

Official Transcript of Proceedings
NUCLEAR REGULATORY COMMISSION

Title: Advisory Committee on the Medical Uses
 of Isotopes: Open Session

Docket Number: (n/a)

Location: Rockville, Maryland

Date: Thursday, September 20, 2012

Work Order No.: NRC-1867

Pages 1-152

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1 UNITED STATES OF AMERICA

2 NUCLEAR REGULATORY COMMISSION

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4 ADVISORY COMMITTEE ON THE MEDICAL USES OF ISOTOPES

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6 OPEN SESSION MEETING

7 + + + + +

8 THURSDAY,

9 SEPTEMBER 20, 2012

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11
12 The Open Session portion of the meeting was
13 convened in Room T-2B3 of Two White Flint North, 11545
14 Rockville Pike, Rockville, Maryland, at 8:30 a.m., Leon
15 S. Malmud, M.D., ACMUI Chairman, presiding.

16 MEMBERS PRESENT:

17 LEON MALMUD, M.D., Chairman

18 BRUCE THOMADSEN, Ph.D., Vice Chairman

19 DARICE BAILEY, Agreement State Representative

20 MILTON GUIBERTEAU, M.D., Diagnostic Radiologist

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

22 STEVE MATTMULLER, Nuclear Pharmacist

23 CHRISTOPHER PALESTRO, M.D., Nuclear Medicine
24 Physician

25 JOHN SUH, M.D., Radiation Oncologist

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1 ORHAN SULEIMAN, Ph.D., FDA Representative

2 WILLIAM VAN DECKER, M.D., Nuclear Cardiologist

3 LAURA M. WEIL, Patients' Rights Advocate

4 JAMES WELSH, M.D., Radiation Oncologist

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

6
7 NRC HEADQUARTERS STAFF PRESENT:

8 BRIAN McDERMOTT, Director, Division of
9 Materials Safety and State Agreements

10 PAMELA HENDERSON, Deputy Director,
11 Division of Materials Safety and State
12 Agreements

13 CHRISTIAN EINBERG, Chief, Radioactive Materials
14 Safety Branch

15 MICHAEL FULLER, Alternate Designated Federal
16 Official, Team Leader, Medical Radiation
17 Safety Team

18 ASHLEY COCKERHAM, Alternate Designated Federal
19 Official, ACMUI Coordinator

20 SOPHIE HOLIDAY, Alternate ACMUI Coordinator

21 NEELAM BHALLA, FSME/DILR/RB-B

22 SUSAN CHIKADEL, OGC/GCLR/RMR

23 JACKIE COOK (via webcast), RIV/DNMS/NMSB-B

24 SAID DAIBES, Ph.D., FSME/DMSSA/LISD/RMSB

25 SARA FORSTER, RIII/DNMS/MLB

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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:

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JEFFREY BOVA, Bayer
UWE BUDDE, Bayer
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4 Molecular Imaging

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6 DENNIS PHILLIPS, U.S. Department of Energy

7 JOE RODGERS, Theragenics

8 GLORIA ROMANELLI, American College of Radiology

9 RUTH SCHUKMAN-DAKOTAS, University of Kansas
10 Hospital

11 MICHAEL SHEETZ, University of Pittsburgh

12 JEFFRY A. SIEGEL, Nuclear Physics Enterprises

13 CINDY TOMLINSON, American Society for Radiation
14 Oncology

15 MONA WAHBA, Bayer

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

18 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

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

3 The function of the Committee is to advise
4 the staff on issues and questions that arise on the
5 medical use of byproduct material. The Committee
6 provides counsel to the staff, but does not determine or
7 direct the actual decisions of the staff or the
8 Commission.

9 The NRC solicits the views of the Committee
10 and values their opinions. I request that, whenever
11 possible, we try to reach a consensus on the issues that
12 we will discuss today. But I also recognize that there
13 may be minority dissenting opinions. If you have such
14 opinions, please allow them to be read into the record.

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

18 CHAIRMAN MALMUD: Here.

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

21 VICE CHAIRMAN THOMADSEN: Here.

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

24 MEMBER BAILEY: Here.

25 MR. EINBERG: Dr. Mickey Guiberteau,

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1 diagnostic radiologist.

2 MEMBER GUIBERTEAU: Present.

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

5 MEMBER LANGHORST: Here.

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

8 MEMBER MATTMULLER: Present.

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

11 MEMBER PALESTRO: Present.

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

14 MEMBER SUH: Here.

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

17 MEMBER SULEIMAN: Here.

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

20 MEMBER VAN DECKER: Present.

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

23 MEMBER WELSH: Here.

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

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1 MEMBER WELSH: Present.

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

4 MEMBER ZANZONICO: Here.

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

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

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

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

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

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

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

22 DR. DAIBES: Said Daibes with the medical
23 team.

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

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

3 (No response.)

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

6 MS. COCKERHAM: They should be able to
7 respond.

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

11 Okay. And I would also like to add that this
12 meeting is being webcast, so other individuals may be
13 watching online. We have a bridge line available, and
14 that phone number is 888-864-0940. Once again,
15 888-864-0940. The pass code is 71341 pound. 71341 pound.

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

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

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

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

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

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

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

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

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

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

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

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

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

23 MR. EINBERG: In the next few months.

24 MR. McDERMOTT: -- in the next few months.

25 So the rulemaking process, when we talk about the Part 35

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

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

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

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

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

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

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

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

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

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

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

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

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

23 CHAIRMAN MALMUD: Thank you, Mr. McDermott.

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

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

4 CHAIRMAN MALMUD: Please do.

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

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

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

11 (No response.)

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

14 (No response.)

15 Okay. Thank you, Dr. Malmud.

16 CHAIRMAN MALMUD: Thank you.

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

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

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

9 If you go to 2009, there are no changes
10 there, and those items are also pending rulemaking. And
11 for 2010, every single item on this list is closed from
12 2010. So this chart will go away.

13 2011, Item Number 6 says ACMUI created an
14 action item to reevaluate its satisfaction with the
15 reporting structure annually. So this is something that
16 was talked about in January of 2011. So this is the first
17 time in 2012 that we are going to visit this, and it's
18 an agenda item that Sophie will be talking to you about
19 later today.

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

25 Item Number 23, Dr. Malmud added several

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

7 And on the third page for 2011, this also
8 deals with the abnormal occurrence criteria. So we can
9 see that ACMUI has made recommendations in 2008, also in
10 2011, and then we expect there may be more to come
11 tomorrow morning.

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

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

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

24 Any questions about any old
25 recommendations?

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

3 (No response.)

4 There being none, thank you for the report.

5 MS. COCKERHAM: Thank you, Dr. Malmud.

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

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

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

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

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

20 MS. COCKERHAM: He is here right now.

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

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

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1 CHAIRMAN MALMUD: Yes. We will reconvene at
2 1:00. And the 1:00 item on the agenda is the use of dose
3 calibrators in medicine, and Dr. Suleiman will present
4 that.

5 Thank you.

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

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

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

13 (Laughter.)

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

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

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

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1 fact, pretty much on.

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

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

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

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

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

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

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

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

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

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

11 Now, in contrast of that when you talk about
12 calculating radiation dose from unsealed sources or from
13 drugs, essentially, it's much more challenging. Not only
14 do you need to know the amount of administered activity,
15 again, as I said earlier you need to know the
16 biodistribution, and you need to know patient
17 dimensions. So, calculating radiation dose doesn't have
18 20 percent precision or accuracy by anybody's stretch of
19 the imagination.

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

25 Well, in imaging it's becoming much more

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

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

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

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

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

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

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1 yttrium-90.

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

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

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

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

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

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

25 And the other regulation is in terms of

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

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

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

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1 the radiation is used.

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

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

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

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

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

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

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

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

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

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

25 So, one question I think that may come up

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

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

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

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

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

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

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1 administration? That's it. Thank you.

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

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

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

25 I think the radiolabeled therapeutics are,

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

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

18 CHAIRMAN MALMUD: Dr. Welsh.

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

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

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

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

16 CHAIRMAN MALMUD: Next question.

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

19 CHAIRMAN MALMUD: Yes, please.

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

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

8 CHAIRMAN MALMUD: Dr. Thomadsen.

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

15 CHAIRMAN MALMUD: Dr. Guiberteau.

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

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

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

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

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1 not here.

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

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

6 MEMBER SULEIMAN: Well, the reg --

7 CHAIRMAN MALMUD: They differ.

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

10 MEMBER GUIBERTEAU: I'm talking about for
11 unsealed.

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

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

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

19 VICE CHAIRMAN THOMADSEN: I have no idea.

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

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

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

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

11 MEMBER SULEIMAN: That's one of the
12 questions.

13 CHAIRMAN MALMUD: May I offer an opinion?

14 MEMBER SULEIMAN: Yes, yes.

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

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

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

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

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

16 MEMBER BAILEY: Yes, sir.

17 CHAIRMAN MALMUD: They rely totally upon the
18 radiopharmacy?

19 MEMBER BAILEY: Yes, sir.

20 CHAIRMAN MALMUD: Very interesting.

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

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

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

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

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

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

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

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

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

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

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

24 CHAIRMAN MALMUD: Dr. Langhorst.

25 MEMBER LANGHORST: Thank you. One thing I

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

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

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

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

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

25 MEMBER LANGHORST: Okay.

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

4 MEMBER LANGHORST: Right.

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

7 MEMBER LANGHORST: Certainly.

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

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

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

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

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

8 MEMBER VAN DECKER: I don't disagree with
9 what people have said. I mean, obviously, it needs to be
10 measured at some point. It's all -- when it's unit-based,
11 obviously, it's been measured at a radiopharmacy. And if
12 you're talking about plus or minus 10 percent on a 9 or
13 10 millicurie dose, you're talking about under a
14 millicurie of change. So, it's not usually a huge amount
15 that's going to make a major difference.

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

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1 CHAIRMAN MALMUD: Please.

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

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

22 CHAIRMAN MALMUD: Mr. Einberg.

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

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1 radionuclides?

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

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

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

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

25 And for certain radionuclides I would agree

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

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

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1 know.

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

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

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

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

6 MEMBER SULEIMAN: No.

7 CHAIRMAN MALMUD: Obviously not.

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

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

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

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1 they cost?

2 MEMBER SULEIMAN: A couple of thousand
3 dollars.

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

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

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

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

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

13 CHAIRMAN MALMUD: Dr. Langhorst.

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

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

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

25 CHAIRMAN MALMUD: What about the private

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1 office?

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

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

12 MEMBER LANGHORST: As far as --

13 CHAIRMAN MALMUD: Or there's very little
14 issues.

15 MEMBER LANGHORST: -- NRC regulatory
16 oversight goes.

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

19 MEMBER WEIL: You can probably say it better.

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

24 CHAIRMAN MALMUD: Thank you.

25 MEMBER WEIL: And my concern regarding the

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

10 MEMBER LANGHORST: Can I respond?

11 CHAIRMAN MALMUD: Please do, doctor.

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

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

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

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

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

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

14 CHAIRMAN MALMUD: Dr. Langhorst.

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

20 MEMBER BAILEY: Right.

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

22 (Simultaneous speech.)

23 CHAIRMAN MALMUD: Other comments? Dr. Suh.

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

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

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

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

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

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

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

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

6 CHAIRMAN MALMUD: Other questions? Dr.
7 Zanzonico.

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

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

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

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

18 DR. ZANZONICO: I think Ashley is going
19 first.

20 CHAIRMAN MALMUD: Ashley will be going
21 first.

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

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

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

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

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

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

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

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

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

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

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

8 So, in our current regulations direct
9 measurement is not required before and after
10 administration. And the appropriate regulation is 10 CFR
11 35.63. And in 35.63 direct measurement is one of three
12 options, so the other two options are a combination of
13 measurement of radioactivity and mathematical
14 calculations, so that's going to be the situation I'm
15 assuming where the radiopharmacy does the measurement,
16 you do math, you get your number, this is what you say
17 you administered.

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

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

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

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

9 So, the next option is for the Committee to
10 change their report to recommend licensing under 10 CFR
11 35.1000. Then you can say we would like the assays before
12 and after.

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

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

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

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1 were. Dr. Malmud.

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

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

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

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1 data and doing research.

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

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

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1 under the 300/1000, or --

2 MS. COCKERHAM: For us, yes.

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

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

8 MS. COCKERHAM: Sue has question.

9 CHAIRMAN MALMUD: Dr. Langhorst.

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

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

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

23 MEMBER BAILEY: Or in this case the
24 manufacturer.

25 MEMBER LANGHORST: Yes. Well, in our case it

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

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

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

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

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

12 CHAIRMAN MALMUD: Dr. Zanzonico.

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

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

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

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

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

23 CHAIRMAN MALMUD: Thank you.

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

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1 chose to put it in 35.1000, that that would be a longer
2 period of time. I don't know that that would necessarily
3 be a longer period of time. It's simply a matter of
4 developing the guidance. And as soon as that guidance is
5 developed, it could contain the requirement to assay
6 before and after. That's the process for that. It's not
7 anything very complicated. Obviously, we can see it fits
8 in pretty nicely with 300 with an exception of a few
9 things, so we have a model to follow. And things in
10 35.1000, the ultimate goal is to eventually put them back
11 into the regulations, to either revise the regulations,
12 or if you I guess get enough data and decide these assays
13 are not required, the guidance is always changeable. You
14 could take it out later. Just I'm trying to get like more
15 of a process and procedure type thing from our
16 perspective of how we would handle it.

17 CHAIRMAN MALMUD: Thank you. Dr. Welsh.

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

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

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

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

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

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

9 MS. COCKERHAM: Rulemaking takes a very long
10 time.

11 CHAIRMAN MALMUD: The answer was?

12 MS. COCKERHAM: Yes.

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

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

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

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1 that's completely done separate.

2 VICE CHAIRMAN THOMADSEN: That's done.

3 MS. COCKERHAM: That's done.

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

6 MS. COCKERHAM: Rulemaking.

7 VICE CHAIRMAN THOMADSEN: -- rulemaking.

8 MS. COCKERHAM: Done by a different group.

9 VICE CHAIRMAN THOMADSEN: Correct.

10 MS. COCKERHAM: Handled separately. Yes.

11 VICE CHAIRMAN THOMADSEN: Correct.

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

19 MEMBER BAILEY: Yes.

20 CHAIRMAN MALMUD: And who at NRC would know?

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

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

25 MR. EINBERG: We can get that data.

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

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

15 I think you were first, then Dr. Thomadsen.

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

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1 up through the NRC database.

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

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

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

9 CHAIRMAN MALMUD: Thank you. Dr. Thomadsen.

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

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

22 DR. ZANZONICO: Can I just --

23 CHAIRMAN MALMUD: Dr. Zanzonico.

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

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

4 MS. COCKERHAM: Yes.

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

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

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

15 MS. COCKERHAM: Just development of
16 guidance. Which like I said, we have a template. I think
17 we have some very clear things of -- it's very close to
18 300, and then we would just add the extra things we need
19 to.

20 CHAIRMAN MALMUD: Dr. Langhorst.

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

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

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

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

15 CHAIRMAN MALMUD: Thank you. Dr. Palestro.

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

25 CHAIRMAN MALMUD: Dr. Langhorst, then Dr.

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1 Welsh.

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

6 CHAIRMAN MALMUD: Thank you. Dr. Welsh.

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

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

17 DR. ZANZONICO: Yes.

18 CHAIRMAN MALMUD: Would you like to make a
19 motion?

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

22 CHAIRMAN MALMUD: Yes.

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

25 CHAIRMAN MALMUD: Absolutely.

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1 DR. ZANZONICO: Okay.

2 CHAIRMAN MALMUD: The presentation will be
3 the motion.

4 DR. ZANZONICO: Yes.

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

7 (Laughter.)

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

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

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

25 And as was pointed out, it's much more

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

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

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

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

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

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

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

20 The issue we've been discussing is should
21 this be a recommendation or requirement? If it's a -- if
22 we recommend it as a requirement, then that moves it from
23 300 to 1000. And I think based on logic, if nothing else,
24 since it is fundamentally no different from other
25 therapeutic radiopharmaceuticals licensed under 300,

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

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

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

16 MEMBER LANGHORST: I'll second.

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

24 DR. ZANZONICO: Thank you.

25 CHAIRMAN MALMUD: Yes?

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

6 CHAIRMAN MALMUD: All therapeutics?

7 MEMBER WEIL: Yes.

8 CHAIRMAN MALMUD: Are you referring to all
9 functions --

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

11 CHAIRMAN MALMUD: Just therapeutics.

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

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

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

24 CHAIRMAN MALMUD: I see two hands.

25 MEMBER SULEIMAN: Orhan Suleiman. Quick

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

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

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

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

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

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

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

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

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

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

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

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

25 MEMBER GUIBERTEAU: I know this is a somewhat

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

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

20 CHAIRMAN MALMUD: Thank you. Dr. Palestro.

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

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

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

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

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

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

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

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

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

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

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

3 CHAIRMAN MALMUD: Dr. Zanzonico.

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

14 CHAIRMAN MALMUD: That's two of the items.

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

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

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

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

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1 Ashley.

2 MS. COCKERHAM: Thank you.

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

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

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

15 I just wanted to remind the Committee at our
16 July 9 telecon, I had brought the issue of dosage Category
17 3 versus 4. One of the members had agreed that 3 was
18 preferable. One of the members expressed concern that 3
19 and 4 were the same, but I'd like to point out that when
20 you read 390(g) it does say that a minimum three cases
21 are required in each of the four categories. So, unless
22 I'm misreading that I'd like clarification or for
23 somebody from the Subcommittee to make a comment on if
24 it should remain 3 or 4, or if they should recommend
25 further that it be (g)(3). Thank you.

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

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

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

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

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

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

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

4 CHAIRMAN MALMUD: Dr. Zanzonico.

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

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

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

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

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

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1 vote? Would that be even necessary?

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

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

11 CHAIRMAN MALMUD: Thank you. Dr. Welsh.

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

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

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

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

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

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

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

14 MEMBER ZANZONICO: My opinion, yes.

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

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

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

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

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

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

11 MS. HENDERSON: Yes.

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

14 MS. HENDERSON: Yes.

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

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

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

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

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

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

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1 the question that's asked.

2 CHAIRMAN MALMUD: Thank you. Dr. Thomadsen.

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

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

19 CHAIRMAN MALMUD: Dr. Zanzonico.

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

25 VICE CHAIRMAN THOMADSEN: It's a one.

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

3 VICE CHAIRMAN THOMADSEN: It has its own --

4 MEMBER ZANZONICO: Right, but the --

5 VICE CHAIRMAN THOMADSEN: That's a bad
6 example.

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

9 VICE CHAIRMAN THOMADSEN: There you go.

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

15 MS. BHALLA: Correct.

16 MEMBER ZANZONICO: Okay.

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

20 MEMBER ZANZONICO: Okay.

21 MS. BHALLA: It has up to a certain value.

22 Is that --

23 CHAIRMAN MALMUD: Was that the intent of the
24 Subcommittee?

25 MEMBER ZANZONICO: Yes.

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1 CHAIRMAN MALMUD: That's consonant with your
2 understanding?

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

4 CHAIRMAN MALMUD: Dr. Langhorst.

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

8 MEMBER ZANZONICO: Right. Right.

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

10 MEMBER ZANZONICO: It wouldn't be specific.

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

13 MEMBER ZANZONICO: Right.

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

16 MEMBER ZANZONICO: Yes, understood. No,
17 understood.

18 MEMBER LANGHORST: -- a new
19 radiopharmaceutical administration.

20 CHAIRMAN MALMUD: Someone have a comment?

21 MEMBER MATTMULLER: I do, but --

22 CHAIRMAN MALMUD: Please go ahead.

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

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1 radium-223 and its assay procedures by the manufacturer.

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

5 DR. SIEGEL: Absolutely. Thank you very
6 much.

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

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

19 CHAIRMAN MALMUD: Please introduce yourself
20 again.

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

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1 Volume 68, pages 1367-1370.

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

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

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

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1 50, I could do that without a calculator, is 3.5
2 megabecquerels, sorry the SI units, most people don't
3 like the SI units. But then it comes back as 3.5
4 megabecquerels.

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

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

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1 served as a secondary standard.

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

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

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

16 DR. SIEGEL: Yes.

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

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

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

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

2 CHAIRMAN MALMUD: Dr. Langhorst.

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

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

11 MEMBER LANGHORST: Okay.

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

25 CHAIRMAN MALMUD: Dr. Suleiman.

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

4 DR. SIEGEL: Right.

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

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

13 MEMBER SULEIMAN: Okay.

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

16 MEMBER SULEIMAN: Okay.

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

20 MEMBER SULEIMAN: But that was post
21 approval.

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

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

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

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

13 VICE CHAIRMAN THOMADSEN: Correct.

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

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

21 MEMBER SULEIMAN: That was my understanding.

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

24 MEMBER SULEIMAN: Thank you very much.

25 CHAIRMAN MALMUD: Thank you. Mr. Einberg.

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

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

12 (Whereupon, the proceedings went off the
13 record at 3:12:08 p.m., and went back on the record at
14 3:59:13 p.m.)

15 CHAIRMAN MALMUD: Mr. Fuller.

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

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

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

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

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

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

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

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

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

23 Now I will cover some of the current -- or
24 cover the current NRC guidance on this topic. Reg Guide
25 8.39, Release of Patients Administered Radioactive

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

4 NUREG-1556, Volume 9, in Appendix U is
5 another available guidance document, and is based
6 entirely on the information that's contained in Reg Guide
7 8.39. This document was originally published in draft in
8 1998, and finalized in 2002.

9 In March of 1998, Regulatory Issue Summary
10 2008-07 was issued to explain to NRC licensees how to
11 instruct patients for compliance with the rules. And in
12 May of 1998, just two months later, we issued Regulatory
13 Issue Summary 2008-11, precautions to protect children
14 who may come in contact with patients released after
15 therapeutic administration of Iodine-131. This was
16 issued to clarify and amplify the precautions that
17 licensees should take to protect infants and children.

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

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

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1 not encourage and does not encourage this practice.

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

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

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

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

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1 or tasks that come out of this, and those may include an
2 extensive literature review, a review of the assumptions
3 used in Reg Guide 8.39, a survey of the habits of released
4 patients, the performance of empirical measurements, the
5 assessment of internal and external radiation exposure,
6 and perhaps a reassessment of the adequacy of Reg Guide
7 8.39.

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

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

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

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

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

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1 term "habit?"

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

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

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

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

25 MR. FULLER: Actually, that might be one

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

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

21 CHAIRMAN MALMUD: Thank you. Laura.

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

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

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

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

9 MR. FULLER: Do you have it? Yes, we've got
10 some time. I went through that pretty quickly. Yes, the
11 --

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

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

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1 of the instructions.

2 MR. FULLER: Do you all have -- they're
3 looking for it now. I think I might find a better way.
4 Do you have access to the internet? Just go to the SECY
5 website and go to the SRMs, and it will be right there,
6 12-0011. And the reason I hesitated to answer your
7 question, Ms. Weil, is because I know in earlier SRMs we
8 had very, very specific instructions on this point. But
9 in the final SRM, after we sent up the SECY paper, I just
10 don't recall if there were any words that allowed for any
11 --

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

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

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

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

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

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

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

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

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

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

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

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

6 CHAIRMAN MALMUD: So, the law is just for the
7 1 percent or more.

8 MEMBER WEIL: Yes.

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

12 MEMBER WEIL: Yes.

13 CHAIRMAN MALMUD: Albanians.

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

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

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

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

5 CHAIRMAN MALMUD: It will take time.

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

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

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

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

25 And then is the other -- or another

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

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

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

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

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

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

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

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

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

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1 Decker?

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

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

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

23 (Simultaneous speech.)

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

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1 draft to the Agreement States.

2 MEMBER VAN DECKER: Okay.

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

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

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

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

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

19 MS. BHALLA: Right now we are, yes.

20 MEMBER VAN DECKER: Thank you, ma'am.

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

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1 to do this.

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

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

11 CHAIRMAN MALMUD: Thank you. Dr. Zanzonico.

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

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

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

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

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

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

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

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

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

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

25 CHAIRMAN MALMUD: Other questions? I see

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

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

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

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1 Medical Event requirements.

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

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

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

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

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

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

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

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

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

4 This approval came back in 2005, to be specific.

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

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

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

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

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

11 Other ME conditions, using the wrong
12 nuclide, using the wrong source strength, plus or minus
13 20 percent from that which is specified in the Written
14 Directive. The completion of the Written Directive calls
15 for the authorized user to enter in the total source
16 strength and the number of sources involved that were
17 implanted. 20 percent is used for the Medical Event
18 threshold for source strength variance because 10
19 percent is considered too close to the actual variance
20 associated with this quantity and clinically acceptable
21 implant procedures. Again, this reflects input that we
22 have received from the ACMUI.

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

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

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

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

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

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1 number of sources.

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

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

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

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

23 MEMBER BAILEY: Darice Bailey. For the
24 compatibility level?

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

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

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

20 CHAIRMAN MALMUD: Thank you. Dr. Van Decker.

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

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

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

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

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

12 CHAIRMAN MALMUD: Thank you. Dr. Guiberteau.

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

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

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

9 MEMBER GUIBERTEAU: Could this not be
10 confusing?

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

16 MEMBER GUIBERTEAU: Thank you.

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

20 (Laughter.)

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

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

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

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

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

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

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1 So, this brings us to our current reporting
2 structure. As I stated in the previous slide, ACMUI
3 reports to the Division Director of MSSA. On July 21st of
4 2010, NRC Staff received a SRM, a Staff Requirements
5 Memorandum, to work on a Commission paper that outlined
6 possible improved mechanisms for providing the
7 Commission with ACMUI's feedback regarding medical
8 issues, including the pros and cons of restructuring the
9 Committee such that it would report to -- so, from that
10 SRM we then had a teleconference with the Committee on
11 January 5th of 2011 to discuss the pros and cons of
12 restructuring the ACMUI if they wanted to continue to
13 report to the Director MSSA, or if they wanted to report
14 directly to the Commission.

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

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

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

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

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

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

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

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

15 CHAIRMAN MALMUD: Thank you.

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

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

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

7 MS. HOLIDAY: Yes.

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

12 MS. HOLIDAY: Yes.

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

18 MS. HOLIDAY: Yes.

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

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

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

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

15 (Chorus of yeses.)

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

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1 that perhaps that would not be the best format.

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

10 MR. EINBERG: I see.

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

13 MR. EINBERG: Thank you, Ashley.

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

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

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

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

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

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

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

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

15 CHAIRMAN MALMUD: Thank you. Mr. Mattmuller.

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

23 (Laughter.)

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

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

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

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

16 CHAIRMAN MALMUD: Thank you. Mr. McDermott.

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

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

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

6 MS. HOLIDAY: Yes, sir.

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

15 Thank you. See you all tomorrow.

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

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