, we can assume they're not using it. That would give an indication. Could we -- how difficult would it be to collect that information?

CHAIRMAN MALMUD: Well, that's one question. And then the other question was coming from the State Representative.

MEMBER BAILEY: I think there might be a dependence on negative information means it's not happening. And if they're not checking, we don't know if there's a mistake being made or not. So, just because there's no -- or limited data that a mistake was made doesn't mean no mistakes were made, was my concern.

MEMBER WEIL: It just strikes me that we're fitting radium dichloride into a category that is expeditious and appropriate because it's like the other things in that category. Not that it's the best way to manage this radiopharmaceutical, but it's the way other radiopharmaceuticals like it are managed. But there might be better patient protections associated with other ways to manage it.

CHAIRMAN MALMUD: Your point is well made. I would add to it, though, Dr. Zanzonico's point, and that

is let's take a look at -- well, first we don't know the incidences of errors in the past with other agents. I think those data we should see. And the NRC at least has them for the states that do participate.

Dr. Zanzonico's point was a very valid one, however, and that is that if sufficient requirements were put in, it will squelch the use of the product. One of the most frequent cancers in men versus women is prostate cancer, as breast is for women. And we would assume that this product would have broad usage across the United States because of the prevalence of the disease. And, therefore, it may be used in small departments, independent departments. And to discourage its use by requiring standards that don't apply to other therapeutic agents would not be in the best interest of the patient.

On the other hand, there is certainly the potential for misadministration. But we don't have a database for misadministration, so we'd be passing -- we'd be supporting regulation based upon the absence of data. It may be that we know these things are happening -- this sounds like a political issue that's going on right now about voter registration. But we can't prove it. But without the evidence it seems to me that we would be perhaps doing more harm than good in putting

additional regulations in when there is no evidence that the regulation is needed.

If we can get the database that we're requesting, and I know the NRC has that database with respect to misadministrations of therapeutic pharmaceuticals, we could then see what the prevalence -- what the incidence of the problem is. Does that sound reasonable? Your concern is valid. We all have the same concerns. The question is which way is it better? We don't have the data to determine that yet. Other comments? Dr. Suleiman.

MEMBER SULEIMAN: Okay. Again, I -- if a site doesn't have a dose calibrator, how would they even know if they misadministered? I mean -- and the other question from a personal, professional point of view, would you go -- would you get your therapy from a site that had a dose calibrator or one that didn't? I would think a therapy facility, if they took it seriously, I would expect them to have a dose calibrator. I'd feel really uncomfortable in knowing that the site is sort of trusting and not verifying. That's my personal take on this.

CHAIRMAN MALMUD: It's a valid position. I see a hand. Dr. Guiberteau.

MEMBER GUIBERTEAU: I know this is a somewhat

premature discussion since we don't have any data. And I would hope that the data that we get would be divided among therapeutic or written directive required doses and diagnostic doses, if you will. But there are implications here for certain parts of 390, and the data has shown that the treatment of hyperthyroidism in offices, particularly endocrinologist offices has increased over the last 10 years. And these doses are on what we call low dose, less than 33 millicuries of I-131, and a $20,000 investment in a dose calibrator would certainly be a barrier to these continuing to be done in that setting.

So, I'm just bringing this up because when the discussion does come up, I think the economic consequences and a perceived barrier to the availability of care in certain settings could be diminished as Jim Welsh has said. And I think we should -- it is premature, but I just want to bring it up now that if discussion does occur, that we need to think about other things.

CHAIRMAN MALMUD: Thank you. Dr. Palestro.

MEMBER PALESTRO: Yes, just a comment. As I said before, I've never been anywhere without a dose calibrator, and I feel very comfortable using a dose calibrator. But one of the things that I think we tend to overlook is that the dose calibrator itself and the

people using it aren't infallible. And just merely having a dose calibrator in and of itself doesn't assure or insure that the number of misadministrations are going to be reduced, particularly when we don't know what that number is now without the dose calibrator.

VICE CHAIRMAN THOMADSEN: Thank you. This is Bruce Thomadsen. Two points regarding what's been said. One is by -- if we put up any barriers to the use of the radium dichloride, probably the same facilities rather than making the investment would stick with the samarium-153 or the strontium-89, which may or may not be in the patient's best interest, but it could be restricting a potentially improved product from the patients in favor of a potentially less good agent only because of the barriers involved. So, that's one argument against putting it into 1000 and saying they have to do additional quality measurements on that while they don't on the existing.

But, secondly, on the use of the dose calibrator, whether it's -- if it's inappropriate, inappropriately used at a given facility, the use of the dose calibrator in this context is as quality assurance. It's not to establish the dose but to check the dose, so if there is a measurement that shows that it is made incorrectly in the dose calibrator, what it would show

is a discrepancy possibly where one doesn't exist, which should be something that would cause people to stop and question what was going on, and get back in touch with the company before they deliver the dose. So, it's not a matter that if you have a dose calibrator being used inappropriately you're going to be giving inappropriate doses. You're using it as a check on doses that are delivered. So, if you're making an error it should just cause a stop, as opposed to leading to an error in the dose.

CHAIRMAN MALMUD: Thank you for making that point. Ashley.

MS. COCKERHAM: I have two things that I wanted to mention. The first one, the Committee had requested data regarding what's coming from the radiopharmacy being checked, if there were any discrepancies there. And I just wanted to mention, for diagnostic purposes we're not going to have any reports from that. It's not going to trip the medical event criteria. It's not going to be reportable to the NRC. And I think Ms. Bailey touched on this earlier where the states may be tracking this information. We are not going to see that for any diagnostic uses in our database, so we'll have therapy if it trips the medical event reporting criteria.

The second point is, we still have a Subcommittee report that was written and voted on in the previous teleconference in July, and although we do have a recommendation from you, and I don't think there's any question about what your intentions are, I think it would be very helpful to NRC staff to have a final Subcommittee report. And the only way to do that is to vote on it in a public meeting. So, we had three changes, and I think the first change would be captured by you recommend licensing in 300, with a recommendation for assay before and after but not requiring such procedure.

And the second thing is there were two statements that were removed in the report, the first one had to do with whether this applied to all future alpha emitting particles. And the second was removal of the statement that radium-223 dichloride significantly prolongs survival.

So, although we don't necessarily have the Subcommittee report in front of us, I think we could do the same thing that we did the last time when Dr. Suleiman wasn't able to participate and say this is the change we're going to make. This is what the Committee endorses, and as long as your report matches exactly what you say in this meeting when we get it, that can be considered voted on, final, and it would be a Committee report at

that point. So, whenever you're ready to get to that, or if you want to wait.

CHAIRMAN MALMUD: Dr. Zanzonico.

DR. ZANZONICO: I think that -- I'd be perfectly happy removing the comment in terms of it not -- in terms of our recommendations applying to all future alpha emitting radiopharmacy. Even though it may, I don't think that should be a block to concluding the report. And I think actually, Dr. Suleiman pointed this out, you know, speaking to clinical efficacy is really beyond the scope of what we should do. And I may have overreached a bit in including that language, so I would agree in removing that, as well.

CHAIRMAN MALMUD: That's two of the items.

DR. ZANZONICO: Right. And the third item I think we already had essentially a motion and unanimous approval.

CHAIRMAN MALMUD: So, Ashley, would you like Dr. Zanzonico to make that motion.

DR. ZANZONICO: A motion to accept the Subcommittee report with the three changes specified.

CHAIRMAN MALMUD: Second to that motion? Dr. Welsh. And any further discussion of that motion? All in favor of the motion. Any opposed to the motion? Any abstentions? It once again is unanimous. Thank you,

Ashley.

MS. COCKERHAM: Thank you.

CHAIRMAN MALMUD: I think that has concluded the discussion of this particular item which is the licensing of radium -- oh, Dr. Siegel. We've got a member of the public, Dr. Jeffrey Siegel, who wishes to make a comment.

DR. SIEGEL: I want to welcome Dr. Malmud back. He's been gone for the last few ACMUI meetings, and glad to see him here.

Hi, my name is Jeff Siegel. I want to thank the Subcommittee and the NRC for its time in reviewing the radium-223 dichloride licensing and the vote that was just taken.

I just wanted to remind the Committee at our July 9 telecon, I had brought the issue of dosage Category 3 versus 4. One of the members had agreed that 3 was preferable. One of the members expressed concern that 3 and 4 were the same, but I'd like to point out that when you read 390(g) it does say that a minimum three cases are required in each of the four categories. So, unless I'm misreading that I'd like clarification or for somebody from the Subcommittee to make a comment on if it should remain 3 or 4, or if they should recommend further that it be (g)(3). Thank you.

CHAIRMAN MALMUD: Thank you, Dr. Siegel. A member of the Subcommittee will respond.

DR. ZANZONICO: To be honest I'm off -- this is Pat Zanzonico. I'm not sure -- I'm not entirely sure what the exact issue has been. Could somebody --

CHAIRMAN MALMUD: Dr. Siegel, if you could just clarify the issue.

DR. SIEGEL: The issue, if it was placed into Category (g)(3) because all current authorized users have authorized user status pursuant to (g)(3). Then no additional training would be required. However, if it was placed into (g)(4), I would daresay that there are very few current authorized users authorized under Dosage Category (g)(4), and the three cases would therefore apply potentially, that they would need three cases in order to use this, which would be contrary to the Subcommittee's recommendations. I wanted to bring that to your attention. Thank you very much.

CHAIRMAN MALMUD: I would ask a member of the NRC staff, either Mr. Einberg, Mr. McDermott, or Ms. Henderson to respond to Dr. Siegel's concern.

MS. HENDERSON: This is Pam Henderson. Yes, that's true for (3), it involves beta emitters, proton-emitting radionuclides, and for (4) it's administration of any other radionuclide for which a

written directive is required. So, what he's saying is correct. More people are qualified in (3) than in (4), not that many people are qualified in (4).

CHAIRMAN MALMUD: Dr. Zanzonico.

MEMBER ZANZONICO: Yes, thanks, Dr. Siegel, sending this in for the clarification. And I now what recollect what the rationale for suggesting (3) or (4) was, because (3) explicitly mentioned gamma and beta emitters, so we didn't want to exclude the licensing of radium dichloride under 390 on that basis. But, radium-223 is a gamma and beta emitter, so it's not -- to my way of reading the reg, it's not excluded simply because in addition it's an alpha emitter. And I think the intent of the Committee there is it should be (g)(3).

CHAIRMAN MALMUD: Thank you. Does that clarify the issue? Does that answer the question from Dr. Siegel?

DR. SIEGEL: Thank you so much, Dr. Zanzonico. Would there be a need for the Subcommittee to vote that, put that into their --

MR. EINBERG: Excuse me, Dr. Siegel. Can you go to the microphone for the transcriber?

DR. SIEGEL: I'm sorry. I'm sorry. This is a procedural question, Dr. Malmud and Dr. Zanzonico. Would the Subcommittee then revise the report, do a new

vote? Would that be even necessary?

CHAIRMAN MALMUD: I believe that Dr. Langhorst has a comment.

MEMBER LANGHORST: Yes, Sue Langhorst. I think we didn't want to exclude people who had cases in either one of these. Like maybe they had the (g)(3) experience and not (g)(4), or maybe they had (g)(4) and not (g)(3), and I think we didn't want to exclude. So, that's why I was comfortable in saying either/or for those.

CHAIRMAN MALMUD: Thank you. Dr. Welsh.

MEMBER WELSH: As I read the wording in (3) and (4), after (3) it says "and/or," so -- "and/or 4." So, do we really need to worry about this issue at all?

CHAIRMAN MALMUD: I don't believe that we do, but I'll ask Dr. Zanzonico.

MEMBER ZANZONICO: I don't think so, because the recommendation made is we use the word "or," (g)(3) or (g)(4), so it could be meaning either/or.

CHAIRMAN MALMUD: Dr. Siegel, the Committee feels that it has addressed the issue. Does that relieve you of your anxiety regarding which category it would fit into?

DR. SIEGEL: Yes, it does. I have to say I've read 390 probably 85 times. And the and/or suggested to

me that you as an authorized user may apply for that status for the categories or for just one, so the and/or would only be applicable for the and if you want (3) and (4) authorized user status. But if you only wanted (3), then the or would take precedence because it wouldn't matter. But I agree with the language, (3) or (4) is perfect, but the interpretation of (g)(3) and/or (g)(4) in 390 to me is clear that if it was (g)(4), not (g)(3) you would need the cases. But if it's (4), thank you very much, Dr. Malmud.

CHAIRMAN MALMUD: It appears that the recommendation of the Committee includes both. Is that correct, Dr. Zanzonico?

MEMBER ZANZONICO: My opinion, yes.

CHAIRMAN MALMUD: And is that agreeable with the NRC staff that's here, Mr. Einberg, Mr. McDermott? And the answer is shaking of the heads affirmatively, so the concern that you raised appears to have been addressed officially in that both the members of the ACMUI and the NRC staff present today agree that this can move forward as it is.

I believe there is -- was there another hand raised? Who? Oh, I'm sorry.

VICE CHAIRMAN THOMADSEN: Can I get a clarification from the -- this is Bruce Thomadsen. Can

I get a clarification from the NRC staff, it seems to me as I read the regulation here that both under (g)(3) or (4) you are followed by an "and" to the following two, which goes with the one on the previous -- the (b)(1) on the previous page. And (2) would follow for all practitioners in (3) and (4). Is that the case?

MS. HENDERSON: You have to repeat the question. I'm sorry.

MEMBER ZANZONICO: Right. The (g) follows from the (b)(1) on the previous page. Is that correct?

MS. HENDERSON: Yes.

MEMBER ZANZONICO: And the (b)(1) is where you get down to (g)(3) and (4).

MS. HENDERSON: Yes.

MEMBER ZANZONICO: Which both -- that paragraph ends in an "and" followed by that (2), which requires the attestation and the -- all the rest of the paragraph. So, the (2) would follow for both (3) and (4)?

MR. EINBERG: We have Neelam Bhalla who thinks she has an answer for that.

MS. BHALLA: Good afternoon, everyone. I think from the spirit of the regulation, and this is also my understanding because we are in this -- actually, there is a rulemaking activity underway right now, and this is one of the areas that we are addressing. So,

therefore, I think I have maybe a little bit of an understanding of this very complex regulation, the way we have it there.

And it seems like it's saying the experience is for each one of those categories, so it's the betas, low betas. You have the gammas of a certain energy, then it goes to the third one. And for the fourth one which is the catchall is where we talk -- but for our -- from a legal perspective it seems like it doesn't, so we are going to do actually another category, spell it out. And the "and" and "or" is really to -- if you are going to do a subset of the isotopes then you need three of those cases. You want to go to another one, you need three of those cases. And it doesn't just stop at the cases. And then the rest of the requirements, the attestations, et cetera, everything else goes in addition to.

So, it's the number of cases for each one of those three categories, so it's not that if you have it with the first category, the reg is not in front of me, but whatever that says. And it's not that you can just have three of one of this, and one of that, and one of that. The intent is that the experience is needed for three cases of each one of those. And then the and goes for all of those additional things, the attestations, the supervised training, et cetera. So, I hope that answers

the question that's asked.

CHAIRMAN MALMUD: Thank you. Dr. Thomadsen.

VICE CHAIRMAN THOMADSEN: If I understand what you said, then the intention of the Subcommittee in saying either (g)(3) or (g)(4) for the experience would mean that if somebody had had the three cases of experience in (3), and they wanted to use this radionuclide they could, or if they had the experience of three cases in (4) and they wanted to use this nuclide, they could.

MS. BHALLA: Right. So, if they just want the (4), let's go to the (4), whatever that (4) is. So, if the user just wants that (4), then that's where the three cases would be, and in your authorization in the licensing part you will be limited to that particular authorization. So, it's not in any order, it's not in lieu of, but that's the way it is. So, I'm going to —-- I'm sorry, I have not seen the Subcommittee report.

CHAIRMAN MALMUD: Dr. Zanzonico.

DR. ZANZONICO: So, could I -- like a hypothetical example. So, if an individual say had treated three patients with I-131 iodine for hyperthyroidism, that's a beta and gamma emitter. That even though it's a separate category --

VICE CHAIRMAN THOMADSEN: It's a one.

MEMBER ZANZONICO: But it is a beta or gamma emitter. They're not mutually exclusive.

VICE CHAIRMAN THOMADSEN: It has its own --

MEMBER ZANZONICO: Right, but the --

VICE CHAIRMAN THOMADSEN: That's a bad example.

MEMBER ZANZONICO: Well, let's say quadra med.

VICE CHAIRMAN THOMADSEN: There you go.

MEMBER ZANZONICO: If the use quadra med, if they use -- they could use it without any additional specific training or experience. In other words, they wouldn't need three cases of radium dichloride training, so to speak.

MS. BHALLA: Correct.

MEMBER ZANZONICO: Okay.

MS. BHALLA: Because then your authorization will be limited to the -- whatever column it falls, the betas --

MEMBER ZANZONICO: Okay.

MS. BHALLA: It has up to a certain value. Is that --

CHAIRMAN MALMUD: Was that the intent of the Subcommittee?

MEMBER ZANZONICO: Yes.

CHAIRMAN MALMUD: That's consonant with your understanding?

MS. BHALLA: Yes, but Sue has a --

CHAIRMAN MALMUD: Dr. Langhorst.

MEMBER LANGHORST: I just wanted to clarify what Pat just said. You do have to have additional training when you do new procedures and so on.

MEMBER ZANZONICO: Right. Right.

MEMBER LANGHORST: I mean, it's not like --

MEMBER ZANZONICO: It wouldn't be specific.

MEMBER LANGHORST: You wouldn't have to do three cases. That's correct.

MEMBER ZANZONICO: Right.

MEMBER LANGHORST: But I did want to clarify, there is always new training when you start --

MEMBER ZANZONICO: Yes, understood. No, understood.

MEMBER LANGHORST: -- a new radiopharmaceutical administration.

CHAIRMAN MALMUD: Someone have a comment?

MEMBER MATTMULLER: I do, but --

CHAIRMAN MALMUD: Please go ahead.

MEMBER MATTMULLER: Well, it's in regard to —-- I'm sorry, Steve Mattmuller. It's not in regard to the specific training requirements, it's in regards to

radium-223 and its assay procedures by the manufacturer.

CHAIRMAN MALMUD: Before you ask the question, may I ask the member of the public who raised this issue if this is clarified for him. Dr. Siegel?

DR. SIEGEL: Absolutely. Thank you very much.

CHAIRMAN MALMUD: Dr. Siegel says absolutely, thank you very much. So, that issue is closed. We may move on to your question.

MEMBER MATTMULLER: Okay, very good. Steve Mattmuller. In our conversations and discussions on this there was some uncertainty as to the manufacturer, or what their procedures were at the manufacturing facility as far as how well calibrated their equipment is, and its accuracy and precision. And recently, the NRC has asked them the same question, and I'm very pleased to see that they came one day later after getting a letter. Fair comment on any of the questions raised in the letter.

CHAIRMAN MALMUD: Please introduce yourself again.

DR. SIEGEL: Hi, Jeff Siegel. Thanks, Dr. Mattmuller for the questions. I'd like to say I had some slides prepared. I don't know if we can show them, but there were a NIST study performed and published in 2010 in the Applied Radiation and Isotopes Journal. It's 2010,

Volume 68, pages 1367-1370.

The manufacturer, which is IFE, the Institute for -- I'm sorry, what does that stand for? Energy Technology, which is in Norway, participates with NIST in measurement standard determinations. NIST has developed, as somebody mentioned, a radioactivity measurement standard which they have provided to the manufacturer. The manufacturer has used that NIST-traceable, NIST-supplied source to calibrate their calibrators. And to be clear, the calibration is very simple. All it is, is you put in the known activity, adjust your dial setting until you measure that activity. You now have a calibrated dose calibrator using a NIST primary standard.

That then represents how the manufacturer calibrates their dose calibrator. They then ship that activity to a central radiopharmacy in the United States. That central pharmacy in the United States gets a NIST-traceable primary standard and they calibrate their dose calibrator.

Then they make up unit dosages. And how that do that is based on the 50 kilogram per -- 50 becquerel per kilogram body weight, not unlike Zevalin, which is the .3 or .4 millicurie per kilogram. They call, they tell the pharmacy that our patient is 70 kilograms, 70 times

50, I could do that without a calculator, is 3.5 megabecquerels, sorry the SI units, most people don't like the SI units. But then it comes back as 3.5 megabecquerels.

And I'd like to say the study that NIST has done, because as somebody mentioned there is no current manufacturer supplied dial setting for the dose calibrator, it must be determined for each dose calibrator. And NIST has done this, and they have I think 10 different dose calibrators. They did this in vials, they did it in syringes, different volumes in that article I mentioned. And what they found was irrespective of vial, syringe or volume that they studied, that they got plus or minus 4 percent. So, the conclusion was only a single dial setting, not a dial setting for different volumes, different syringes, for different vials was necessary. So, the procedure for the end user of the licensee when it comes to them from the radiopharmacy is exactly the procedure that's used for Zevalin.

This was an article, I hate to say who the first author was, it was me. I wrote it with NIST and all the dose calibrator manufacturers. It's a consensus document, but this was for Zevalin, with a recommended best accurate method for an end user was to get the calibrated unit dosage from the pharmacy which then

served as a secondary standard.

Each then had to calibrate their dose calibrator with that secondary standard by dialing in, and they couldn't even participate in the original study unless they were -- and that's what the manufacturer and the company is recommending as a procedure to receive and treat patients with radium-223 dichloride. Does that answer your question?

CHAIRMAN MALMUD: Thank you for that explanation. Are there questions for Dr. Siegel?

MEMBER MATTMULLER: Steve Mattmuller. So, again, the company will be recommending that the final site reassay the dose is based on their calibration factor determined from three measurements from three doses from the centralized pharmacy.

DR. SIEGEL: Yes.

MEMBER MATTMULLER: Okay, good. That's great. I think that's good.

CHAIRMAN MALMUD: How would they reassay it if they don't have the dose calibrator?

MEMBER MATTMULLER: No, no, they will have a dose calibrator, but they're not going to get the NIST standard to check their calibrator with. They're going to be at the secondary process with a calibrated unit dose from the pharmacy that has calibrated their dose

calibrator with an NIST dose -- standard, excuse me.

CHAIRMAN MALMUD: Dr. Langhorst.

MEMBER LANGHORST: Dr. Siegel, would you say that that measurement at the end user is a quality check, or is it recalibrating and saying what the activity actually is?

DR. SIEGEL: I think it -- because it came from NIST and the dose calibrator manufacturers, that's what they consider best practice to make an accurate measurement.

MEMBER LANGHORST: Okay.

DR. SIEGEL: And I have to say in the last discussion there was some mix-up in terms of accuracy and prescribed dose. The NRC requirement per 35.63(d) is that unless the authorized user changes it, the prescribed dosage can be used if it's greater than 20 percent. But the authorized user given the regulatory framework that the NRC now finds itself in giving the licensee more flexibility, because the authorized user may decide no, I want it to be plus or minus 5 percent, or I want it to be plus or minus 50 percent. He can so do that, and that has nothing to do with accuracy because accuracy is plus or minus what's expected, not plus or minus from the prescribed activities, two different separate issues.

CHAIRMAN MALMUD: Dr. Suleiman.

MEMBER SULEIMAN: Two questions. I consider that a calibration, if it's using a reference standard traceable back to NIST.

DR. SIEGEL: Right.

MEMBER SULEIMAN: Second point, the test for Zevalin, that was not part of the original approvals for Zevalin. If you -- I don't remember. I'm asking you. I mean, Zevalin was approved about 10 or so years ago, and you're coming up with this verification in 2010. So, that tells me it's an improvement in protocol --

DR. SIEGEL: No, no, that reference -- this is a separate reference.

MEMBER SULEIMAN: Okay.

DR. SIEGEL: That reference was in the Journal of Nuclear Medicine 2004.

MEMBER SULEIMAN: Okay.

DR. SIEGEL: Volume 45, page 450-454. I'll be happy to give it to anybody that may want the reference.

MEMBER SULEIMAN: But that was post approval.

DR. SIEGEL: Well, it was approved in 2002 if I remember correctly.

VICE CHAIRMAN THOMADSEN: Just a minor -- this is Bruce Thomadsen, just a minor detail for Dr.

Suleiman. Because the NIST standard goes to calibrate the dose calibrator at the nuclear pharmacy, that would be now directly traceable to NIST. But when they assay another vial which is now -- that one carries a direct traceability. When they put that in the facility's dose calibrator, you no longer have what's defined as a directly traceable calibration. And that means that you are doing quality assurance on the measurements, not calibration on the measurements.

MEMBER SULEIMAN: So, the reference -- this is Orhan again. The reference source was not tested on site, it was just tested at the nuclear pharmacy.

VICE CHAIRMAN THOMADSEN: Correct.

MEMBER SULEIMAN: But if a reference source traceable to NIST was used at the site --

VICE CHAIRMAN THOMADSEN: Yes, if the site were to get an NIST standard and calibrate its dose calibrator, that dose calibrator is then directly traceable to the calibration, and that's directly traceable to NIST.

MEMBER SULEIMAN: That was my understanding.

CHAIRMAN MALMUD: Thank you. It appears that we have a consensus and an understanding.

MEMBER SULEIMAN: Thank you very much.

CHAIRMAN MALMUD: Thank you. Mr. Einberg.

MR. EINBERG: Yes. I just wanted to thank the Committee for their recommendation here and for their work on this report. And we'll take this information with the report and consider it as we go forward with our licensing decision on this, and then we'll communicate that back to the Committee. And, of course, the manufacturer, as well.

CHAIRMAN MALMUD: Thank you. I believe that completes the discussion of the licensing of radium-223, which means that we are in time for a break. We will resume promptly at 4:00.

(Whereupon, the proceedings went off the record at 3:12:08 p.m., and went back on the record at 3:59:13 p.m.)

CHAIRMAN MALMUD: Mr. Fuller.

MR. FULLER: Thank you. Good afternoon. As Dr. Malmud had said, I am Mike Fuller. I'm the team leader of the Medical Radiation Safety Team here at the Nuclear Regulatory Commission, and it is my pleasure to be here today to speak with you.

I'm pleased to be here to provide you with an overview of an update -- I'm sorry, and an update of NRC initiatives related to the release of patient's administered Iodine-131, especially those who do not immediately return to their primary residences.

As you are all well aware, and it has been discussed by the ACMUI many times, when patients are released they may take them to a hotel or perhaps go to some other location other than their primary residence. I will even go so far as to say that some patients don't have a primary residence.

First I'll cover some of the background information related to the release of patients. Most of you have heard all of this before, but for those of you who have not been quite as involved as some of the others, and certainly for folks that are listening in today, I would like to go over some of this background information briefly.

So, in May of 1997, NRC revised the patient release regulations in 10 CFR 35.75 to allow for the release of patients based upon the dose to the maximally exposed member of the public. Prior to this, the rules and the release criteria were based primarily on activity. And, specifically, patients can be released if the dose to any other individual from exposure to the released patient is not likely to exceed 5 millisieverts or 500 millirem.

The NRC regulations also require that written instructions on how to keep doses to other individuals as low as is reasonably achievable or ALARA

be given to patients if there is a possibility that doses to any other individual, any other member of the public would exceed 1 millisievert, or 100 millirem. The licensee is required to maintain a record of the basis for authorizing the release in either case.

So, since the regulations do not specifically refer to Iodine-131, why have we been focused on this isotope? And there are a number of reasons. First, there has been a high rate of use of this isotope for many years for the treatment of thyroid cancer and other diseases. The dosages administered were increasing for many years in some cases to very high quantities of activity. And lately, contrary to that, some authorized users are starting to administer lower quantities, so there is some variability in the activities administered to the patients.

There are some unique characteristics associated with Iodine-131 including the volatility of the material in some instances that may result in increased potential for external or internal radiation doses and contamination of surfaces. And the emissions of Iodine-131 are relatively high in energy, as well.

Now I will cover some of the current -- or cover the current NRC guidance on this topic. Reg Guide 8.39, Release of Patients Administered Radioactive

Materials, was issued in April of 1997, and provided the basis for the rule, and provided guidance for compliance with the rule.

NUREG-1556, Volume 9, in Appendix U is another available guidance document, and is based entirely on the information that's contained in Reg Guide 8.39. This document was originally published in draft in 1998, and finalized in 2002.

In March of 1998, Regulatory Issue Summary 2008-07 was issued to explain to NRC licensees how to instruct patients for compliance with the rules. And in May of 1998, just two months later, we issued Regulatory Issue Summary 2008-11, precautions to protect children who may come in contact with patients released after therapeutic administration of Iodine-131. This was issued to clarify and amplify the precautions that licensees should take to protect infants and children.

The most recent guidance that NRC has issued on this topic was issued in January of 2011. And that's entitled "NRC Policy on Release of Iodine-131 Therapy Patients Under 10 CFR 35.75 To Locations Other Than Private Residences."

In this RIS we explained that while the rules do not prohibit the release of patients to locations other than to private residences, the NRC did

not encourage and does not encourage this practice.

So, now I will go over our more recent efforts related to the release of patients who are treated with Iodine-131. In May of 2011, the Commission directed the NRC staff to evaluate whether there are gaps in the available empirical data on doses received by members of the public from release of patients treated with medical isotopes, to determine how the Agency would go about collecting additional data if needed, and to assess the feasibility of revisiting the dose assessment used to support the 1997 patient release rulemaking.

Now, in response to this Commission direction the staff developed SECY-12-0011. And after sharing it with the ACMUI and receiving your comments, we provided that paper to the Commission in January of this year. In this paper we discussed what we believed was feasible and provided a number of suggested options.

So, in March of this year, the Commission directed the staff to perform analytical and limited empirical research and data collection, and revisit the calculations and methods described in Reg Guide 8.39 for patient release.

So, at this time we're working with our Office of Research in developing plans for coordinating this effort. There will most likely be a number of stages

or tasks that come out of this, and those may include an extensive literature review, a review of the assumptions used in Reg Guide 8.39, a survey of the habits of released patients, the performance of empirical measurements, the assessment of internal and external radiation exposure, and perhaps a reassessment of the adequacy of Reg Guide 8.39.

This is expected to be a multi-year project. It is still somewhat uncertain, but I would estimate that we are looking at a two to four-year time frame for carrying out this research and reporting the results.

Of course, what we ultimately do related to this effort will depend on what we learn from this research, but we expect to update Reg Guide 8.39 at a minimum. And at next spring's ACMUI meeting, we will be fully engaged in this project and we should be able to report out more specifics as far as the research is concerned, and maybe even provide some preliminary results.

And that's all I have on this particular topic, but I'm happy to take questions.

CHAIRMAN MALMUD: Thank you, Mr. Fuller. Are there questions for Mr. Fuller? Dr. Zanzonico.

MRMBRT ZANZONICO: Pat Zanzonico. What exactly is meant by survey habits? What's meant by that

term "habit?"

MR. FULLER: Well, we were directed to collect some empirical data, time motion studies, if you will. So, it will be -- it remains to be seen exactly how that particular task or that particular aspect of the study will be developed, but we are anticipating that perhaps there'll be some real time motion studies on how patients act, and what the dose rates are, and so forth. It's going to be very difficult to design it without having some -- we recognize this is going to be a difficult task to design a study, but we are prepared to look into it.

MEMBER ZANZONICO: And another question. Will this be a purely internal NRC effort, or will there be extramural grantees, or contractors?

MR. FULLER: We suspect that some of this will be done in house, and some of it will be contracted out. And, hence, the time frames involved. So, it would have to go through the process of developing Statements of Work, and Requests for Proposals, and things like that.

CHAIRMAN MALMUD: Other questions? The study will basically be one of patient compliance with their advice at the time of therapy?

MR. FULLER: Actually, that might be one

thing that we wouldn't involve or get involved with, other than to study some of the more normal habits and so forth. But no, the focus of this really is to collect data that would help us to reassess some of the fact -- the assumptions in Reg Guide 8.39, and also some of the -- so, the dose conversion factors, and also lean more about the -- well, the bottom line is that when we did our analysis of the data that was available back last year, the gaps that were identified had to do with the fact that when we developed the rule we really didn't look at the situation where people were leaving and going somewhere other than their primary residence. So -- because there's a certain amount of -- well, it limits the assumptions that we had to make. So, we're going back and revisiting that.

First of all, we're going to do an extensive literature research and see -- and extensive literature search and see if there is something there that could help to fill those gaps. And if not, then we'll have to do some research.

CHAIRMAN MALMUD: Thank you. Laura.

MEMBER WEIL: Laura Weil. Are you going to do any assessment of patient's understanding of the written instructions that they receive?

MR. FULLER: At this point in time, I don't

think that's part of the scope, but -- and I'm sorry, I don't have the SRM in front of me so I could give you the exact words, but we did get some fairly specific instructions from the Commission on that point. And let me also make a commitment to get back to you and let you know exactly what the SRM says on that.

MEMBER WEIL: I think that's disappointing if it doesn't.

MR. FULLER: Do you have it? Yes, we've got some time. I went through that pretty quickly. Yes, the --

MR. EINBERG: This is Chris Einberg. I believe the SRM basically stated to assume that the patient --- or that the patients are following the guidance or directions as provided. However, having said that, though, when we're doing a time motion study, you're going to observe the patients, how they interact, so whether they follow instructions or not, it kind of works its way into the --

MEMBER WEIL: It's certainly related, although -- what I'm getting at is that there's fairly good literature out there that says patients don't necessarily understand discharge instructions. And what we're not teasing out is what is done deliberately and what is done inadvertently caused by poor understanding

of the instructions.

MR. FULLER: Do you all have -- they're looking for it now. I think I might find a better way. Do you have access to the internet? Just go to the SECY website and go to the SRMs, and it will be right there, 12-0011. And the reason I hesitated to answer your question, Ms. Weil, is because I know in earlier SRMs we had very, very specific instructions on this point. But in the final SRM, after we sent up the SECY paper, I just don't recall if there were any words that allowed for any --

MS. COCKERHAM: This is Ashley. Mike, could you please tell us the number?

MR. FULLER: Well, that's the SECY paper. Oh, no, that is the SRM, yes. Okay. That -- back up. Okay. So, the staff -- yes. It says, "The staff should design its limited empirical research data collection such that the information collected will be representative of behaviors of a majority of members of the public to the maximum extent possible." So, yes, it -- like I said, an earlier direction that we got when we were actually asked to do the gap analysis, there were some constraints put simply because if you didn't have some constraints we would be off on a research project right then, and we couldn't get results reported back very timely. So, in

this case, this was after we had done our gap analysis, and it seems to be that -- I'm looking through it again. It doesn't address it point on point.

MR. EINBERG: However, I would say that it says that that information collected will be representative of behaviors of a majority of members of the public to the maximum extent possible. So, it could possibly catch the misunderstanding of the guidance.

MEMBER WEIL: Could, but wouldn't attribute it to that. It's not upstream, it's contemporary.

MR. FULLER: But the point we'll make is that the earlier SR -- when we were directed to do the gap analysis, we needed to get that back right away, you know, getting -- be able to estimate what it would cost to do further studies. So once we did that, then the SRM that we got that actually directed us to do the research and work with the Office of Research on that, everyone recognized this is a longer term project that allows for appropriate study.

CHAIRMAN MALMUD: Thank you. I do think, though, that Laura's point is a valid one, and that is that the patient should have an understanding in the patient's native language, whether that be English, or Spanish, or what have you of what the guidelines are, because without that, then the issue of compliance and

behavior on the part of the patient is really not terribly valid. That's a good beginning, is that they should have that information available to them, and have it explained to them.

The vast majority of patients are very compliant because they're very concerned about their family. And I'm smiling because I can think of a few patients that I knew would not be compliant, though they said they would be compliant, and one can't challenge a patient when he or she says he's going to be compliant. But you can pretty well predict who's not going to behave well. And it's going to be a very interesting study. We'll look for the results.

So, I do think that Laura's point -- that the kickoff point has to be that the patient does understand what has been explained by way of radiation safety. If that's missing, then the whole theory will be distorted. I assume that all of us function under the same federal guidelines, and that is the patient is required to be given instruction in the language that is the patient's native language. We all use translators. That's a federal guideline, isn't it?

MEMBER WEIL: It's a federal guideline for the new threshold for 1 percent -- if 1 percent of your population, your catchment, your population speaks a

particular language you have to have essential documents in that language. I don't know if these instructions fall under that essential documents guideline or whether private endocrinologist offices that are administering Iodine-131 would come under that 1 percent threshold.

CHAIRMAN MALMUD: So, the law is just for the 1 percent or more.

MEMBER WEIL: Yes.

CHAIRMAN MALMUD: I see. It's interesting because we use a translation service, and we have some very obscure languages.

MEMBER WEIL: Yes.

CHAIRMAN MALMUD: Albanians.

MEMBER WEIL: Lots of hospitals do, but other facilities may not.

CHAIRMAN MALMUD: Yes. For Spanish we have translators on site, and they're required to be present. And we also have the material printed out, not that we're a glaring example of what should be done. This is what we do, and we have it in Spanish and in English. But after that, everything is verbal, but very carefully done. Very interesting. But that's certainly an essential first step, that the patient understand. That we understand that the patient has been given the opportunity to understand. We can't comprehend for the patient, we can

only explain to the patient. Be a very interesting study.

MR. FULLER: Yes, I look forward to next spring. Hopefully, we'll have something a little more informative.

CHAIRMAN MALMUD: It will take time.

MR. FULLER: Yes. We're kicking it off and developing the Statements of Work and things like that at this point.

CHAIRMAN MALMUD: Thank you very much. We'll move on to the next item on the agenda, and that is 10 CFR Part 35 rulemaking update. And who will be the first presenter for that? Ms. Bhalla.

MS. BHALLA: Good afternoon. I'm Neelam Bhalla from the Rulemaking Branch of the same office that we all are in. And just the next slide, can I go this way?

I'm not going to go too much into what the —-- what rulemakings we are continuing to do right now, but because we have discussed those before. Last May, not this immediate, but 2011, that whole ACMUI meeting was dedicated to the rulemaking issues. So, in a nutshell we have two medical rulemakings. One is, we call it the expanded rulemaking because it does have a whole lot of sections of Part 35, which are being considered for amendment.

And then is the other -- or another

rulemaking, we call it the medical event rulemaking. And that has to do with the implementation of our current regulations as they pertain to brachytherapy implants.

So, with these two rulemaking, what happened is in we call it as an SRM that was referred to, even Mike's talk. This is the Staff Requirement Memorandum, and it came to for the permanent implant brachytherapy paper, SECY-12-0053, and I think the paper had -- the paper's title is the "Regulatory Improvements To -- Or Recommendations for the Brachytherapy Implants, The Permanent Implants."

So, in that SRM so far as our rulemaking goes there, the Commission gave us direction on two things. There's other things also, but I'm not -- so far as rulemaking goes, these are the two things that the Commission directed us. One is to include the medical event rulemaking into the expanded rulemaking so that it will all be one total package. And then the next one is -- and this is important for us, for all of the staff here. And that is to -- the Commission said very clearly that provide the Commission with a new paper at any time a substantive delay in the completion schedule for this rule becomes apparent.

And then in this paper, the Commission is looking for the reason for the delay, and also going back

to the choice of impact of separate medical event rulemaking from this combined rulemaking.

So, what is the schedule right now is the Commission is expecting the proposed rule to the Commission in mid-2013, and final is late 2014. And in between the time that the rule goes -- the proposed rule gets posted in the -- published in the Federal Register notice, we invites comments on the rule. And we go over and resolve comments. And the last step, the very last step in that process is the actual publication of the rule. And these all happen pending Commission approval.

This schedule is very important for the ACMUI because we are going to request the Committee to review the draft Federal Register Notice before it goes to the Commission. And our plan is to have it ready for you, the FRN by end of this year. And then our procedure gives the ACMUI 90 days to do the review. And, therefore, we would be expecting your comments March 2013. And we would definitely consider the comments, and have the proposed rule out to the Commission by mid-2013.

So, that's the schedule, and we -- as I said, we will be sending it to the Commission for their review, for comments, and we look forward to that.

CHAIRMAN MALMUD: Thank you. Are there any questions for Ms. Bhalla regarding rulemaking? Dr. Van

Decker?

MEMBER VAN DECKER: Just a couple of questions about time line for those of us who are ever mindful of the fact that the Agreement States have three years for compatibility after a rule becomes final. So, for those people really working in the trenches, this is like a 2017 kind of thing. I appreciate the agreement from the Agreement States.

So, you know, it's very nice I think for the Agency to give ACMUI the first review of the document, and I think we all appreciate that. So, I guess my comment on the first time line is if our comments are due by March 13th, then the April 2013 meeting of this would be a time line where there's adjudication of any of the ACMUI comments with what your draft was. So, after that meeting we're good to go from this group, and then it will go on to the Commission from there. You'll have enough time between March and April to adjudicate whatever the ACMUI comments are so that we're not waiting to the October 2013 meeting to adjudicate that piece of the puzzle before we move to the Commission in an open commentary period?

MS. BHALLA: That is correct. We cannot --

(Simultaneous speech.)

MS. BHALLA: Yes, because I -- it's not only the ACMUI's comments. We would also be providing the

draft to the Agreement States.

MEMBER VAN DECKER: Okay.

MS. BHALLA: Then we would -- we also give it to our -- it's called the Office Conferences, so we give it to, for example, our Office of General Counsel must confer, our Admin Staff must confer. So, there are four different entities that must all come together. And I know it's a very tight time frame that we are shooting for, but we just feel that after all those -- the workshops that we did last year and the Commission direction that we have now gotten on -- that Dr. Zelac is going to talk about after I speak, with all those we are hoping that we will not have a whole lot of comments at that stage. And whatever comments will be, that we'll be able to resolve them in about a month's time. And, therefore, be able to meet the schedule.

MEMBER VAN DECKER: So, in the best of all worlds those commentary periods are going on simultaneously at those upper level groups, and hopefully you would be able at least the ACMUI to give us some concept of what those other stakeholders at that level are talking about at our April meeting so that some -- or whether you see a stumbling block in any of that.

MS. BHALLA: We do -- we actually do not because when our working group is working on this

rulemaking, we do have our co-regulators, members from the Agreement States. We have persons from the General Counsel, we have folks from all the -- our inner NRC folks, the Region, so that we really don't expect at that point a whole lot of comments. And then I'm always -- I think all of us are so optimistic, we just go with the, you know, ideas that it should not be. So, it should be smooth sailing.

MEMBER VAN DECKER: And my last question if I may, I guess, is the slide that talks about an update if there's been a delay in the schedule so far. I guess at this point in time since there hasn't been any statements or any papers at this point time, you don't see any roadblocks to the combination of the brachytherapy piece of this rule and the expanded rulemaking, because there's all kinds of different constituents trying to get this through. Right now we're moving along okay?

MS. BHALLA: Right now we are, yes.

MEMBER VAN DECKER: Thank you, ma'am.

MS. BHALLA: Just to add on that, just yesterday the working group started to work on the ME portion, or the Medical Event portion of the rule, so as I said before now, we have gotten Commission approval and direction ahead of the -- so, hopefully, we'll be able

to do this.

CHAIRMAN MALMUD: Thank you. Was -- does that complete the comments for this section? You've handled the whole thing?

MS. BHALLA: Yes. It was basically to give a schedule for the ACMUI. I think I need to add one more thing, that it's not just the rulemaking, the draft FRN, but there will be some forming guidance that we'll be developing, the staff, so that should also come for ACMUI review.

CHAIRMAN MALMUD: Thank you. Dr. Zanzonico.

MEMBER ZANZONICO: Pat Zanzonico. I'm just trying to understand the scope of the expanded rulemaking. Should that culminate in a new or revised NUREG-1556. Is that the intent?

MS. BHALLA: There I think two things, in my view. Usually, the 1556 volumes are supposed to get revisions every so often, but then there -- when a rule is being changed, then we just go and do conforming changes to parts of that volume which would be impacted by the rule. So, the intent for the rulemaking purposes is to go and make conforming changes to only the affected parts.

For example, in this rulemaking we are not going to touch 35.75, Patient Release, so we don't need

to touch that part. But we are going to touch the generators, for example, and reporting of the failed generators and so on. So, those portions from the guidance, they will be pulled out and changes to it will be in question and answer form, or it will be exactly, pull out the documents and say now this is what it says now, but with the revised rule this is how you meet the requirements.

MEMBER ZANZONICO: So, from a nuts and bolts point of view, it sounds like it's going to be largely -- the NUREG-1556 is going to be largely in tact except for changes impacted by the rulemaking. So, just from an end user point of view, how would you identify -- like what notation or otherwise, like you're searching on the internet, for example, what notation do you look for to identify the latest version, when it's completed, the latest version of NUREG-1556 that incorporates these changes?

MS. BHALLA: We have different ways. One would be on the web, like you to go our -- we have a lot of information on the medical toolkit, so that toolkit gives, in fact, what our regs are, what our RISs are, what our guidance documents are. And any time there's a major change, there would be another document which is going to address that, that these are the changes right now.

And then when we do a future in total revision of this volume, then these will be included in there. So, there will be notification. There'll be a way to --

MEMBER ZANZONICO: Not to belabor the point, but I think a lot of people, myself included, the first document you consult if there's a specific question and so forth is NUREG-1556. So, I mean, will there be like a revision number, or is there a specific identifier that one can go to to make sure you're looking at the latest version of it?

MR. EINBERG: Our plan is to make conforming changes as Neelam indicated, and these conforming changes have to accompany the proposed rule. So, it's going to go out for comment, as well. So, we haven't clearly identified how we're going to set this out in the Federal Register Notice, but one thought that we had is that we'll provide a link in the Federal Register Notice that will take you to a redlined strikeout document that will show where the changes are. So, that's one of the strategies that we're thinking about.

And then as Neelam pointed out, subsequently then we'll do a wholesale revision, or we're doing a wholesale revision to Volume 9 currently as we're developing guidance.

CHAIRMAN MALMUD: Other questions? I see

none. Thank you very much. We'll go on to the next item on the agenda, which is the Update on Proposed Regulatory Changes for Permanent Implant Brachytherapy Programs. Dr. Zelac.

DR. ZELAC: In case I'm unknown to any of you, which is probably not worth doing. As Ms. Bhalla has said, we're trying to give you up to the minute information about where we stand with this whole process, of things to which ACMUI has had various amounts of input. This one, permanent implant brachytherapy and medical events is clearly something that ACMUI has had input on since day one. And you will be very familiar with what I'm going to say, I believe. And I'm simply conforming to the process of letting you know where we stand at the moment with these various recommendations that had originated with the ACMUI. So, my presentation is focused on NRC staff-developed and Commission-endorsed recommendations for modifying the current Written Directive and Medical Event reporting requirements with permanent implant brachytherapy medical use.

This gives a little history of this. As you all know, the main objectives in these recommendations were to change the treatment site medical event criterion from dose-based to source strength-based. And, secondly, to remove the ambiguity from Written Directive and

Medical Event requirements.

The nearly unanimous position of stakeholders is that a dose-based criterion for the treatment site limits the physician authorized user's ability to provide optimum patient care without resulting in inappropriately identified medical events. So, clearly that's something we'd like to change, and intend to change.

The basis for the current recommendations, again, the staff developed and Commission endorsed recommendations are as follows. The ACMUI Revised Final Report, which as you may recall was transmitted to us, the NRC staff this February. Stakeholder input from workshops and public meetings as has been alluded to, the public workshops you may recall were held during the summer of 2011 in New York and in Houston. And, of course, all ACMUI meetings involving this subject were open to public participation.

Concerning ASTRO's recommendations and the Organization of Agreement State recommendations, these were received both during the workshops last summer and afterwards via letter.

The status of these recommendations. The history, we, staff, sent to the Commission a paper with our recommendations on these regulatory changes. It was

received by the Commission last April, and in August, this past month, we received the requirements from the Commission based on those recommendations.

I can tell you that the Commission accepted the staff's recommendations in their entirety without modification. These recommendations, which I will describe in the following few slides, are being worked into regulatory language, and as Ms. Bhalla told you, will be published next year for public comment as part of the proposed rule for Part 35 modifications.

And here are the recommendations on this slide and the next several slides. First was to define separate ME criteria for permanent implant brachytherapy utilizing radioactive sources. Medical event criteria for all other and permanent implant brachytherapy, all other medical uses are primarily dose-based, accordingly separate ME criteria were recommended for the site, and will be implemented. Getting to a specific, the treatment site medical event will be declared and reported, hopefully, if 20 percent or more of the implanted sources are outside the intended implant location.

Now, clearly source strength and positioning is the measurable metric or the surrogate for dose as related to harm or potential harm. And the 20 percent variance limit from physician and clinician,

that was approved by the Commission on the recommendations of the ACMUI for all medical uses of byproduct materials.

This approval came back in 2005, to be specific.

When we get into normal tissues, we can speak about those in neighboring structures to the treatment site itself. A medical event would be declared and reported hopefully if dose to contiguous five ccs exceeds 150 percent of the absorbed dose prescribed for the treatment site. Now, 50 percent excess dose to a normal tissue is already a medical event criterion in the current rule, so we're not making a change there. But I'd like to note that we will be seeking when the proposed rule is published further input, further stakeholder input on the size of the normal tissue contiguous volume being highly irradiated that would trigger a medical event. There are some differences of opinion as to how large this volume should be.

And, finally, I should also mention with respect to these criteria this particular criterion, that these absorbed dose determinations are to be made within 60 days of the implant unless a longer time is justified in writing.

Because of this criterion, there is an implicit operational requirement for post implant

imaging as strongly recommended during the public workshops, and as practiced in most clinical facilities.

For normal tissue structures within the treatment site, an ME will have occurred if dose to contiguous greater than 5 ccs exceeds 150 percent on the expected absorbed dose of tissue. Now, again, absorbed dose determinations are to be made in writing within 60 days of the implant, and staff will again for this tissue volume, as well, be seeking further stakeholder input during the publication of the proposed rule.

Other ME conditions, using the wrong nuclide, using the wrong source strength, plus or minus 20 percent from that which is specified in the Written Directive. The completion of the Written Directive calls for the authorized user to enter in the total source strength and the number of sources involved that were implanted. 20 percent is used for the Medical Event threshold for source strength variance because 10 percent is considered too close to the actual variance associated with this quantity and clinically acceptable implant procedures. Again, this reflects input that we have received from the ACMUI.

And I think, finally, with respect to Medical Event reporting this ME will have occurred and reported if treatment is administered with implantation

directly into the wrong site or body part, with delivery using the wrong modality, or, of course, using leaking sources.

The first item listed, implantation directly into the wrong site or body part, applies to other distant from the treatment site locations, not to the neighboring structures which have their own dose-based limit.

All of these proposed Medical Event criteria reflect circumstances which there is actual or potential harm to patients being treated. Now, this characteristic is consistent with ACMUI's recommendations and input that was received, and continues to be received from stakeholders.

For the corresponding changes to the Written Directive requirements, there are only a few modifications there currently. Again, defining separate criteria for permanent implant brachytherapy, deleting total dose as an option for completion of the Written Directive. That will no longer appear. What will be called for is the total source strength and number of sources that were implanted. So, what will be required is, again, total source strength and exposure time as the required entry field along with the other and current entry fields of radionuclide, treatment site, and the

number of sources.

And, finally, replacing the wording "before completion of the procedure," has a lot of ambiguity to it, with "before the patient is released from the AU's control and leaves the post procedure recovery area." And, again, this wording reflects the ACMUI's position.

NRC Staff's position on these current recommendations. We clearly are supporting them because we believe the patient's interests will be protected and the physicians, the authorized users, would be able to take medically necessary actions. And, additionally, NRC would be able to continue detecting failures in process, procedures, and training, plus misapplications by authorized users. And, finally, we definitely hope that we have adequately conveyed in these recommendations various pieces of stakeholder input that we have received as best we possibly can to reach a balance.

This concludes my presentation. If you have any questions, I'll be more than happy to try to address them.

CHAIRMAN MALMUD: Thank you, Dr. Zelac. Are there questions? Yes.

MEMBER BAILEY: Darice Bailey. For the compatibility level?

DR. ZELAC: We do not at the moment have a

compatibility level. That will be an additional issue upon which we will be requesting input from stakeholders during publication of the proposed rule, if not before. There are different camps on this, clearly, with the Agreement States preferring strongly that the compatibility level remain as it is now. And the reason for that, I guess I can state, is that the Agreement States would prefer to be able to keep a criterion for the treatment site that is dose-related, in addition to the source strength, which we are introducing now, and which would be the only specific criterion for the treatment site with outputs any longer.

Of course, there are other stakeholders who have facilities, for example, in multiple states, or practice in multiple states that would clearly like to have this be one category higher in terms of compatibility such that the Agreement States would not be in a position to be able to retain that characteristic of a criterion which is both based on the treatment site.

CHAIRMAN MALMUD: Thank you. Dr. Van Decker.

MEMBER VAN DECKER: So, a personal horse in the race, allow me to ask Ms. Bailey. I assume that means you believe that there's a large portion of the Agreement States that want this to be a Compatibility C or something along that line? And then in your mind set how many states

do you think would be keeping old criteria, and how much of the nation would be split? I mean, because the whole concept of going to --

MEMBER BAILEY: In general, the Agreement States would like everything to be a C, but there --

MEMBER VAN DECKER: So, she said that and I did not.

MEMBER BAILEY: I know of a few, one in particular Agreement State that would stick with dose very clearly. I don't know the majority, but I don't know that --

CHAIRMAN MALMUD: Thank you. Dr. Guiberteau.

MEMBER GUIBERTEAU: Dr. Zelac, when you said that there are some states that would like to keep the dose-based criteria in addition to the source-based criteria, does that mean they would have two sets of criteria, they could pick and choose between the two, or would they adopt one or the other?

DR. ZELAC: What I have heard expressed verbally is, and I may have it actually in writing, as well. I don't recall. The Agreement States do not seem to have a problem with the introduction of the criterion which is source strength-based. Now, how much -- what fraction of the activity was implanted was within the treatment site, what fraction was without, exceed 20

percent that's outside of the treatment site, and you have a medical event. Now, that's the basic that we are talking about. The Agreement States, apparently, don't have a problem with introducing, but in addition wish to retain the criterion as an additional criterion, not an "and," but an "or," I suspect with -- dealing with dose. So, again, 20 percent out from the intended dose would be a medical event.

MEMBER GUIBERTEAU: Could this not be confusing?

DR. ZELAC: Extremely so. Except for the Agreement State Regulatory Agencies, we have heard from no one that would be in favor of any way, shape, or form of maintaining, keeping a criterion which is dose-based for the treatment site.

MEMBER GUIBERTEAU: Thank you.

CHAIRMAN MALMUD: Other questions? There being none, thank you, Dr. Zelac. That's a summary of how many years of discussion in this room?

(Laughter.)

CHAIRMAN MALMUD: The next item on the agenda is that to be presented to us by Sophie Holiday, that's the ACMUI's reporting structure.

MS. HOLIDAY: Good afternoon. I have the pleasure of giving you the last presentation of the day,

and then we'll be good to go when Dr. Malmud gives us the adjournment.

So, today I will speak to you about the ACMUI reporting structure. Okay. I will discuss the current reporting structure as it is, go over our annual review, discuss a Staff Requirement Memorandum, highlight some points from the September 22nd, 2011 ACMUI meeting, and asks for discussion.

So, our current reporting structure for the ACMUI is as follows. ACMUI essentially reports to the Director of Materials Safety and State Agreements Division in the Office of FSME, so in this case it would be to Mr. McDermott. If you will notice here, RMSB is the Radioactive Materials Safety Branch, which is the branch that actually myself, Dr. Daibes, Dr. Zelac, Michael Fuller, we all are in that particular branch, and we report to Mr. Einberg. So, everyone in Mr. Einberg's branch and the ACMUI, we all fall under the jurisdiction, if you may, of Mr. McDermott.

Then Mr. McDermott falls under the direction of the Director of the Office of Federal and State Materials and Environmental Management Programs. As a program office we fall under the EDO's guidance, and then they then report to the Commission. So, as you can see the hierarchy we're under the Director of MSSA.

So, this brings us to our current reporting structure. As I stated in the previous slide, ACMUI reports to the Division Director of MSSA. On July 21st of 2010, NRC Staff received a SRM, a Staff Requirements Memorandum, to work on a Commission paper that outlined possible improved mechanisms for providing the Commission with ACMUI's feedback regarding medical issues, including the pros and cons of restructuring the Committee such that it would report to -- so, from that SRM we then had a teleconference with the Committee on January 5th of 2011 to discuss the pros and cons of restructuring the ACMUI if they wanted to continue to report to the Director MSSA, or if they wanted to report directly to the Commission.

It was during this 2011 teleconference that ACMUI made the recommendation to maintain their current reporting structure with the possibility of increased staff support so that current reporting structure again is to report to the Director of MSSA.

So, during the teleconference held a week later as the Committee asked for a separate teleconference so they would have time to review that pros and cons paper that Ms. Cockerham created to provide to the Commission on the ACMUI reporting structure, it was then made a recommendation from Dr. Welsh that the

Committee would have an annual review of this reporting structure which was due today.

So, in the SECY paper that we wrote, we got an SRM that directed staff to provide feedback on the pros and cons for restructuring the Committee to report to the Commission. And this SECY paper included both ACMUI recommendations, as well as NRC staff recommendations. And this paper proposed maintain the reporting structure or reporting through the ACRS, the Advisory Committee on Reactor Safeguards.

So, then after we submitted our SECY paper that highlighted the pros and cons of our restructuring, the Commission then gave back an SRM that approved ACMUI's and the staff's recommendations to keep the current reporting structure, and the Commission also acknowledged the ACMUI's intent to review your reporting structure annually. And they directed a consideration of increasing the resources for fiscal year 2013 which begins, of course, this October to the budget proposal, and they directed us to consult with the ACRS.

So, then in the September 2011 meeting that we had last year, I gave a presentation to the Committee that outlined the differences between ACMUI and ACRS. Essentially, the largest difference is that ACRS reports directly to the Commission; whereas, you saw our

hierarchy in which we have to report. ACMUI, of course, approved the current reporting structure but there was a request for additional staffing resources. At the previous meeting in April, there was a follow-up question from Dr. Malmud where he asked if we had considered getting additional staffing resources. At the time, we did not have an answer, but due to the current economical status across all agencies in the nation, there's just simply not the resources available, so we currently cannot increase our staff resources for the ACMUI. So, we pretty much have Ashley and myself helping you and hope that's sufficient.

MR. EINBERG: I would add that we did request additional resources, but it was denied.

CHAIRMAN MALMUD: Thank you.

MS. HOLIDAY: For those reasons. So, I would like to have a discussion. My proposal is to the Committee, that we would hold our annual reporting structure discussion every other year versus the original intention of having it every year. This two-year gap, essentially, gives us a better overview of how the Committee is being handled versus a year, because while there are Subcommittees and discussions that are held throughout the year, there's not really too much change that can happen, so it's easier to measure the

differences, if there should be any, within a two-year gap. So, I ask if the Committee is satisfied with your current reporting structure. Thank you.

CHAIRMAN MALMUD: Thank you. So, you are asking us if we are satisfied with the current reporting structure?

MS. HOLIDAY: Yes.

CHAIRMAN MALMUD: The Committee already has expressed its desire for additional staffing to existing personnel, and that has been denied by the Commissioners on the basis of the budgetary constraints.

MS. HOLIDAY: Yes.

CHAIRMAN MALMUD: The alternative to the current reporting lines doesn't exist, so you're asking us if we're happy. My feeling is, I'm the old person here in terms of number of years here, that the reasons that stimulated all this really don't exist any longer --

MS. HOLIDAY: Yes.

CHAIRMAN MALMUD: -- in the sense that there is a better feedback mechanism to us from the Commissioners when decisions are made which do not agree with our recommendations. I mean, that was one major irritant in the past.

Number two, we've had wonderful staff to work with. And I feel that things are being delayed

unnecessarily. We've begun to learn why they've been delayed, but we don't believe it's unnecessary. Your question is about one or two-year reports. I would still prefer the one-year with the option of just saying we don't need it this year, rather than saying it's two years and not having an opportunity to do it on an annual basis in case things change in a way which is not satisfying to the Committee.

So, I think the Committee, from the feedback that I've been getting, is pleased with the way things are going, but things could change, and we'd still like to have the opportunity to address the issues on an annual basis rather than every other year. Does that summarize the feelings of the Committee?

(Chorus of yeses.)

MR. EINBERG: Dr. Malmud, Chris Einberg here. The one thought I had, and we can have some discussion with Ashley on this, is that every other year there's a biennial survey done on how the Committee has worked and the satisfaction of the Committee. My personal thought would be that we could perhaps add a question to that biennial survey and ask, you know, whether the Committee is still happy with the existing reporting structure. And then every other year have a presentation from either Sophie or Ashley. But Ashley indicated to me

that perhaps that would not be the best format.

MS. COCKERHAM: This is Ashley. It's not that it's a bad format, it's just the questions that are developed right now are approved by the Commission, so if we make any revisions to that biennial evaluation that you get every other spring, staff would need to go to the Commission and propose those changes and get them approved back from the Commission, which is something we need to do internally.

MR. EINBERG: I see.

MS. COCKERHAM: But it doesn't mean that it can't be revised.

MR. EINBERG: Thank you, Ashley.

CHAIRMAN MALMUD: My recommendation would be annual with the option of not having it. It is not currently, but having a long history here, that was missing previously, the feeling that the opportunities were available was missing. And I think if we take away the opportunity, even though we don't exercise it, it will be a movement in the wrong direction. Dr. Welsh.

MEMBER WELSH: Jim Welsh. And I would add to that that perhaps we don't need a formal presentation on an annual basis. We could just have perhaps a survey ahead of time saying do we or do we not need to bring this up this year. If we are all happy with the status quo, raise

the question again next year, and my prediction is that we might not have presentations for many years to come.

CHAIRMAN MALMUD: That's certainly true. Is there another opinion, other comment? So, the feedback to you is we understand the situation. We're pleased with it. I also think that some of the members of the Committee really were opposed to going the same route as the other committee which reports directly, because the time -- the demand on time is very great. And that would be very difficult particularly for the clinicians who have to leave a practice in order to be here. And the clinicians include both the physicists and the physicians, I assume the pharmacists, as well, because we're busily engaged in other activities. So, we enjoy being here, but at the same time if the need doesn't exist, everyone is better served if we don't make meetings more frequent than necessary.

We do feel, though, that we've had superb staff historically, and certainly now. And there may be times when they need more support, and we hope that that will be coming through the existing staff. They've just reassigned you temporarily, should the need arise. At the moment it hasn't, but I understand the NRC is more concerned with other things at the moment given what's happening elsewhere in the world, as well as here. So,

I think that's the opinion, but there's one more comment.

MEMBER WEIL: One comment. Would it make it easier for you if we had a formal process to waive the discussion that came to you in a timely way so that you wouldn't have to do work on a presentation that doesn't need to happen?

MS. COCKERHAM: This is Ashley. Just thinking off the top of my head here, one suggestion might be we always ask you for input on the agenda when we solicit for agenda topics. So, at that time we could solicit for input on whether or not that particular topic needed to be on the agenda. If there is any feedback to give it that time, we would have that documented in writing from you.

CHAIRMAN MALMUD: Thank you. Mr. Mattmuller.

MEMBER MATTMULLER: Yes. Steve Mattmuller. As part of this, we at one point requested maybe a little bit greater visibility, and at the time there was an organizational chart for FSME. And since looking at the current website, I see a response to just do away with the FSME organizational chart rather than trying to fit us into it.

(Laughter.)

MS. HOLIDAY: Actually, we actually have someone who is on rotation to our branch right now. The

gentleman's name is Jeff. He's sitting right next to Ashley. He will actually be handling your request.

MS. COCKERHAM: I would also add to that, there was a request from Dr. Langhorst to add historical documents or some sort of history to the ACMUI web page. He's working on that, as well. I had actually given just an informal presentation yesterday to a different group of individuals that covered that particular topic, so I'm planning to present that to the Committee in April, and then we'll somehow use that information to feed into the website.

The other request that Dr. Langhorst had was to include historical membership. And we have -- Jeff is going to be working on that, as well, and adding it to the website.

CHAIRMAN MALMUD: Thank you. Mr. McDermott.

MR. McDERMOTT: I'd just like to offer that I fully respect the opinions and the decision of the Committee to continue to have the annual briefings. It's always good to have the opportunity to get feedback from all of you. I would just offer that it doesn't have to be only at that point, so if at any point there is a problem perceived by the Committee working through the Chair, I'd certainly be happy to get that feedback from all of you and do everything we could do to address it

without having to wait until some semi-annual or annual meeting to get to the topic.

CHAIRMAN MALMUD: I've always been able to get through. Telephone works, too. Does that complete your report, Sophie?

MS. HOLIDAY: Yes, sir.

CHAIRMAN MALMUD: In that case, I will call for a recess until tomorrow morning. And tomorrow morning's session begins at 8:00 with discussion of abnormal occurrence criteria by Angela McIntosh. And then there'll be a break, and if the agenda stays in tact we will be out of here by 12:30 tomorrow for those of you who have travel plans so you can plan on being out of here certainly by 12:30.

Thank you. See you all tomorrow.

(Whereupon, the proceedings went off the record at 5:09 p.m.)