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UNITED STATES OF AMERICA
NUCLEAR REGULATORY COMMISSION

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ADVISORY COMMITTEE ON THE MEDICAL USES OF ISOTOPES

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MEETING

+ + + + +

OPEN SESSION

+ + + + +

TUESDAY,

APRIL 17, 2012

The meeting was convened in room T2-B3 of
Two White Flint North, 11545 Rockville Pike,
Rockville, Maryland, at 8:00 a.m., Bruce Thomadsen,
Ph.D., ACMUI Vice Chairman, presiding.

MEMBERS PRESENT:

BRUCE THOMADSEN, Ph.D., Acting Chair

DARICE BAILEY, Agreement State Representative

MILTON GUIBERTEAU, M.D., Diagnostic Radiologist

SUE LANGHORST, Ph.D., Radiation Safety Officer

STEVE MATTMULLER, Nuclear Pharmacist

CHRISTOPHER PALESTRO, M.D., Nuclear Medicine
Physician

JOHN SUH, M.D., Radiation Oncologist

ORHAN SULEIMAN, Ph.D., FDA Representative

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MEMBERS PRESENT (Continued):

WILLIAM VAN DECKER, M.D., Nuclear Cardiologist

LAURA M. WEIL, Patients' Rights Advocate

JAMES WELSH, M.D., Radiation Oncologist

PAT ZANZONICO, Ph.D., Nuclear Medicine Physicist

NRC STAFF PRESENT:

PAMELA HENDERSON, Acting Deputy Director,
Division of Materials Safety and State Agreements

CHRIS EINBERG, Designated Federal Officer

ASHLEY COCKERHAM, Alternate Designated Federal
Officer

MICHAEL FULLER, Alternate Designated Federal
Officer

SOPHIE HOLIDAY, Alternate ACMUI Coordinator

NEELAM BHALLA, FSME/DILR/RB-B

TAMMY BLOOMER (via webcast), RIII/DNMS/MIB

ANNE BOLAND (via webcast), RIII, DNMS

SUSAN CHIDAKEL, OGC/GCLR/RMR

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

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

SANDRA GABRIEL, Ph.D., RI/DNMS/MB

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

DONNA-BETH HOWE, Ph.D, FSME/DMSSA/LISD/RMSB

AARON McCRAW (via webcast), RIII/DNMS/MIB

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NRC STAFF PRESENT (Continued):

PATRICIA PELKE (via webcast), RIII/DNMS/MLB
GRETCHEN RIVERA-CAPELLA, FSME/DMSSA/LISD/RMSB
SHIRLEY XU, FSME/DMSSA/LB

MEMBERS OF THE PUBLIC PRESENT:

SCOTT BERTETTI, Bayer HealthCare Pharm.
COLIN BIGGIN, Ph.D., (via webcast), Algeta ASA
JEFF BOVA, Bayer HealthCare Pharm.
DARRELL BROWN (via webcast), Fox Chase Cancer
Center
KEITH BROWN, Ph.D. (via webcast), University of
Pennsylvania
ROBERT DANSEREAU (via webcast), New York State
Dept. of Health
WILLIAM DAVIDSON (via webcast), University of
Pennsylvania
MOHAN DOSS (via webcast), Fox Chase Cancer Center
BRYAN EDWARDS (via webcast), Fox Chase Cancer
Center
LYNNE FAIROBENT, American Association of
Physicists in Medicine
MARIA GARRIGAN, Bayer HealthCare Pharm.
JUERGEN GAY, Ph.D., Bayer HealthCare Pharm.
JOSEPH GERMINO, M.D., Bayer HealthCare Pharm.

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1 SHAEMUS GLEASON (via webcast), Cardinal Health

2 TRACI HOLLINGSHEAD (via webcast), Avera McKennan

3 DEEPIKA JALOTA, Bayer HealthCare Pharm.

4 GARY LUNGER (via webcast), *Unknown Affiliation*

5 RALPH LIETO (via webcast), St. Joseph Mercy
6 Hospital

7 PETER LUHRS, Bayer HealthCare Pharm.

8 ANDREW MCKINLEY, American Society of Nuclear
9 Cardiology

10 JANETTE MERRILL, Society of Nuclear Medicine

11 ERIK MERTEN, Ph.D., Bayer Healthcare Pharm.

12 MARY E. MOORE (via webcast), Philadelphia VA
13 Medical Ctr.

14 DONNA MOSLEY (via webcast), Fox Chase Cancer
15 Center

16 MICHAEL PETERS, American College of Radiology

17 SOBHA PHILLIPS (via webcast), Fox Chase Cancer
18 Center

19 WILLIE REGITS (via webcast), Cardinal Health

20 JOE RODGERS, Theragenics

21 GLORIA ROMANELLI, American College of Radiology

22 GERHARD SCHULETER, Bayer HealthCare Pharm.

23 KAREN SHEEHAN (via webcast), Fox Chase Cancer
24 Center

25 JEFF SIEGEL, Ph.D., Nuclear Physics Enterprises

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1 MICHAEL N. STEPHENS (via webcast), Florida Dept.
2 of Health

3 ROSE TALARICO, Bayer HealthCare Pharm.

4 JOHN TALIAN, Ph.D., Bayer HealthCare Pharm.

5 CINDY TOMLINSON, American Society for Radiation
6 Oncology

7 CHRISTOPHER VASCOE, Bayer HealthCare Pharm.

8 DIMITRIS VOLIOTIS, M.D., Bayer Healthcare Pharm.

9 MONA WAHBA, Bayer HealthCare Pharm.

10 EVAN WESTERN (via webcast), Cardinal Health

11 GARY E. WILLIAMS, VA NHPP
12

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A-G-E-N-D-A

Medical Use of Radium-223 Chloride

Bayer Pharmaceuticals 7

P. Zanzonico, ACMUI 57

Strontium/Rubidium Update - FDA Perspective . . . 89

O. Suleiman, ACMUI

Strontium/Rubidium Update - NRC Perspective . . 126

D.B. Howe, NRC

Administrative Closing 158

Statement of The American Society for 164

Radiation Oncology (ASTRO)

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

8:01 a.m.

ACTING CHAIR THOMADSEN: I would like to call the meeting to order for our second day. We will be beginning with a presentation from Bayer Pharmaceuticals. I will turn this right over to whoever it is who will be presenting.

DR. VOLIOTIS: Thank you very much. I would like to start the meeting in thanking the NRC staff for organizing the meeting and giving us the opportunity to present the data here.

ACMUI members, Mr. Chairman, my name is Dr. Dimitris Voliotis. I am the head of the clinical development at Bayer HealthCare for Alpharadin. And I will start with the presentation here.

The content of our presentation is in three sections. Section 1 contains the purpose and introduction of the meeting as well as the clinical overview. This will be done by myself. Section 2 deals with handling and safety of radium-223 chloride, and the presentation will be done by my colleague Erik Merten. And Section 3 is talking about licensing issues and recommendations for NRC consideration and will be delivered by Jeff Siegel.

The purpose of the meeting today is to

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1 present to the advisory committee the clinical and
2 radiation safety aspects of radium-223 chloride and to
3 discuss licensing options for radium-223 chloride. The
4 preferred option for the sponsor, for Bayer, is
5 licensing under Paragraph 35.300. There is of course
6 also the option for licensing under 35.1000. We also
7 would like to obtain the advisory committee's
8 perspective regarding licensing of the compound.

9 The product name is radium-223 chloride
10 solution for injection. The interim trade name is
11 Alpharadin or Alpharadin. The chemical name is radium-
12 223 chloride. The proposed indication is for the
13 treatment of castration-resistant (hormone refractory)
14 prostate cancer for patients with bone metastases.

15 The dosage form is a sterile, isotonic
16 aqueous solution of radium-223 chloride for
17 intravenous injection. The intended dosing regimen is
18 50 kilobecquerels per kilogram body weight which
19 equals 95 microcurie for a 70 kilogram individual. The
20 drug is given at 4-week intervals for six cycles. The
21 manufacturer is the Institute for Energy Technology
22 (IFE) in Norway and for the release is responsible
23 Algeta ASA also in Norway.

24 The drug is currently under investigation
25 for the treatment of castration-resistant or hormone

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1 refractory prostate cancer in patients with bone
2 metastases. We intend to file for NDA in the second
3 quarter of this year. This will be based on the
4 results of the pivotal ALSYMPCA Phase III trial of
5 which I will present the results of the interim
6 analysis that was performed in June of 2011. We have
7 been granted fast-track designation by the FDA on
8 August 18, 2011, and we have an expanded access
9 program in place that actually has enrolled the first
10 patient in the last week.

11 The clinical overview. Radium-223 belongs
12 to the alkali earth metals. It acts as a calcium
13 mimetic. It therefore naturally targets new bone
14 growth formation in and around bone metastases.

15 Radium-223 is an investigational alpha-
16 emitting pharmaceutical with a half-life of 11.4 days.
17 It decays through a series of alpha-, beta- and gamma-
18 emitting daughters as shown in the blue box.

19 The parent compound is the one with the
20 longest half-life of 11.4 days. The decay daughters
21 have a half-life that is much shorter, ranging from
22 the maximum of 36 minutes for lead-211 to just a few
23 milliseconds. Actually, the largest amount of total
24 decay energy is delivered through alpha particles, 95
25 percent to be precise. Only 3.6 percent are emitted as

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1 beta particles, and 1.1 percent are emitted as photons
2 that can easily be measured with standard equipment.

3 As already mentioned, radium-223 acts as a
4 calcium mimetic. The target of the compound is
5 hydroxyapatite which is the basic bone matrix
6 structure for all of the entire skeleton that is shown
7 here on this histologic section. The pink areas on the
8 slide represent the hydroxyapatite and you can easily
9 see that this represents the main area of the bone
10 formation. In this case, since this is an osteoblastic
11 section the light part of the slides are the
12 osteoblastic cells or the tumor cells that are
13 tracking the hydroxyapatite.

14 This slide shows an autoradiograph from
15 injected radium-223 in an animal study. And you can
16 see on the left-hand side of the slide where there is
17 normal spongy bone that there is essentially very
18 little integration of radium-223 in a normal bone as
19 opposed to an osteoblastic bone as shown on the right-
20 hand side where there's a large area of new bone
21 formation. And radium-223 really shows here a
22 preferential uptake as represented by the black rods.

23 The clinical program consists of a number
24 of Phase I studies that are summarized here. Those
25 represent basic safety, toxicity, PK and

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1 biodistribution studies.

2 The results of these studies led to the
3 initiation of the Phase II study program which is
4 shown on this slide here. This program contains a
5 series of studies that are looking at multiple- or
6 single-dose injections. One of the trials, BC1-02 is a
7 randomized trial that already showed very early a
8 survivor benefit in patients. And the results from the
9 Phase II program ended up in the design of the
10 ALSYMPCA randomized Phase III study results that I
11 represent on the next two slides.

12 This is a schematic overview of the
13 pivotal Phase III ALSYMPCA trial. The trial enrolled
14 921 patients with symptomatic castration-resistant
15 prostate cancer and skeletal metastases in 136 centers
16 in 19 countries of which 7 centers were in the U.S.
17 The trial randomized patients in a 2:1 fashion to
18 receive best standard of care together with either
19 placebo in one arm or alfaradin in the other arm. The
20 clinical certification factors are shown here in the
21 box in the middle of the slides.

22 The results off the ALSYMPCA trial are
23 shown here. As already mentioned previously, the trial
24 was unblinded in June of 2011. This was based on a
25 pre-planned, pre-specified interim analysis. The

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1 Independent Data-monitoring Committee after looking at
2 the results concluded that the trial met the primary
3 endpoint which was to prolong median overall survival
4 and recommended to us to stop the trial, unblind the
5 population and cross over patients to radium-223
6 chloride.

7 The hazard ratio was positive with 0.695
8 and a P value of 0.0185. The median overall survival
9 for the radium-223 population was 14.0 months versus
10 11.2 months in the placebo arm. I would like to note
11 that this is based on a data cutoff of October 2010.
12 We did perform an additional analysis right before the
13 unblinding and the crossover of the patients, so we
14 have another updated analysis from July of 2011.

15 This updated analysis confirmed the
16 results with a hazard ratio of 0.695 and the median
17 overall survival increased in this updated analysis
18 from 2.8 months as shown here to 3.6 months for median
19 overall survival radium-223 versus placebo. The
20 updated analysis of course will be included in the
21 submission package.

22 In terms of side effects, the main
23 hematologic side effects are summarized on this slide.
24 What you can see is that for the adverse events
25 thrombocytopenia and anemia, essentially there's no

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1 difference between radium-223 and placebo. You would
2 have to please focus on the numbers in the brackets.
3 Because of the 221 randomization the absolute numbers
4 are higher of course in the radium-223 arm because
5 twice as many patients are randomized to receive
6 radium-223 versus placebo. So the percentages in the
7 brackets represent the numbers of interest.

8 What was slightly higher was the
9 percentage of patients with neutropenia, all grades,
10 in the radium-223 arm, but not for grade 3 and 4
11 neutropenia.

12 Those are, on this slide here are the main
13 non-hematologic adverse events summarized. And you can
14 see again that for the adverse events, nausea,
15 vomiting and constipation there was no difference
16 between radium-223 and placebo. There was a slightly
17 incidence of diarrhea, all grades, for radium-223
18 compared to placebo, but not for grade 3 and 4. And I
19 would like to point out that the incidence of adverse
20 event bone pain was actually higher in the placebo arm
21 compared to radium-223 arm, both for all grades as
22 well as the grade 3 and 4 category.

23 So to summarize, the ALSYMPCA Phase III
24 study evaluated the treatment with radium-223 in
25 patients with castration-resistant hormone refractory

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1 prostate cancer with bone metastases. Radium-223
2 showed significant prolongation of median overall
3 survival compared to placebo. Radium-223 was well
4 tolerated compared to placebo.

5 As of to date we have more than 1,000
6 patients that have been treated with radium-223
7 chloride within the entire clinical development
8 program. And during the ongoing 3-year follow-up
9 period for the ALSYMPCA Phase III trial there have
10 been no reports of secondary malignancies associated
11 with the exposure to radium-223 chloride to date.

12 And with that I would like to conclude the
13 clinical part and hand over to Dr. Merten for the
14 handling aspects.

15 MEMBER ZANZONICO: Can we raise some
16 questions at this point?

17 DR. VOLIOTIS: Yes.

18 MEMBER ZANZONICO: The indication in one of
19 the slides was for treatment of prostate-resistant --
20 of castrate-resistant prostate cancer. But is it
21 expressly for survival or for pain relief?

22 DR. VOLIOTIS: No, the endpoint of the
23 trial is overall survival.

24 MEMBER ZANZONICO: Is overall survival.

25 DR. VOLIOTIS: This was the endpoint based

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1 on which the trial was also stopped. So the indication
2 will be for prolongation of median overall survival.

3 MEMBER ZANZONICO: Was pain relief
4 evaluated, bone pain relief?

5 DR. VOLIOTIS: Pain was only captured at
6 baseline. There was no pain scores under the treatment
7 evaluation. So pain was only recorded as baseline and
8 of course as an adverse event as shown on the slide
9 previously, but not as an efficacy endpoint.

10 MEMBER ZANZONICO: Is that like a flare pain,
11 something pretty acute after the treatment?

12 DR. VOLIOTIS: Again, pain was recorded as
13 an adverse event, but we didn't have any bone scales
14 evaluated as an efficacy endpoint. The efficacy, the
15 primary efficacy endpoint was median overall survival.

16 MEMBER ZANZONICO: And in this slide you
17 say there were no secondary malignancies associated
18 with exposure to radium-223 chloride. Were there any
19 secondary malignancies that normally wouldn't be
20 considered radiogenic that were observed?

21 DR. VOLIOTIS: We have seen none so far.

22 MEMBER ZANZONICO: None at all.

23 MEMBER PALESTRO: I have a couple of
24 questions. Number one, the uptake mechanism of radium
25 is that it -- whether it accumulates in osteoblastic

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1 cells. Of course, osteoblastic processes aren't unique
2 to malignancy. They can be seen in conditions such as
3 Paget's disease and even benign non-pathologic
4 fractures. So my question regarding uptake and
5 fractures is do you have any patients in the series
6 with non-pathologic fractures in whom uptake was
7 demonstrated, and if so, was there any adverse impact
8 on healing of those fractures?

9 DR. VOLIOTIS: I can't say. I don't think
10 we have any data on non-pathologic fractures. The
11 patients were all suffering from pathologic, you know,
12 bone metastases. And the adverse events, the bone
13 fractures that we saw in the Phase III trial were all
14 related to the underlying disease. We would have to
15 look up if there's any patient with non-pathologic
16 bone fractures. We have no data that demonstrate to
17 what extent the radium-223 would be accumulated in
18 non-pathologic bone fractures.

19 MEMBER PALESTRO: And my second question is
20 when you list the adverse events, particularly the
21 hematologic adverse events, neutropenia, anemia, and
22 so forth, are those at the end of the cumulative
23 series of doses, or after each dose, or how were they
24 tabulated?

25 DR. VOLIOTIS: They are captured during the

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1 entire duration of the trial. So it may be after just
2 one cycle, or two, or the entire. The results that are
3 shown here are of course cumulative, but for the time
4 point this may be after one, two, or after six cycles.
5 But the results that are shown here are for the
6 cumulative number of patients that were captured for
7 this analysis.

8 ACTING CHAIR THOMADSEN: Dr. Suleiman?

9 MEMBER SULEIMAN: Why didn't you include
10 pain relief as an indicator to track? Historically
11 this actually reduces pain is how I understand it, so
12 why did you miss that opportunity?

13 DR. VOLIOTIS: Well, the trial was designed
14 by our partner company, Algeta, and at that time point
15 the inclusion of a pain scale was felt to be too
16 complicated and potentially not relevant enough for
17 this kind of drug. And because of the early results
18 from the BC1-02 trial that already indicated a
19 prolongation of the median overall survival in this
20 first randomized Phase II trial there was a very
21 strong indicator of an effect on median overall
22 survival. And since this of course is the major
23 endpoint that is also interesting for the scientific
24 community and for the regulators it was felt this was
25 the more important endpoint to be captured and

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1 therefore used as a primary endpoint.

2 MEMBER SULEIMAN: So the increase is by 2.8
3 months?

4 DR. VOLIOTIS: 2.8 months, it is for the
5 interim analysis, and 3.6 months for the updated
6 analysis.

7 ACTING CHAIR THOMADSEN: Dr. Guiberteau.

8 MEMBER GUIBERTEAU: Can you tell us a
9 little bit about the selection criteria for the
10 patients here? Were there any other than just having
11 prostate -- I'm sorry, hormone resistant refractory
12 metastases?

13 DR. VOLIOTIS: Yes. Patients had to be
14 hormone refractory. They had to have all symptomatic
15 bone metastases. Patients could have received prior
16 dosetaxel or not depending on their status, their
17 choice and whatever decision they took together with
18 their treating physician. So we have both dosetaxel
19 pre-treated and non-dosetaxel pre-treated patients in
20 this study. And all patients were selected based,
21 again, on their status in terms of the underlying
22 disease bone metastases. No visceral metastases and
23 only a limited amount of lymph node metastases.

24 MEMBER GUIBERTEAU: Were there any criteria
25 related to estimated survival? In terms of, in some

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1 therapies, particularly bone therapies, patients who
2 have a prognosis of less than 6 months are really not
3 in some cases candidates for such therapies.

4 DR. VOLIOTIS: Patients had to have an
5 adequate performance status. So ECOG performance
6 status zero and 1. A few cases with performance status
7 of 2 only. So by that we, the defined nature of that,
8 we could enroll patients that would have a potential
9 benefit from the treatment still.

10 MEMBER GUIBERTEAU: Thank you.

11 ACTING CHAIR THOMADSEN: Dr. Welsh?

12 MEMBER WELSH: Thank you for coming here
13 and giving this presentation. The majority of the
14 ACMUI is very familiar with this as I personally gave
15 this presentation a few years back. But I see there
16 are a number of new members here and so this is most
17 appropriate.

18 But I understand that the trial was not
19 designed by Bayer but by Algeta and the indication was
20 not primarily for pain control. However, this presents
21 a hurdle for future applications of this drug when it
22 comes to FDA approval for pain control or management
23 of osteoblastic metastases in, say, breast cancer or
24 other malignancies in which other radiopharmaceuticals
25 are commonly used. Will Bayer address this issue in

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1 upcoming studies?

2 DR. VOLIOTIS: In future studies?

3 MEMBER WELSH: Yes.

4 DR. VOLIOTIS: We are currently discussing
5 the development program in prostate cancer, taking
6 this forward and also in other indications like, for
7 example, in breast cancer as you already mentioned.
8 And yes, we are currently discussing to what extent we
9 can include pain scales as an efficacy endpoint.

10 MEMBER WELSH: So as a follow-up question,
11 do you anticipate that with your current FDA
12 submission that there will be any indication for uses
13 outside of prostate cancer?

14 DR. VOLIOTIS: No. We -- that's not our
15 intention. The filing that we intend to do is for the
16 study population as described by the ALSYMPCA study.

17 ACTING CHAIR THOMADSEN: Seeing no other
18 questions, please continue.

19 DR. MERTEN: So good morning from my side
20 as well. My name is Erik Merten. I am heading the
21 department that is responsible for the technical
22 development of radiopharmaceuticals at Bayer. So for
23 Alpharadin as well.

24 I would like to present the general aspect
25 of handling and safety of Alpharadin and especially

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1 present that although with radium-223 chloride a novel
2 approach in radiotherapies followed from a clinical
3 perspective, this drug from all positions perfectly
4 fits in the established radiosafety practice
5 environment in the field.

6 The unit dose comes in a vial. It's ready
7 to be injected via a syringe so there are no further
8 sophisticated manipulations necessary, no generators
9 involved, no chelating like for some other
10 radiopharmaceuticals. The unit dose is a calibration
11 date 6 megabecquerel. So it's substantially lower than
12 compared to other radiopharmaceuticals currently
13 commercialized. And I think it's very important to
14 emphasize when talking about safe handling.

15 As my colleague Dimitris already
16 presented, there are some photons involved which have
17 to be taken care of but as well allow for measurement
18 with standard equipment. Predominant decay follows the
19 alpha decay.

20 The shelf-life of the product is 28 days
21 with a half-life of 11.4 days for radium-223. The
22 product allows for decay in storage.

23 This slide elucidates a little more
24 detail. The aspect of external radiation exposure
25 associated with radium-223. If you look on the left

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1 side of the table you can see that the exposure rate
2 constants of radium-223 are similar to technetium-99m
3 but because of the substantially lower dose that is
4 applied the risk of external exposure is substantially
5 lower. These calculations are based on the assumption
6 of unshielded handling of the source and you can see
7 that the factor of 200 lower dose directly of course
8 results in lower exposures if you handle radium-223.

9 And this holds true if you compare this
10 with the common radiopharmaceuticals that are
11 commercialized. Not only for radiotherapeutics but as
12 well for radiodiagnostics. Radium-223 really stands
13 out in terms of activity to be handled and to be
14 applied.

15 As we are talking about an alpha emitter
16 of course we have to take specific care about the risk
17 of accidental intake. And this is one reason why this
18 product has been developed for a very straightforward
19 use and application. So it comes in a vial, in
20 shielded container, and the only thing that has to be
21 done at the clinical site is to calculate the patient
22 dose, draw up the desired volume and then inject the
23 product into the patient.

24 So what you might miss in the procedure is
25 the use of a dose calibrator. This is of course, we

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1 think that the use of a dose calibrator is not, at
2 least not mandatory. It is by current NRC regulations
3 not mandatory for the verification of the dose pre-
4 administration. This is already up to the clinical
5 site if this is done or not. But for radium-223 we
6 think that this is not the best to speak -- so to
7 speak, the best method for verification of the
8 administration. And this has to do with the very low
9 activities that are handled here.

10 Our data from the clinical trials indicate
11 that on average less than 1 percent of the
12 administered activity remains in the syringe. So this
13 results in a -- for a typical administration in a
14 residual activity of below 1 microcurie which can be
15 correctly quantified in a dose calibration.
16 Considering as well that the administered activity
17 based on the protocol can vary by +/- 10 percent, a
18 flushing procedure followed by a visual assessment of
19 the syringe is recommended as a standard procedure
20 being even superior against very fine vitals
21 calibrator.

22 Nevertheless, in the event of an issue
23 that occurs during administration there needs to be
24 some equipment that allows direct measurement of
25 activity. But as well this is not necessarily to be

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1 done with a dose calibrator, but could be done with a
2 calibrated survey meter as well.

3 Waste disposal. I already said that this
4 product allows for the decay-in-storage due to the
5 half-life of 11.4 days. The photon emission involved
6 in the decay cascade allows for monitoring and control
7 of the residual activity by a standard 7 meters so
8 that there is no dedicated instrumentation for alpha
9 emission detection as needed.

10 With regard to patient handling, this
11 slide shows the calculation of the external radiation
12 exposures that can result from patients treated with
13 radium-223 to others. And it shows that the dose rate
14 at 1 meter from a patient is about 0.007 millirem per
15 hour. So if you assume 1,000 hours of constant
16 exposure this results in an exposure of 7 millirem
17 which is far below the limit of 500 millirem per case
18 that allows for all outpatient treatment. And it's
19 even far below the 100 millirem limit for patient
20 information.

21 Nevertheless, we are planning for the
22 commercial setting to provide some patient
23 information. But this will focus more on the aspect of
24 accidental intake, although this risk is seen as well,
25 very low because the radiation is excreted from the

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1 body mainly via the feces so that if everybody follows
2 standard routine hygiene rules the risk of
3 contamination at intake is highly unlikely.
4 Nevertheless, because we are dealing with an alpha
5 emitter special precautions should be taken here and
6 this is why we are planning to provide patients with
7 some information.

8 As shown in the slides before, application
9 of radium-223 is very much in line with established
10 application methods if not even more straightforward
11 and easier. So there's no in-depth training needed for
12 experienced staff that are trained and experienced in
13 the use of radiopharmaceuticals. Instead of that, the
14 staff will be provided with specific information on
15 radium-223 with especially information on how to
16 calculate the dose for a patient, and as I said
17 before, some patient information.

18 Nevertheless, we have already, and this
19 will remain for the commercial setting as well,
20 established a help desk with technical staff which is
21 mainly for centers that are not that experienced and
22 may need support.

23 So, summarizing, radium-223 chloride is a
24 ready-to-use radiopharmaceutical that is suitable for
25 an outpatient treatment. The dose as handled and

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1 applied is substantially lower compared to other
2 radiopharmaceuticals. The presence of photon emissions
3 allow for tracking of activity and measurement of
4 activity with standard instrumentation. As the doses
5 handled are relatively low, the risk of radiation
6 exposure is minimal and manageable when established
7 standard radiation safety practices are implemented
8 and followed.

9 Some drug-specific information is needed,
10 especially on dose preparation and will be provided.
11 And following these rules, as Dimitris has already
12 said, more than 1,000 patients have been applied, have
13 been treated with radium-223 without any radiation
14 safety incident. So to us this gives a lot of trust
15 that radium-223 can be handled in the established
16 radiosafety practice environment.

17 And with this I end my talk and would hand
18 over to Jeff or ask for questions.

19 ACTING CHAIR THOMADSEN: I would ask first
20 are there questions on this particular presentation by
21 the committee? Dr. Palestro.

22 MEMBER PALESTRO: Yes. I have a question
23 regarding the potential for dose infiltration at the
24 time of administration. Has that been observed among
25 any of the patients that have received the radium, and

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1 if it hasn't what would the anticipated side effects
2 be? The local side effects.

3 DR. MERTEN: I think this is rather a
4 clinical question. I'm not aware of the side effects.

5 DR. VOLIOTIS: I'm not aware of any side
6 effects in the ALSYMPCA study or any other Phase III
7 study. Phase I or II studies either.

8 ACTING CHAIR THOMADSEN: Dr. Welsh.

9 MEMBER WELSH: I'm just going to ask Dr.
10 Palestro if you think that it would be any different
11 from what we've seen with other radiopharmaceuticals
12 for therapeutic purposes. To my initial impression I
13 would be surprised if there's any significant
14 difference from what we use with strontium, samarium,
15 other.

16 MEMBER PALESTRO: The answer is I don't
17 know which is why I asked the question. I just don't
18 know.

19 ACTING CHAIR THOMADSEN: I have a question.
20 From the days in brachytherapy with radium-226 when it
21 was radium chloride one of the big concerns was in
22 volatilized radium and inhalation which quickly would
23 go to the bones of the people exposed. Do you have
24 measurements or indications such that if a vial were
25 to break how much volatilization takes place?

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1 DR. MERTEN: We have no measurements on
2 that and I think it's a little bit sophisticated to
3 measure because it's very, very small amounts involved
4 here. We have theoretical assessments. It comes in an
5 aqueous solution and the solubility of radium-219
6 which is the volatile daughter isotope is very high in
7 water, it's 200 ml per liter. And so the volume that
8 can be produced is 2.3×10^{-16} . So it's very, very
9 small volumes. So from this theoretical approach the
10 risk of inhalation is very, very low from our
11 perspective. But I have to say we have no experimental
12 confirmation of this assessment so far.

13 ACTING CHAIR THOMADSEN: Okay. Any other
14 questions from the committee? Please continue.

15 DR. SIEGEL: Good morning. I'd like to
16 start by extending my best wishes to Chairman Malmud,
17 Vice Chairman Thomadsen and members of the ACMUI
18 committee. Good morning. My name is Jeff Siegel. I'm a
19 consultant for Bayer and I'm going to present very
20 briefly some licensing recommendations and seek your
21 counsel or your perspective in terms of the licensing
22 options I'm going to present for radium-223 chloride.

23 First off, as the previous speakers have
24 mentioned, radium-223 chloride is a
25 radiopharmaceutical that is an unsealed source. And

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1 pursuant to NRC's 35.300 licensees may use any
2 unsealed byproduct material prepared for medical use
3 and for which a written directive is required that is
4 either obtained from or prepared by those specified in
5 the rule itself. The administration of and the
6 radiation safety support for the radiopharmaceutical
7 radium-223 chloride are similar to any other
8 radiopharmaceutical already regulated pursuant to
9 35.300.

10 In addition to alphas, radium-223 emits
11 beta particles as well as photons. Treatment involves
12 very low administered activities in the microcurie
13 range. And dose rates are very low due to the low
14 activity and the photon yield being so low.

15 The only additional training that is
16 needed is instructional and informational in nature.
17 Really only product-specific information such as
18 ordering, dosage administration, preparation will be
19 provided to the licensee by the manufacturer.

20 In order to license pursuant to 35.300 a
21 decision has to be reached, and here is where we will
22 be seeking ACMUI's perspective, in terms of authorized
23 user training and experience pursuant to 35.390.

24 Pursuant to 35.390 under Subpart G there
25 are four dosage categories that are available for an

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1 authorized user. The first two aren't relevant because
2 they pertain only to oral sodium iodide. So there's
3 really only a decision between Category 3 and Category
4 dosage in which you would place radium-223 chloride.
5 If the decision is reached to put it into the
6 parenteral administration of any beta emitter -- after
7 all, one could state that radium-223 is any beta
8 emitter, although it's primarily an alpha emitter, but
9 that's not the language of dosage Category 3 -- that
10 would be one thing. And all authorized users currently
11 would then be able to administer and treat patients
12 with this agent.

13 Alternatively, you may decide that it's
14 more appropriate to place it into Category 4 because
15 this is the only other currently available dosage
16 category in which to place it into. In that case we
17 would again like ACMUI's perspective in terms of NRC's
18 35.57 which seems to grant "deemed" status to those
19 physicians who've been identified as AUs on licenses
20 prior to April 24th of 2005.

21 In the Federal Register notice for the
22 final rule in 2002, I mean these AUs were granted or
23 stated to have deemed status. So we'd like to seek
24 ACMUI's perspective on whether or not they indeed
25 would have it for radium-223 chloride.

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1 We note that this decision is important
2 because in order to attain authorized user status in a
3 particular dosage category a minimum of three cases
4 are required. If placed into Category 3 as I said all
5 current AUs would be able to, without any cases if
6 placed into Category 4, I dare say most if not all
7 would need the three cases unless those authorized
8 users were granted deemed status.

9 As you are all aware and Bayer is
10 certainly aware, there is expanded Part 35 rulemaking,
11 and 35.390 is currently draft language being altered
12 to expand the four dosage categories into six. And
13 there is now a primarily alpha radiation dosage
14 category. This in our opinion forecasts NRC intention
15 to license alpha emitters under 35.300, that is
16 assuming that there are no specific risks that are
17 identified in NRC's assessment of this agent that
18 would so warrant placement into 35.1000.

19 And of course, if this were the case we
20 would also ask again for the committee's advice in
21 terms of whether deemed status would still apply to
22 those authorized users identified prior to 2005.

23 As I said, obviously you can certainly
24 determine if licensing of radium-223 would require it
25 to be placed under 1000 such as if specific risks are

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1 identified during the assessment which would so
2 warrant such placement. However, Dr. Voliotis and, I'm
3 sorry, Voliotis and Merten have so stated that while
4 this is a novel technology indeed, we believe that
5 this new technology is a type of use that's already
6 regulated under 35.300. And unlike yttrium-99
7 microspheres which were placed under 35.1000, these
8 were brachytherapy devices unlike radium-223 chloride
9 which is an unsealed source of a radiopharmaceutical.

10 So in conclusion, our most appropriate
11 option would be option one, would be to license under
12 35.300 and place AU T&E under Category 3 of 390.
13 Alternatively, if it was placed into Category 4 then
14 we'd like to find out the ACMUI's perspective on
15 deemed status. And lastly, still licensing under 300
16 but maybe placing temporarily into 1000 until
17 rulemaking is finalized. And we realize that
18 significant language change may occur during the
19 rulemaking process, that this would be a final option.
20 And I thank the committee for its attention.

21 ACTING CHAIR THOMADSEN: Thank you. Dr.
22 Suleiman?

23 MEMBER SULEIMAN: I have a more fundamental
24 question. How hazardous is this? I mean forget -- we
25 know it's smaller amounts in terms of activity and

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1 it's far more hazardous than a beta emitter. How
2 dangerous is this to the workers who handle it? And if
3 there were to be contamination, forget external,
4 somehow gotten into a worker. Obviously you're using
5 it for therapy but these are --

6 DR. SIEGEL: Well, I guess when you say
7 risks to workers we all know that there are two
8 aspects of radiation exposure. There's external
9 exposure and internal intake. So, the likelihood of
10 any untoward consequence of external exposure from
11 radium-223 is minimal. Dose rates are very low and as
12 you saw in the slide on the tech-99m unshielded
13 they're a factor 200 less than tech-99m. So, as an
14 alpha emitter, internally there's a greater risk.

15 But what's the likelihood that there will
16 be an ingestion after handling this particular agent?
17 Well, I daresay that I don't know of any, not to say
18 that there never have been, but I don't know of
19 routine ingestion by radiation workers or authorized
20 users or nuclear medicine technologists of radioactive
21 agents, whether it be technetium or I-131m. So, it
22 would be more hazardous if it was accidentally in-
23 taken but because of the radiation safety precautions
24 in place and any radiation protection program due to
25 the ALARA requirement of the emission we feel that the

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1 likelihood of an internal intake is no greater or no
2 less than any other intake from any other agent.

3 MEMBER SULEIMAN: Let me rephrase that.
4 Would this require more special handling conditions
5 than other particulate radiation?

6 DR. SIEGEL: Actually, it would handle less
7 because one could argue that shielding isn't even
8 required as opposed to for I-131 where you need thick
9 lead.

10 MEMBER SULEIMAN: No, but again I'm talking
11 about potential for somehow getting internally
12 contaminated. I'm really not concerned about the
13 external exposure.

14 DR. SIEGEL: Right, but again it's a
15 liquid. So as far as somebody taking it in there are
16 no added precautions. I mean, you would wear gloves,
17 for example, if cleaning up a spill because you'd be
18 worried about if there was a wound maybe you'd get it
19 into your skin, but these would be the normal things
20 that any radiation safety officer would instruct their
21 staff to do. So, no, nothing special would be
22 required. No, you know, ventilatory equipment.

23 ACTING CHAIR THOMADSEN: Dr. Welsh?

24 MEMBER WELSH: So, I will follow up with an
25 answer to Dr. Suleiman's question. And the reason why

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1 I think this is an important question that is very
2 realistic is that from our annual report on medical
3 events yesterday we see that there's this unfortunate
4 phenomenon called human error in which the wrong
5 isotope can be administered. And we saw a case in
6 which a therapeutic radiopharmaceutical was given when
7 a diagnostic one was intended. That fortunately
8 happens very infrequently but it does happen and it
9 probably will happen in the future and hopefully it
10 will never happen with Alpharadin but there is
11 precedent for it. So, given that it is possible it's a
12 very important question to begin to consider.

13 Looking at the table presented this
14 morning, although there was no actual red marrow
15 dosimetry presented in the table we can see from all
16 grades of hematological toxicity would perhaps be the
17 major concern with IV administration of this
18 particular radiopharmaceutical, that the -- all grades
19 of anemia, thrombocytopenia and neutropenia were not
20 very different from placebo. And therefore I would
21 predict that the actual red marrow dose might not be
22 sufficient to cause severe toxicity, even if
23 administered inadvertently to the wrong patient which
24 would be a worst case scenario I believe of internal
25 contamination to an unintended individual.

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1 ACTING CHAIR THOMADSEN: Thank you for your
2 comment, Dr. Welsh.

3 DR. SIEGEL: I think the comment was very
4 well spoken, but I interpreted Dr. Suleiman's question
5 as would there be anything above that close scrutiny
6 of making sure that you've injected the right patient.
7 Obviously NRC's regulations are not intended to
8 prevent human error. No regulation can prevent human
9 error. They will happen. But in a risk-informed
10 performance-based environment the best you can do is
11 to make sure that you identify by five different
12 methods that you're identifying the correct patient,
13 by five different methods that you're giving the right
14 radiopharmaceutical. But I agree, there is no way that
15 every error is going to be prevented by any regulation
16 or by any procedure that's put in place.

17 MEMBER WELSH: But that would be the worst
18 case scenario, giving the full dose to the wrong
19 patient. So concerns about the radiopharmacist, the
20 authorized user, the medical physicist, others who are
21 handling and administering the material are probably
22 on a far smaller scale than that extreme and unlikely
23 example. But even if that extreme unlikely example
24 were to occur from data thus far it might not be as
25 disastrous as some might have anticipated with other

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1 radiopharmaceuticals, for example.

2 DR. VOLIOTIS: I would agree with that.
3 Thank you for that comment. And as you can see, from
4 the adverse event, from the hematologic adverse event
5 table keeping in mind that, you know, this includes
6 intravenous injection of up to six cycles, you know.
7 This is if you wish the maximum dose for the intended
8 usage and still there is no difference in terms of
9 hematologic adverse events for anemia and
10 thrombocytopenia. So even with the maximum intended
11 dose the difference between placebo and radium-223 is
12 actually not there.

13 MEMBER LANGHORST: Yes, Dr. Suleiman, we
14 were at Washington University in St. Louis, one of the
15 locations that utilized Alpharadin and that was one of
16 my concerns about how do we see contamination and so
17 on. It was very easy to survey for this contamination
18 because of the betas and the photons that are
19 associated with this. So, we felt very comfortable in
20 handling it in the normal radiopharmaceutical way.

21 ACTING CHAIR THOMADSEN: Thank you for your
22 comment.

23 DR. SIEGEL: I just had one last comment.
24 Dr. Welsh, I was in no way trying to minimize your
25 concern or your comment. In fact, I was agreeing with

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1 it and I think it was a very thoughtful thing to say
2 that in spite of that that the expected toxicity would
3 be less than taking in a full dose, for example, of
4 300 millicuries of I-131.

5 I was just trying to mention that all the
6 precautions will be in place as per any other agent.
7 And as you so acutely and adroitly pointed out, even
8 in the worst case event that wouldn't be as bad as
9 some other therapeutic agents being administered to
10 the wrong patient.

11 ACTING CHAIR THOMADSEN: Thank you. Other
12 questions from the committee? Yes, Dr. Suh.

13 MEMBER SUH: Just getting back to the
14 clinical trial design here, is there a group of
15 patients with castration-resistant symptomatic
16 prostate cancer who are not candidates for this
17 product? Like, what were the ineligibility criteria
18 for the study?

19 DR. VOLIOTIS: The eligibility criteria
20 again were existence of symptomatic bone metastases,
21 absence of visceral metastases. The intended label is
22 for treatment again with -- for patients who are
23 castration-resistant and otherwise following the
24 inclusion/exclusion criteria of the trial. Obviously
25 this is a drug that only works in patients with bone

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1 metastases, so presence of extended visceral
2 metastases or any visceral metastases make this
3 patient not eligible for treatment. We have no data so
4 far in combination with chemotherapy in patients who
5 also have visceral metastases. So the only data that
6 we have had is for patients with bone disease.

7 MEMBER SUH: So was there a minimum
8 hemoglobin platelet level of these patients required
9 to go into the study?

10 DR. VOLIOTIS: They had to have just
11 adequate hematologic parameters. But there was no
12 specific cutoff level required for entrance into the
13 trial.

14 MEMBER SUH: And in the arm were there any
15 differences in hospitalization rates between the
16 placebo arm versus the treatment arm?

17 DR. VOLIOTIS: For any hospitalization?

18 MEMBER SUH: Yes.

19 DR. VOLIOTIS: No, overall not.

20 ACTING CHAIR THOMADSEN: Dr. Guiberteau.

21 MEMBER GUIBERTEAU: Were there any studies
22 performed, I assume there were, either in animals or
23 humans in terms of the dose titration for patients
24 with different degrees of metastatic disease?

25 DR. VOLIOTIS: There is no dose titration

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1 intended. It would be the intended dose is the same
2 for all patients, 50 kilobecquerels per kilogram body
3 weight.

4 MEMBER GUIBERTEAU: And how was the dose of
5 50 kilobecquerels per kilogram of body weight
6 determined?

7 DR. VOLIOTIS: This was determined based on
8 the Phase I and Phase II trials, primarily the BC1-03
9 and BC1-04 trial where those were trials with
10 multiple- and single-dose injections and with efficacy
11 parameters primarily being bone ALP. And the dose
12 range here was between 50 and 100 kilobecquerel per
13 kilogram. And there was essentially no difference
14 between the 50 and the 80 or the 100 kilobecquerel
15 dose. And therefore the safer or lower dose with the
16 50 kilobecquerel was considered for the Phase II
17 trials. It yielded positive results in the randomized
18 Phase II trial, the BC1-02 as already mentioned, and
19 therefore was carried forward into the Phase III
20 trial.

21 MEMBER GUIBERTEAU: Thank you.

22 ACTING CHAIR THOMADSEN: Dr. Welsh.

23 MEMBER WELSH: So, I'll just reiterate my
24 comment earlier to my appreciation for you being here.
25 Apparently my conversation here I think in 2009 has

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1 been forgotten by most including myself, so it was
2 nice to see a refresher on this particular subject.
3 But if I recall correctly I strongly recommended back
4 then that this parenteral radiopharmaceutical therapy
5 be licensed under Section 390. And of the choices that
6 Dr. Siegel eloquently presented my personal
7 recommendation to staff would be to consider the 300
8 as was recommended a few years back.

9 ACTING CHAIR THOMADSEN: Thank you, Dr.
10 Welsh. Other questions or comments from the committee?

11 DR. SIEGEL: Just to say, Dr. Welsh, I did
12 read that transcript from 2009 and you very eloquently
13 presented your recommendations.

14 ACTING CHAIR THOMADSEN: Ms. Henderson or
15 Mr. Einberg, are there questions from the NRC staff to
16 the presenters?

17 MR. EINBERG: Does the medical team have
18 any questions?

19 MR. FULLER: I have -- can everyone hear
20 me? I have a couple of questions. First of all, and I
21 guess this is for Dr. Welsh. If you could remind us,
22 under 35.390, your recommendation, do you recall if
23 you recommended it under Subcategory 3 or Subcategory
24 4. Do you recall?

25 MEMBER WELSH: I don't recall offhand. I'd

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1 have to review.

2 MR. FULLER: Okay. I guess what it then
3 boils down to is do you believe that it should be
4 licensed in such a manner that we would require under
5 the training and experience considerations that a
6 minimum of three cases be done under the supervision
7 of an authorized user, or would it be okay -- as
8 currently authorized to do, parenteral administrations
9 without any additional cases?

10 MEMBER WELSH: I believe back then I was
11 equivocating because I didn't have an answer for your
12 question because the clinical experience at that time
13 was still in its infancy. But today given what we
14 heard during the presentations my recommendation would
15 be in favor of the latter.

16 MR. FULLER: Meaning we would require
17 three.

18 MEMBER WELSH: No.

19 MR. FULLER: That we wouldn't require
20 three.

21 MEMBER WELSH: Would not require additional
22 experience for someone who is already trained and
23 experienced in parenteral administration of
24 radiopharmaceuticals.

25 MR. FULLER: Okay, thank you. And the other

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1 question that I had, I know we had heard from Bayer
2 earlier, I guess back in February, I had some
3 preliminary conversations there. And we were told I
4 believe, and I can -- and please correct me if we
5 misunderstood, but that your plans were to market this
6 to broad scope licensees until we could have an
7 opportunity to learn more and figure out our path
8 forward with licensing.

9 We have recently received quite a bit of
10 interest, or I should say a number of cases where
11 specific licensees are coming in and asking for -- to
12 be licensed. I think we have one application and a
13 number of inquiries. Is your plans to -- or do we
14 misunderstand something, or are you planning to market
15 this immediately to licensees who were specifically
16 licensed under 300?

17 DR. MERTEN: I would like to get Jeff Bova
18 involved from the marketing side of the organization.

19 MR. BOVA: Hi, my name is Jeff Bova. Mr.
20 Commissioner, can I answer -- permission to answer the
21 question?

22 So, our plans have not changed. We
23 certainly are going to come out to -- at launch if
24 approved we will target those sites that are licensed
25 under 300. However, we know from research within our

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1 urology and medical oncology and radiation oncologists
2 that there is an interest, even those that are
3 licensed under sealed license of 400, 500 and 600,
4 those that do EBRT and brachytherapy, that there is an
5 interest in radium-223 chloride. So we would be
6 prepared from a training standpoint to assist those
7 folks in everything that they would need since they
8 currently don't have 300. But right from the very, you
9 know, upon approval, if approved we would go with
10 those broad licensed folks that are licensed out of
11 300. However, we've heard the same thing that I think
12 you may have seen in that there is an interest with
13 others.

14 ACTING CHAIR THOMADSEN: Thank you.

15 MR. FULLER: If I might follow up because
16 that actually -- and Dr. Howe might be able to speak
17 to this so I'm going to turn it over to her next. She
18 might be able to speak to this as well.

19 But if the question is whether or not it
20 should be licensed under 300, either Subcategory 3 or
21 4 which we can hear more about, then that makes it
22 more immediately available for those who would use it
23 more under the traditional radiopharmaceutical
24 therapy. If you're talking about wanting to get folks
25 licensed as authorized users who are currently not

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1 authorized at all under 300 then the hurdle may be
2 higher for 35.300 than it would be for 35.1000 because
3 under 35.1000 we can customize or appropriately assess
4 the risk and the needs and so forth for those folks
5 who are not authorized under 300 to do something which
6 might be a little more tailored. So it's just a
7 thought and it's a consideration.

8 So, and the other thing is the difference
9 -- I think there was some confusion maybe on both
10 sides about marketing or trying to move, or have the
11 radiopharmaceutical used in a broad scope setting
12 versus a specifically licensed setting. Under a broad
13 scope it is up to the radiation safety committee and
14 the internal infrastructure for the licensee to make a
15 determination as to someone's training and experience.
16 So, and I see from Dr. Langhorst that there's a
17 disagreement on that.

18 But anyway, the point is, is that there is
19 currently if you're a medical broad scope licensee you
20 could under the terms of that license this could be
21 used, as opposed to 35.300 -- I'm sorry, someone who
22 wasn't, who was specifically licensed at 35.300 then
23 we still have this question about licensing. So, this
24 is sort of the sorts of things that we wrangle with.

25 ACTING CHAIR THOMADSEN: Thank you, Mr.

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1 Fuller.

2 DR. HOWE: My question is different from
3 that. So I guess I would like to hear from Sue
4 Langhorst how she believes the broad scope doesn't
5 have the broad authorization to use this currently
6 under radiation safety.

7 ACTING CHAIR THOMADSEN: Dr. Langhorst.

8 MEMBER LANGHORST: If you were licensed for
9 radium-223 you could -- the radiation safety committee
10 can approve that. But licensees, even broad scope
11 licensees may not be licensed for the radium-223 so
12 you have to go in for the license to possess that
13 isotope. So, in our case we already had license
14 coverage for that isotope and so we were easily able
15 to get up and running and utilize that isotope.

16 Now, I don't remember what specific
17 licensees for medical use that have a 300 level, if
18 they have the isotopes listed. I can't remember. It's
19 strictly 300? They'd be ready to go much faster than
20 some broad scope licensees were if the broad scope
21 licensees were not licensed for the radium. So that
22 was my reason I was shaking my head.

23 DR. HOWE: I guess one of the things that
24 we would like to see is we would like to see more of
25 your quantitative data on why you believe that you can

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1 use the Alphasadin even after concern for its alpha
2 particles as far as measuring contamination or other
3 radiation safety practices. And so we'd like to see in
4 detail your rationale for why you can use the gammas
5 and why you can use the betas and quantify that,
6 please.

7 And I guess another thing is if you're
8 talking about internal contamination we now have an
9 oral administration. So we would like to see if there
10 is a difference between an oral administration and an
11 injection.

12 ACTING CHAIR THOMADSEN: Do you know if you
13 have some animal results from that?

14 DR. VOLIOTIS: No, I don't know that right
15 now. But there is no intended oral formulation for
16 this drug at this point.

17 DR. HOWE: We understand that. The
18 contamination --

19 DR. VOLIOTIS: No, I understand the
20 question. I -- you would have to go back and look for
21 that. I'm not aware of data right now.

22 DR. HOWE: And I guess the concern would be
23 whether it's -- what the lower levels of detection
24 would be with the gammas and the betas when you're
25 doing contamination. You still have an alpha issue

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1 there even though you might not be able to detect it
2 with your gamma. We would like to see that data in
3 detail. And I guess even though there is no
4 requirement, if you get a unit dosage you don't have
5 to make a direct measurement. We'd still like to see,
6 because people may be using dose calibrators, how you
7 would determine the activity if a dose calibrator is
8 the device or not. Explain that in detail with a lot
9 of quantification.

10 ACTING CHAIR THOMADSEN: Dr. Welsh?

11 MEMBER WELSH: I fully agree with Dr.
12 Howe's comment and question about obtaining more
13 rigorous data. But my initial overall qualitative
14 perspective is that since approximately 75 percent of
15 a dose is excreted within a week and it's excreted
16 primarily through the fecal route there is already
17 evidence of what the GI toxicity might be, and
18 therefore concerns of a small amount of oral
19 contamination might not be a very significant clinical
20 or radiation safety concern. Nonetheless, the question
21 does have to be answered, but my prediction is that it
22 would be relatively minimal.

23 ACTING CHAIR THOMADSEN: Thank you. Dr.
24 Suleiman?

25 MEMBER SULEIMAN: Yes, these are more just

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1 some concerns or observations, not necessarily even
2 directed to your product. I think radio-labeled
3 therapeutics have been an emerging treatment I think -
4 - I feel promises great efficacy. I've been most
5 distressed across the board by the lack of real
6 dosimetry. I think these, the first generation of such
7 products are basically dose -- chemotherapy drugs are
8 dosed to maximum toxicity.

9 To give you an analogy, I think if we
10 treated patients with radiation like we treat them
11 chemo we'd basically give everybody whole body doses
12 and wouldn't focus on the tumor burden, wouldn't focus
13 on the target itself. So I think radiation is really
14 an order of magnitude way ahead of the rest of
15 medicine.

16 But I haven't seen -- it's unfair to
17 compare radiolabeled therapy with external beam
18 radiation therapy or brachytherapy. The precision and
19 accuracy are, they're just two different worlds. And
20 I'm aware of your dosing weight which is how it's
21 done, which is what the current state of the world is
22 today, but I really -- this is a dilemma we get faced
23 with both at FDA and here. You want to move the field
24 forward, you don't want to constrain it so that you
25 never get out to market, but at the same time, and

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1 I've faced this personally professionally where I've
2 argued we should have required better dosimetry and
3 I've been -- the other side has been well, if it
4 doesn't get out there then the medical community won't
5 be able to use it and learn.

6 So, I'd like to see better dosimetry. I
7 don't have an answer. I mean, your clinical trials are
8 true evidence-based medicine. It's trial and error.
9 You give them a dose by whatever metric -- your given
10 activity. You really don't know the exact dose that
11 the bone is picking up necessarily. And you observe
12 that patients are surviving longer. We need to somehow
13 inject a little bit more science into it.

14 It's a common -- it's not a specific
15 criticism to you, but the other problem that I have
16 seen and I shared with the committee, once a product
17 is approved and once you're licensed the companies
18 really don't pay as much attention as they should. And
19 so it's important to take some of our concerns
20 seriously I think now.

21 I don't know whether you consider the
22 extent of disease in the patient when you do the
23 dosimetry or one size, you know, basically if they
24 weigh so many pounds or kilograms you give them a
25 certain amount of activity. I don't know at this point

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1 whether you can do anything about that, but I'm sure
2 this has been discussed internally as well. But just
3 to move the science along a little bit more.

4 I appeal to the -- and you've contacted
5 and you've had, I feel more relieved that these have
6 been tested with people who I trust because I don't
7 have the personal experience, the professional
8 experience with this myself, but when you talk to
9 others who have had that experience, and I am
10 convinced it's probably not as hazardous as I was
11 concerned about, but I'm sure anybody else who hasn't
12 worked with it would have the same concerns until
13 they've had some experience to say it's really not
14 bad. But still there is potential for contamination. I
15 think it's important we know what kind of impact that
16 would have on people who would be contaminated.

17 ACTING CHAIR THOMADSEN: Thank you very
18 much, Dr. Suleiman.

19 DR. GERMINO: Chairman?

20 ACTING CHAIR THOMADSEN: Please identify
21 yourself.

22 DR. GERMINO: My name is Joseph Germino.
23 I'm with U.S. Medical Affairs for Bayer.

24 We fully agree with your content. We've
25 heard a lot of comments from physicians that they are

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1 very interested in what really is the effective dose.
2 We know the effective dose is 50 but there might be
3 better doses. And so there are plans already in place
4 to discuss possible trials of different doses, more,
5 higher doses, lower doses in patients depending upon
6 their extent of disease. So, that's a very important
7 interest of clinicians as well as the company. So I
8 think that will be addressed in the development of the
9 product.

10 MEMBER SULEIMAN: Thank you very much.

11 ACTING CHAIR THOMADSEN: Dr. Welsh.

12 MEMBER WELSH: I will take a stab at a
13 reply or comment to Dr. Suleiman's points.

14 It is true that other radiopharmaceutical
15 agents in their history have been largely ignored once
16 approval has been granted and further follow-up
17 studies have not been performed. And this has been to
18 the detriment of radiopharmaceutical therapy in
19 general. And it has led to a problem of perhaps
20 underutilization of very effective therapies that
21 involve radiopharmaceuticals. So, follow-up is a very
22 wise suggestion and it's a wise suggestion for the
23 company and for the medical community at large because
24 we know from history that radiopharmaceuticals tend to
25 be underutilized as a general category.

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1 And although Dr. Suleiman's point is right
2 on as far as a world of difference between
3 brachytherapy and external beam radiation therapy and
4 radiopharmaceuticals there is also a world of
5 difference between radiopharmaceuticals and
6 chemotherapy, at least in terms of the potential for
7 more accurate dosimetry. So right now the approach is
8 a practical one that is very similar to how we would
9 administer chemotherapeutic agents per kilogram, per
10 square meter of surface area, et cetera.

11 But once a chemotherapeutic agent is
12 administered you really don't have any idea where in
13 the body that is going, whether it's going to the
14 tumor, whether it's going strictly to the liver,
15 lungs, the kidneys, et cetera, and bone marrow causing
16 toxicity. But you could take advantage of the gamma
17 photons and maybe do some type of imaging after
18 administration to attempt to quantitate in an
19 individual case where the isotope has gone, whether or
20 not it's really going to the anticipated tumor sites.
21 And if the answer is no maybe that would not be a good
22 candidate for further administrations. But if the
23 answer is yes it might be possible to quantitate that
24 through MIRD or some other formalism and get an
25 assessment of what the dose is and correlate that with

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1 clinical outcomes. I don't know if that has been
2 rigorously investigated yet. I'd be interested in
3 knowing whether that's been looked at or will be.

4 DR. VOLIOTIS: It is nothing that we have
5 investigated so far, but certainly something that I
6 agree with you is very important to discuss taking
7 this drug further into the next generation of clinical
8 studies. So this would be something that we could
9 discuss, yes.

10 ACTING CHAIR THOMADSEN: Ms. Weil.

11 MEMBER WEIL: I'd like to echo the
12 disappointment that others in the committee have
13 expressed regarding the fact that you didn't
14 explicitly study the palliative effect on bone pain.
15 And just say that I hope that going forward you'll be
16 able to look at that specifically so that this drug
17 might be used for other indications.

18 DR. VOLIOTIS: We did not study
19 specifically a pain scale as a palliative endpoint,
20 but we do have secondary endpoints, for example, that
21 deal with skeletal related events. And here we have
22 clearly very positive results from the ALSYMPCA trial
23 that show that the effect on skeletal related events
24 is definitely there. Skeletal related events also
25 includes treatment with external beam radiation for

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1 pain therapy which we have a secondary parameter that
2 does show us that for those concerns that are really a
3 major impediment to the patients subjectively in terms
4 of, again, events that are related to the metastases
5 themselves, skeletal related events, that there is a
6 very positive effect with a very strong P value and
7 hazard ratio.

8 So, although I agree, you know, having not
9 studied pain is something that we would have to do in
10 future studies, we do have really good evidence from
11 the secondary endpoints that we do affect patient
12 outcomes as well. But thank you for the comment and I
13 agree this is something we have therapy for and
14 something we will take forward into the next
15 generation of the studies, yes.

16 ACTING CHAIR THOMADSEN: Thank you.

17 DR. GERMINO: Mr. Chairman, may I speak
18 again? In response to Dr. Welsh's question I think
19 there are --

20 ACTING CHAIR THOMADSEN: Identify yourself
21 again just so they know before you begin.

22 DR. GERMINO: Joseph Germino. In regards to
23 Dr. Welsh's question about the uptake. I think we have
24 two slides from the BC1-05 and -08, the two backup
25 slides. It shows that the drug does go to sites of

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1 both.

2 DR. VOLIOTIS: The backup slides on study
3 BC1-05 and BC1-08. I believe you are familiar already
4 with the slides. You already recorded the 75 percent
5 so this is the reason why I didn't show them. But to
6 the extent that we have data available they are shown
7 on this slide here. This is from the BC1-05 study that
8 investigated six patients. It was a PK and
9 biodistribution study with two Alpharadin injections 6
10 weeks apart of 100 kilobecquerel per kilogram is shown
11 here.

12 And what you can see here basically from
13 the imaging is that the Alpharadin is rapidly taken up
14 by bone and bone metastases and excreted through the
15 GI tract, the small intestine. There is no exposure
16 for the kidneys here, very low radiation exposure to
17 the kidneys at this point. And in terms of the
18 clinical side effects, as already mentioned, very low
19 incident of myelosuppression.

20 And in BC1-08 which was the other PK and
21 dosimetry biodistribution studies, with 10 patients
22 having received single treatment with dosages between
23 50 and 200 kilobecquerel per kilogram the results are
24 shown here. Total body clearance was primarily, again,
25 determined by transition through the GI system. The

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1 Alpharadin showed up within approximately 10 minutes
2 of the dosing in the small intestine and was generally
3 well tolerated. And in terms of clinical endpoints in
4 this dose -- in this study, I'm sorry, there was also
5 a decline in PSA and bone turnover markers.

6 ACTING CHAIR THOMADSEN: Thank you.
7 Questions from the committee? In that case I will
8 thank you very much and get -- move onto Dr.
9 Zanzonico's presentation on the medical use of radium-
10 223 chloride.

11 MEMBER ZANZONICO: Thank you and good
12 morning everyone. I wanted to thank first the
13 representatives from Bayer for their really very, very
14 thorough and very lucid presentation of the clinical
15 aspects of the use of radium-223 chloride.

16 I was not going to attempt to reiterate
17 everything that was said, and certainly there's no
18 need for that, but rather focus on some pertinent
19 regulatory and technical considerations.

20 First, I think by now you will recognize
21 there's a compelling rationale for therapy of skeletal
22 metastases with radium chloride. It's a calcium
23 mimetic as we heard. It's a bone-seeker and we've seen
24 this -- these microradiographs already showing the
25 concentration of the agent at foci of active bone

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1 generation. And in particular what this emphasizes,
2 these microradiographs emphasize is the very limited
3 range of alpha rays in vivo in general and in bone in
4 particular, with a range of no more than several cell
5 diameters. So that the radiation dose is really
6 delivered over an extremely limited distance, much
7 more localized than that of gamma rays and even beta
8 rays.

9 And moreover, there's a well known
10 relationship between the relative biological
11 effectiveness of radiations, ionizing radiations, and
12 their linear energy transfer, their ionization
13 density, with alpha rays typically having a linear
14 energy transfer of about 100 keV per micron and
15 therefore a maximal relative biological effectiveness,
16 that is a maximal biological effect per unit absorbed
17 dose because of its propensity for inducing double
18 strand DNA breaks. So as I say there's a very
19 compelling rationale biologically that radium-223
20 chloride should deliver really uniquely high
21 biologically effective doses to malignant cells and
22 bone.

23 And notably, and in contrast with more
24 conventional bone-seeking radiopharmaceuticals with
25 sparing of hematopoietic stem cells simply because the

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1 range of the alpha rays is so limited that it really
2 doesn't reach many of the otherwise at-risk stem cells
3 within bone.

4 And as we've seen in the clinical trials
5 to date, now including over 1,000 castrate-resistant
6 prostate cancer patients, both the safety and efficacy
7 data are really very compelling. Compared with placebo
8 there's really very mild GI toxicity and mild to
9 moderate myelosuppression, really no different than
10 that in placebos for the most part. And even though
11 data on bone pain reduction was not explicitly
12 addressed, I believe there are such data in the
13 literature which demonstrate a bone pain reduction
14 with radium-223 chloride.

15 And another unique feature of this agent
16 is a statistically significant survival advantage
17 which I don't think has been observed with any of the
18 existing bone palliative agents to date.

19 We've heard as well about the physical
20 data, the relevant physical data of radium-223. It has
21 a half-life of 11.4 days. It decays into a series of
22 daughters as all of the transuranics do, with 95
23 percent of the total decay energy emitted in the form
24 of alpha particles, less than 1 percent in the form of
25 gamma rays. And as has been stated, this really has

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1 very favorable implications for radiation safety in
2 terms of shielding and so forth, yet there are
3 abundant enough gamma rays and otherwise easily
4 detectable radiations to assay the agent and to check
5 for contamination and so forth.

6 And importantly, the daughters are very
7 short-lived. They're of the order of seconds or less
8 to perhaps minutes so that the issue of alpha particle
9 recoil is unimportant. That is as we saw, radium binds
10 to hydroxyapatite by a, basically an ionic bond which
11 has a finite binding energy. And alpha rays are
12 emitted typically with energies of Mev. So the recoil
13 energy in principle could overcome that binding
14 energy.

15 But even if it were to occur the half-
16 lives of the daughters are so short that all of that
17 energy, all of that alpha particle energy would still
18 be emitted at the point of deposition of the radium-
19 223 itself. So the issue of migration of daughters is
20 negligible which is not at all the case for many other
21 alpha particle emitters that are being investigated
22 for radionuclide therapy. So again, a very positive
23 aspect I think of radium-223 as a systemic
24 radiopharmaceutical.

25 Bayer, as was alluded to at the very end,

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1 has collected biodistribution and dosimetry data, and
2 here are some of the pertinent normal organ doses from
3 those studies. And these are for the -- these are the
4 mean doses in centigray or rad for the prescribed
5 single-dose administered activity of 50 kilobecquerels
6 per kilogram. And the highest dose tissues include the
7 gut. As we saw, the gut is the main route of excretion
8 with about 17 centigray per 50 kilobecquerel per
9 kilogram administration. Red marrow is only about 51
10 centigray, and bone, about 420 centigray. And what's
11 important to note is that all of these doses are well
12 below the thresholds for deterministic effects or
13 significant, clinically significant deterministic
14 effects in any of these three organs.

15 And it's likely in fact that the actual
16 doses to the at-risk cells, for example, the
17 hematopoietic stem cells in bone is less than the
18 dose, than the mean organ dose because of the very
19 limited range of the alpha particles themselves. I
20 know Dr. George Sgouros at Johns Hopkins who has
21 consulted to Bayer has made that point.

22 As was also emphasized, the radiation
23 safety aspects of alpha ray didn't appear to be very
24 favorable. The administered activities are orders of
25 magnitude less than are used for more familiar

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1 diagnostic radiopharmaceuticals such as technetium-99m
2 labeled agents and F-18 FDG with a 95 microcurie
3 administered activity for a 70 kilogram standard man
4 as opposed to millicurie, that is thousands of
5 microcurie administered activities typically used for
6 diagnostic radiopharmaceuticals.

7 Correspondingly, the external radiation
8 hazard is far less for alpha rad than for typical
9 diagnostic and certainly other therapeutic
10 radiopharmaceuticals. And a yellow II transport index
11 or DOE transport label is probably excessive, but it's
12 certainly no more than that.

13 Again, the half-life of the radium-223
14 itself as well as the daughters is so short that it
15 can easily be disposed of by decay-in-storage within
16 the nuclear medicine department. And in terms of
17 outpatient therapy, the hazard therefore to staff, to
18 family members, to the general public is really
19 negligible.

20 The contamination hazard remains, as it
21 always does, with any unsealed source of
22 radioactivity, but I think as we have heard and as we
23 have every reason to believe, given standard
24 precautions, universal precautions really that are
25 used with administration, frontal administration of

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1 unsealed sources of radioactivity there's no reason to
2 expect that there would be any greater risk of
3 contamination from Alpharadin than with any other
4 unsealed source of radiopharmaceuticals.

5 Apropos of that point I think the material
6 is provided in a ready-to-inject solution, in a crimp-
7 sealed vial so that the user would withdraw the
8 patient's specific volume from the vial and then
9 presumably attach it to an indwelling venous catheter
10 of the patient. So there's really minimal for any
11 contamination, therefore any internalization by staff
12 or anyone else.

13 It's a stable, vialled product. It's a
14 radium chloride salt. It's not a chemical, so there's
15 no issue of radiolysis or chemical decomposition from
16 the time of production to administration. The shelf
17 life of 28 days I think is related only to the
18 physical half-life of the isotope and really has
19 nothing to do with chemical stability since that's a
20 non-issue.

21 And it's provided in a calibrated activity
22 concentration I believe of 1,000 kilobecquerels per
23 milliliter at calibration, and there's a very
24 straightforward formula for deriving the volume of
25 this solution, no dilution required, to a particular

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1 patient based on the patient's body weight. And these
2 sorts of calculations are done routinely in nuclear
3 medicine departments. They don't represent anything
4 onerous at all from what's routinely done in nuclear
5 medicine department or even private practice offices
6 currently.

7 So, in conclusion, up to this point
8 radium-223 chloride is a safe, effective and
9 convenient treatment for skeletal metastases
10 delivering really uniquely high, biologically
11 effective radiation doses to malignant cells in bone
12 with sparing of hematopoietic marrow and other normal
13 tissues. You know, so at this point it sounds like
14 there's very little to complain about.

15 So, are there any issues? Well, one issue
16 which was touched upon is that of secondary
17 malignancies, and I'll touch upon each of these
18 briefly in the coming slides. The other issue which
19 was also mentioned is that of calibration, meaning end
20 user calibration of the radiopharmaceutical. And
21 finally, as was discussed at length by Dr. Siegel, the
22 issue of licensure.

23 Now, as many of you know I'm sure, there
24 has been a definite causal association demonstrated
25 between alpha emitters and human cancers. I mean,

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1 there's the historically famous radium dial painters
2 who ingested radium-226 in luminescent paint used to
3 paint luminescent watch dials. And they developed a
4 very high incidence of bone cancer.

5 Thorotrast patients. Thorium-232 was used
6 in the form of a thorium oxide colloid as a
7 radiographic contrast agent. Because it was a colloid
8 there was extensive localization in the liver as well
9 as in the RES system of the bone marrow, so they
10 developed high incidences of both liver and leukemia.
11 And ankylosing spondylitis patients were treated with
12 radium-224 and developed high incidences of bone and
13 leukemia.

14 So there's no doubt that alpha emitters in
15 sufficiently high radiation doses will cause human
16 cancer. The question that I asked and was answered was
17 had there been any secondary malignancies, in
18 particular bone or leukemias which would be the most
19 at-risk human cancers, if any, associated with radium-
20 223 chloride, have any been observed to date. And we
21 heard that there have been none. Not only no bone
22 leukemias, bone cancer leukemias, but no secondary
23 malignancies of any sort.

24 And frankly, the issue as to whether
25 radium-223, radium-223 chloride is or is not

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1 carcinogenic in man is likely moot given the very
2 short life expectancy of castrate-resistant prostate
3 cancer patients. As we saw, untreated patients or
4 patients receiving placebo have a median life
5 expectancy of less than a year, and even with the
6 survival advantage of Alpharadin it's only slightly
7 more than a year. Based on the foregoing historical
8 studies the latent period for even alpha-induced
9 cancer is probably of the order of many years with
10 peak incidences approaching a decade. So this is
11 unlikely a practical consideration, but it's worth at
12 least raising theoretically.

13 The question of calibration of the
14 administered activities. I think all of us in nuclear
15 medicine and in medicine clinically are uneasy, let me
16 put it that way, with not confirming in some fashion
17 the administered activity of a therapeutic agent to an
18 individual patient. That is not placing the dose in a
19 dose calibrator and verifying with our own eyeballs
20 that it's what we anticipate or what we're prescribing
21 to inject.

22 We understand from Bayer with their
23 excellent safety record that there's been no instances
24 of misadministrations or inappropriate administered
25 activities, but as we all know from all human

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endeavors mistakes happen. They happen at the manufacturing site, they happen at the administration site. And another level of safety with calibration or assay of the activity at the point of administration just seems prudent, especially given that this is a therapeutic agent and an agent which unlike diagnostic agents the safety margin in terms of the radiation dose to at-risk tissues below the threshold for significant deterministic effects is not of the order of magnitude, but is of the order of maybe two- to threefold. So even a relatively small error in administered activity can cross the threshold from subtoxic to acutely toxic.

So, although dose calibrators do not have a radium-223 setting there are many radiopharmaceuticals that we use dose calibrators to assay which have no such setting and it's not a difficult issue. I think of when Metastron was first introduced and there was no such thing for strontium-89 and there was a very straightforward procedure using a precalibrated activity to calibrate one's dose calibrator.

It's -- radium-223 is in secular equilibrium with its daughters, so even though it has a complex decay scheme it would seem that a NIST-

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1 traceable standard could be formulated and distributed
2 to sites for an initial calibration of their
3 instrumentation.

4 The point that was made by Bayer is very
5 well taken, namely that the activities involved are so
6 low, typically 95 microcuries in total, that you're
7 approaching the range of activities where dose
8 calibrators are simply not very accurate. Typically
9 they're used to measure activities of millicuries,
10 perhaps as low as hundreds of microcuries. So are we
11 potentially introducing an artifactual measurement by
12 trying to measure activities in dose calibrators at
13 which they are not optimally accurate?

14 It's a point well taken but I think it's
15 still worth considering the possibility of eliminating
16 the catastrophic misadministration by a grossly
17 miscalibrated product, even if one is not attempting
18 to precisely measure what was administered as the
19 difference between the pre-injection syringe activity
20 and the residual activity.

21 Finally, with the issue of licensure,
22 should there be any special credentialing required for
23 radium-223, radium chloride, or really any parenteral
24 alpha emitters? And I agree with the Bayer folks that
25 35.300 applies and should apply. The credentialing

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1 options then become 390 Cat 3, or 390 Cat 4, or as was
2 I think -- is being considered in a pre-rulemaking, a
3 new category for alpha emitters, or possibly 1000 with
4 a licensing amendment.

5 My personal opinion or recommendation
6 would be that it should be under Cat 3. I mean, I
7 think from a clinical perspective there's nothing
8 fundamentally different in terms of clinical
9 administration, clinical indications, clinical
10 sequelae between unsealed alpha emitters versus
11 unsealed beta emitters. And I think any authorized
12 user who's currently authorized, currently experienced
13 and knowledgeable in using Cat 3 radiopharmaceuticals
14 for therapy is automatically equally well qualified to
15 use unsealed alpha emitters such as Alpharadin.

16 And the issue of whether -- are AUs
17 already satisfying the 3-case requirement, whether
18 they should be grandfathered, well, based on what I
19 just said I think that should be the case as well. I
20 think such users have demonstrated the necessary
21 training, experience, et cetera, et cetera in using
22 such agents.

23 And the final two slides are simply the
24 abbreviations and acronyms. And I'd be happy to take
25 any questions.

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1 ACTING CHAIR THOMADSEN: Thank you, Dr.
2 Zanzonico. Are there questions from the committee? Dr.
3 Langhorst.

4 MEMBER LANGHORST: As I said, we had used
5 Alphasadin at Washington University in St. Louis. And
6 I was very skeptical at first too on what is it going
7 to take to survey for this alpha emitter and what kind
8 of additional safety issues will we have to put into
9 place.

10 And as it turned out, with -- there's an
11 abundance of beta particles that makes it very easy
12 for us to use our normal GM survey meters to look for
13 contamination of this. And our biggest challenge in
14 this whole use was in the double-blind study. And I
15 told them radiation safety can't be blinded as to
16 whether this is a placebo or a radioactive material.
17 So that was one thing we had to work out to make sure
18 that our doctors remained blinded as far as their use
19 goes. So, I agree with you, Pat, that it should be 390
20 and it should be that Category 3.

21 There's no additional security or safety
22 issues as far as survey and so on. There is the added
23 perspective that yes, this is an alpha emitter, and
24 there is some additional precautions that you tell the
25 workers about, but it's really not much different than

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1 any other radiopharmaceutical. And so I strongly urge
2 that that be the category it's used in.

3 ACTING CHAIR THOMADSEN: Dr. Suleiman?

4 MEMBER SULEIMAN: Thanks, Pat, a really
5 nice presentation. I too have real concerns about
6 calibration. Dose calibrators may have settings but
7 they don't mean they're calibrated. It means that
8 they've provided that setting so they can establish a
9 calibration traceable to a national standard. People
10 are just not aware of this. And I would clearly think
11 it would be important to have a quality check onsite
12 because mistakes happen. We've had examples where the
13 user has identified a problem with a product that the
14 manufacturer was unaware of. So, mistakes happen, they
15 should be accepted as routine life. And I think to
16 dial the end user out of the formula here would be a
17 mistake.

18 ACTING CHAIR THOMADSEN: You also have
19 cases where somebody's picked up the wrong syringe,
20 and you had identified that it was the wrong syringe
21 for that. Dr. Guiberteau?

22 MEMBER GUIBERTEAU: I have the same concern
23 as Orhan and Pat. And I just wanted to ask Sue from
24 her experience, your experience with calibrating these
25 tests.

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1 MEMBER LANGHORST: We used the unit dose.
2 We had it drawn up at a local pharmacy and they just
3 administered the dosage. But I would think that there
4 would be other alternatives that you could use that
5 could be calibrated in a way to meet the concern
6 outside of a dose calibrator because the activities
7 are so low.

8 MEMBER ZANZONICO: I think it's worth
9 noting, I mean the places where at least some of the
10 clinical trials were done were Washington University,
11 Johns Hopkins, Sloan-Kettering. These are not the only
12 places that are going to be using it obviously when
13 it's on the market. I mean, those, like many large
14 academic facilities, the staff is very fastidious and
15 very careful. And I think one has to project when
16 materials such as this are going to be used more
17 generally where there may not be quite the care with
18 the staff to minimize errors.

19 ACTING CHAIR THOMADSEN: Dr. Palestro.

20 MEMBER PALESTRO: Yes, I would just echo
21 Orhan's and Dr. Guiberteau's sentiments over
22 calibration, that I think it would be very important
23 to at least have the ability to calibrate.

24 ACTING CHAIR THOMADSEN: Thank you very
25 much. Does the NRC staff have questions for Dr.

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1 Zanzonico?

2 MR. EINBERG: Does the medical team have
3 anything at this time?

4 MR. FULLER: I've got a couple of
5 questions. First of all, and I think I've heard a
6 number of folks on the committee advocate for 35.300
7 Category 3. But I guess what I would like to know, or
8 like to hear more about is if we do that and there may
9 be an exception, but to my knowledge it would be the
10 first time that we ever authorized something new,
11 especially therapeutic, and we didn't require a
12 minimum of three cases for a training experience. So
13 I'd like to hear more about why this would be the
14 exception to that practice. It's not a policy, but
15 that's what we've historically done. And then also
16 would like to hear the committee's perspective on what
17 precedents that might set. So I'd like to hear that.

18 And then also I want to hear more about
19 the dose, the calibration of the dose by those who are
20 not sort of our large medical broad scope licensees.
21 Because the way I understand the rules now if we go
22 with 35.300 then if someone received a unit dose from
23 a manufacturer then there would be no requirement for
24 this dose being, or this dosage being assayed by the
25 person who's administering it. And I want to know if

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1 the committee feels comfortable with that in all
2 cases, or if in fact we need to consider a requirement
3 that unit doses, or a licensing condition that unit
4 doses be calibrated, or the calibration be done. So
5 I'd like to hear what the committee, I mean yes, what
6 the ACMUI thinks about that.

7 MEMBER ZANZONICO: Well, if I may, I'll
8 take a stab at those two questions. I mean, I
9 appreciate the prevailing practice of requiring three
10 cases for new therapeutic agents, or new agents, but
11 frankly I don't entirely understand the rationale. To
12 me there is nothing fundamentally different about a
13 parenterally administered alpha emitter than
14 parenterally administered I-131 sodium iodide or any
15 such thing as that. There's a risk potentially of
16 myelosuppression and other side effects, and
17 physicians who have managed, who have administered
18 such agents in the past and have managed patients
19 receiving such agents are already qualified by
20 training and experience and temperament so to speak to
21 safely administer these agents, to perform the
22 necessary calculations and to manage patients
23 appropriately.

24 I just don't see a compelling advantage to
25 requiring patients already so trained and so

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1 experienced in -- to undergo three additional cases.
2 I mean, I just think they have the demonstrated
3 training, experience, and so forth in essentially
4 identical procedures.

5 The issue of calibration is, again, when I
6 showed that table with the doses, the normal organ
7 doses were of the order of many tens of rads to
8 hundreds of rads. So for example, the red marrow dose,
9 the mean red marrow dose was of the order of 50
10 centigray per the therapeutic administration. That's
11 less than a factor of 10 than what's normally
12 considered -- 10 below what's normally considered the
13 tolerance dose for red marrow.

14 At Sloan-Kettering, for example, we use a
15 200 rad dose to blood as the maximum permissible dose
16 for treating metastatic thyroid cancer patients with
17 I-131 sodium iodide. That's probably a little
18 conservative, but the point is it's only one-quarter
19 of this 50 rad dose. So, a relatively small error at
20 some point in the manufacturing and dispensing step
21 means you can cross that threshold from, as I said, a
22 subtoxic dose to an acutely toxic dose.

23 That's not the case for a diagnostic
24 radiopharmaceutical. So even if one made a gross error
25 with a diagnostic radiopharmaceutical it will still be

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1 well -- probably still an order to several orders of
2 magnitude below a threshold dose. I think given that,
3 some independent verification of the administered
4 activity just seems prudent in this case. And that's
5 my opinion.

6 ACTING CHAIR THOMADSEN: Dr. Guiberteau?

7 MEMBER GUIBERTEAU: I would very much agree
8 with that. I think in terms of the safety culture that
9 we are -- that we've instituted in nuclear medicine,
10 nuclear radiology, that you know, there is something a
11 little bit unsettling about just taking a syringe that
12 you haven't verified, particularly in a therapeutic
13 agent, and injecting it into a patient. And given the
14 heterogeneity of practices doing this you have various
15 levels of sophistication. As Orhan was saying, you see
16 a button, you press the button and you presume it's
17 going to measure whatever radiopharmaceutical is on
18 the button, and that's not the case.

19 So, I mean, I think there are issues here.
20 I'm not proposing any particular solution, but I think
21 there are issues here that need to be carefully
22 considered. And maybe part of this would be education
23 rather than regulation and guidance. But I think in my
24 mind there are definite issues here that relate to the
25 safety culture.

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1 ACTING CHAIR THOMADSEN: Thank you very
2 much. Dr. Langhorst?

3 MEMBER LANGHORST: I wanted to remind the
4 committee, I think it was in Dr. Merten's slides. And
5 I don't see a slide number, but it was the one on
6 dosing at administration talking about dose calibrator
7 not required. He mentions about instruments other than
8 a dose calibrator such as a calibrated survey meter
9 can be used for this purpose. And I would hope that
10 the folks at Bayer would provide that kind of
11 instruction for alternative ways to make this assay to
12 prevent that gross misadministration of the wrong
13 activity.

14 DR. MERTEN: So this is Erik Merten. I can
15 confirm that we will provide these data. It's not yet
16 available but we are making respective measurements in
17 the future.

18 MR. FULLER: We can't hear you if you don't
19 speak into the microphone.

20 MEMBER LANGHORST: It's on, you just have
21 to talk a little bit louder.

22 ACTING CHAIR THOMADSEN: And directly into
23 it.

24 DR. MERTEN: Okay. So I can confirm that we
25 will provide this data on calibrated studies.

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1 ACTING CHAIR THOMADSEN: Thank you very
2 much. Mr. Mattmuller.

3 MEMBER MATTMULLER: I have a couple of
4 comments, clarification and a couple of questions.
5 One, it's been already recognized that Dr. Welsh has
6 been in the forefront in talking about this in 2009. I
7 think we should also recognize that of course Dr. Howe
8 was also in the forefront and she discussed this issue
9 in 2009 too. So we can't get anything past her, just
10 as a reminder.

11 (Laughter)

12 MEMBER MATTMULLER: One clarification. The
13 dose is 95 microcuries and I believe in the Bayer
14 presentation they have millicuries, so that's --

15 ACTING CHAIR THOMADSEN: They corrected it.

16 MEMBER MATTMULLER: I'm sorry.

17 ACTING CHAIR THOMADSEN: That was a mistake
18 that they --

19 MEMBER MATTMULLER: Okay, just to make sure
20 that's clear in case someone looks at that in the
21 future.

22 And so a question for the staff and a
23 question for the clients would be -- or first for the
24 staff would be the first bone therapeutic agent was
25 Metastron, was approved. And then a year or two later

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1 the Quadramet agent was approved, both for their beta
2 emission. Was there a requirement for three case
3 studies for someone who was interested in using
4 Quadramet before they could be licensed to use it? If
5 they had prior experience with Metastron.

6 DR. HOWE: I think we considered it in
7 groups. And so if it was similar then your prior three
8 cases would count. And if it was greatly different
9 then you needed three cases.

10 MEMBER MATTMULLER: Okay. And then my other
11 question, general question would be if I'm following
12 the side effect profile accurately it seems to be
13 dramatically improved versus Metastron or Quadramet in
14 terms of hematopoietic -- so, it seems to me a win-win
15 in that you have a therapeutic effect and fewer side
16 effects than currently approved radiopharmaceuticals.
17 Given the fact that it's different indications, but
18 still an improved side effect profile. Is that true?

19 MEMBER WELSH: Jim Welsh. I would agree
20 with that statement. And although it hasn't been
21 conclusively proven yet I think there's very strong,
22 strong evidence to suggest that this is going to be
23 the case. And that strong evidence is in the form of
24 combination with chemotherapy which has been a very,
25 very practical hurdle for many of the

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1 radiopharmaceuticals in the past.

2 Maybe the strontium-89 was a bit more
3 difficult than the samarium-153 but with this
4 particular agent I think it was wise of the companies
5 to investigate combinations with chemotherapy early on
6 because that proves -- it answers the questions that
7 many clinicians such as myself will have to wrestle
8 with. It's great to have the answer up front. And that
9 answer which is the toxicity is not greatly increased
10 and it does not preclude the use of appropriate
11 chemotherapy argues that the dose to the marrow is
12 sufficiently low that this is not going to be the
13 hurdle that some anticipated it might be.

14 ACTING CHAIR THOMADSEN: Thank you very
15 much, Dr. Welsh. Other questions, comments from the
16 committee? Dr. Guiberteau.

17 MEMBER GUIBERTEAU: I have a question of
18 Mike Fuller. I'm just wondering if you could, in terms
19 of the issue of expanded rulemaking in Part 35
20 category for alpha emitters, what is the staff
21 rationale for that?

22 MR. FULLER: I'm going to turn that over to
23 the member of the working group that's been working on
24 crafting that language and see if she can answer it a
25 little better than I.

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1 DR. HOWE: I guess our rationale was that
2 we believe that there were different considerations
3 for different kinds of radiopharmaceuticals and their
4 use as primarily a beta emitter or a gamma emitter or
5 an alpha emitter. And that we felt that the authorized
6 users in the facilities needed to make sure that they
7 understood the differences between those kinds of
8 emissions for which the pharmaceutical was being used.

9 ACTING CHAIR THOMADSEN: Thank you very
10 much, Dr. Howe. I think we have two comments from the
11 general public. If you could identify yourself,
12 please.

13 DR. SIEGEL: Thanks very much, Vice
14 Chairman Thomadsen. My name is Jeff Siegel. I just
15 wanted to reinforce what Erik Merten said about dose
16 calibrator quality control and calibration. Not only
17 has the company done it -- did it, but so has NIST.

18 And Brian Zimmerman at NIST has published
19 on calibration correct valve-setting. Only a single
20 valve setting is necessary. It's not volume dependent.
21 This is exactly the same thing as we did in the case
22 of Zevalin. And this would be the same procedure where
23 the pharmacy would send the calibrated source which
24 would be traceable to a NIST-traceable standard. It
25 would come to the facility as a secondary standard

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1 which could then be used through the facility to dial
2 its own setting which is the approved method, and
3 that's exactly what would happen. I just wanted to
4 reinforce that NIST has also done this.

5 ACTING CHAIR THOMADSEN: Thank you very
6 much for that clarification.

7 MS. TOMLINSON: Hi. Cindy Tomlinson from
8 ASTRO. I just have a brief statement that I wanted to
9 read on behalf of ASTRO.

10 We appreciate the opportunity to make this
11 statement on the licensing of radium-223 chloride. We
12 just wanted to say that the actual administration of
13 radium-223 chloride is performed in the same manner as
14 other radionuclides such as samarium-153 or strontium-
15 89 which are both beta emitters, but they are
16 administered over a slow IV push by a qualified
17 authorized user in the outpatient clinic setting. The
18 same radiation safety precautions and post
19 administration radiation survey is performed by the
20 RSO or his or her designee.

21 We believe that those physicians who are
22 certified by the American Board of Radiology for the
23 practice of radiation oncology are qualified to
24 administer therapeutic doses of radium-223 chloride.
25 And to require additional training above and beyond

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1 what is already required would impose undue burden on
2 physicians which will in turn limit patient access to
3 safe and effective treatments.

4 ASTRO believes that the requirements found
5 in Section 35.390 are sufficient for regulating the
6 use of radium-223 chloride. We urge the NRC to revise
7 that section to include alpha particles in addition to
8 the beta- and photon-emitting particles currently
9 recognized.

10 We would have concerns about the NRC
11 licensing radium-223 chloride under a different, more
12 restrictive section of current regulations because
13 physicians would be required to obtain the extra
14 training to use a radionuclide whose route of
15 administration is no different from ones already on
16 the market and would thus limit patient access to this
17 radionuclide.

18 We believe that this and other alpha-
19 emitting agents should be made available with easiest
20 and safest route possible for both the patient and the
21 practitioner.

22 ACTING CHAIR THOMADSEN: Thank you very
23 much. Any further comments from the committee? We have
24 a comment from the staff.

25 MR. FULLER: Well, this is Mike Fuller and

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1 I just want to -- and I think I've asked this question
2 before, but I want to make sure I understand, that
3 everyone else understands that if this is licensed
4 under 35.300 that if a licensee then receives a unit
5 dose there would be no requirement for that to be
6 assayed in a dose calibrator.

7 So I want to make sure that the folks who
8 have used it, if they're comfortable with that
9 situation that under 35.300 if the licensee, the
10 specific licensee receives that unit dose there would
11 be no requirement for that unit dose to be assayed. I
12 want to make sure that the folks are comfortable with
13 that.

14 And then the other thing I'd like to ask
15 for, if everyone on the committee feels like they have
16 enough information that they want to make a
17 recommendation it would be helpful to the staff if we
18 had a recommendation.

19 ACTING CHAIR THOMADSEN: Dr. Langhorst.

20 MEMBER LANGHORST: As far as unit dose and
21 requirement to do a dose calibration on it I am as
22 comfortable with this one as I am with any other
23 radiopharmaceutical.

24 (Laughter)

25 MEMBER LANGHORST: If it's a unit dose it's

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1 not required by NRC regulations. We would probably
2 make a measurement on it, but I am as comfortable as I
3 am with any other radiopharmaceutical. So if you're
4 going to require it of this one it seems like you
5 would need to be requiring it every other
6 radiopharmaceutical and I'm not necessarily
7 recommending that.

8 ACTING CHAIR THOMADSEN: Dr. Suleiman?

9 MEMBER SULEIMAN: I think you should figure
10 out which part of the reg it belongs to, but I think
11 it's important to test the pharmaceutical before you
12 administer it. I mean, you may think it's voluntary
13 but as I've said often, the people at this table are
14 not the ones out there. And so you want to make sure
15 that there are minimum standards to assure patient
16 safety. And mistakes happen. And we've had examples of
17 that where users who are testing discover things that
18 eventually reveal a product problem.

19 ACTING CHAIR THOMADSEN: Dr. Langhorst.

20 MEMBER LANGHORST: But my point is this one
21 shouldn't be singled out. That's my point.

22 ACTING CHAIR THOMADSEN: Point well taken.
23 I would like to make a proposal and that is to address
24 Mr. Fuller's second point as far as a recommendation.
25 Rather than trying to come to a recommendation right

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1 now because there are definite options and
2 ramifications, that we establish a subcommittee to
3 bring back a recommendation to this committee. That
4 the subcommittee report back by June 15th so that
5 there's minimal delay.

6 I would propose that Dr. Zanzonico chair
7 the committee. Members would include Dr. Langhorst,
8 Dr. Welsh, Dr. Palestro, Dr. Suleiman, myself. Ms.
9 Bailey, would you want to be on that committee as
10 representing the -- so, and Ms. Bailey. And Mr.
11 Mattmuller, I think you might have something to say
12 about that. It's a very large subcommittee, I realize
13 that, but then -- oh and myself. Did I say that?

14 (Laughter)

15 ACTING CHAIR THOMADSEN: I expect to do
16 twice the work I guess. If that would -- point of
17 order. Ashley, does the chair just do this or does the
18 committee vote? I've forgotten.

19 MS. COCKERHAM: You have the authority to
20 just do it.

21 ACTING CHAIR THOMADSEN: Okay. Consider it
22 done.

23 (Laughter)

24 MR. EINBERG: Yes, Dr. Thomadsen. I would
25 recommend that also as a staff resource we nominate

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1 Dr. Howe to be a staff resource to the committee, or
2 to the subcommittee. I think that's been useful in
3 previous subcommittees when there is a NRC staff
4 resource available to answer any kind of regulatory
5 questions.

6 ACTING CHAIR THOMADSEN: I am delighted
7 with that. I was going to after the meeting try and
8 figure out how we manage to work that, not knowing how
9 the hybrid subcommittees work. Thank you for the
10 suggestion. So, the committee should be charged to
11 bring back a recommendation on the licensing for alpha
12 emitters, at least this one in particular if not a
13 general class with the rationale behind that. And how
14 to deal with any expected ramifications and
15 precautions.

16 Comments from the committee? Questions?
17 Please, Dr. Guiberteau.

18 MEMBER GUIBERTEAU: Since I can't remember
19 who you appointed exactly.

20 ACTING CHAIR THOMADSEN: Not you.

21 (Laughter)

22 MEMBER GUIBERTEAU: No, that's why I speak
23 -- would there, and I'm not sure whether you appointed
24 the representative from the state.

25 ACTING CHAIR THOMADSEN: I did.

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1 MEMBER GUIBERTEAU: Okay, good.

2 ACTING CHAIR THOMADSEN: I actually asked
3 if she wanted to be on and she indicated that she
4 would. So yes, I did.

5 In that case with no other comments on
6 this topic I would like to thank the staff from Bayer
7 for giving us this very informative presentation and
8 their interactions with us. We appreciate that very
9 much. We will now stand adjourned until 10:30.

10 (Whereupon, the foregoing matter went off
11 the record at 10:05 a.m. and went back on the record
12 at 10:31 a.m.)

13 ACTING CHAIR THOMADSEN: I would ask the
14 committee to take their places and we will resume once
15 again. And Mr. Einberg.

16 MR. EINBERG: Yes, thank you, Dr.
17 Thomadsen. Are we on the record, court reporter? Yes,
18 I'd like to make a clarification. Instead of having
19 Dr. Howe as the staff resource for the subcommittee
20 we're going to put Ashley Cockerham as the staff
21 resource, the lead staff resource to the subcommittee.
22 And she'll call upon other resources within the
23 medical team, Dr. Howe, Sandy Gabriel, and so forth,
24 to confer with if there is a need to do so. So, I just
25 wanted to replace Ashley -- or Dr. Howe with Ashley.

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1 ACTING CHAIR THOMADSEN: Thank you very
2 much. We consider that a friendly change to the
3 motion.

4 And now we are going to spend a little
5 time talking about the strontium/rubidium generator
6 breakthrough issue. There's a change in the order of
7 presentations and we're going to begin with Dr.
8 Suleiman.

9 MEMBER SULEIMAN: Donna-Beth always wants
10 me to lead so I guess I'll start off.

11 This is an update of what is still really
12 an ongoing issue that I thought I'd let you know
13 what's going on. And -- okay. Clearly, opinions I
14 express today and the mention or display of any
15 commercial products is neither an endorsement nor
16 necessarily reflect the official position of the FDA
17 or Department of Health and Human Services.

18 As I said, this is still ongoing and the
19 objective of this presentation is simply to provide an
20 informational update to members of this committee
21 during this public meeting. There's a lot that's gone
22 on behind the scenes and since our last meeting
23 there's additional information that I can share with
24 you.

25 A quick review. In the summer of 2011 two

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1 nuclear medicine patients, one of whom was scanned in
2 Las Vegas, the other one who had undergone a CardioGen
3 scan in Sarasota, Florida, went on vacation, left the
4 country. One drove back into the country, the other
5 one flew back into an airport. And at the border,
6 Department of Homeland Security, their Customs and
7 Border Protection people detected that they had
8 radioactivity.

9 Their protocol from the best I've been
10 able to put the pieces together is then they do a
11 spectral analysis. They actually use a survey meter
12 that is commonly available; it's called an isotope
13 identifier. It's just a handheld survey meter and they
14 collect data on the nuclide because they want to know
15 -- even though they knew these were nuclear medicine
16 patients, they wanted to verify what it was they had.
17 And usually the Customs people at the border make that
18 decision. They'll recognize the nuclide.

19 In this case, they didn't recognize the
20 nuclide and so their protocol is they then send this
21 data to Los Alamos National Lab where there's a group
22 that this is their job because they're looking at far
23 more dangerous things and they want to analyze what
24 the nuclide was. And they nailed it. I mean, these
25 people deserve an award. They not only identified that

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1 this was strontium, part of the rubidium generator,
2 but they came up with estimates that very surprisingly
3 in my opinion were consistent with what happened later
4 on when the patients were whole body counted.

5 They subsequently notified FDA and later
6 on when these two patients which we refer to as index
7 patients, they were whole body counted at Oak Ridge
8 National Labs which also verified that in fact what
9 they had detected were trace elements, quantities of
10 strontium-82 and strontium-85.

11 The two patients -- now understand,
12 rubidium-82 has a half-life of 75 seconds. It's pretty
13 much gone within 15 to 30 minutes. These two patients
14 had been scanned 2 and 4 months previously so they
15 were just as surprised as anybody else to find out
16 that they were radioactive.

17 During this period of time, to share with
18 you the frustrations that we have to deal with, we had
19 some pretty high visibility people making statements
20 that the FDA reacted quickly. They should have
21 consulted with Department of Energy to know what was
22 going on. Well, it was the Department of Energy that
23 contacted the Food and Drug Administration. Different
24 people in DOE were not aware of what other components
25 of DOE were doing.

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1 Bracco eventually met with us in July, but
2 prior to meeting with us in July our field, our Office
3 of Regulatory Affairs conducted inspections of their
4 manufacturing facilities and eventually cited them for
5 numerous GMP, good manufacturing practice, violations.
6 And along with the concern about the contaminated
7 patients they came and they met with us.

8 They recalled the product and very
9 recently the product has been reintroduced and we've
10 allowed it to go back to market. And I'll discuss some
11 of that.

12 Our initial concern, there were two
13 concerns. One was what was the root cause and how
14 widespread was this. I mean, were these two patients
15 that happened to be picked up because they happened to
16 leave the country and got picked up at the border,
17 were they in fact the highest doses that were out
18 there or was it possible we had more patients out
19 there that were contaminated. And rather than get into
20 a debate about how much they had received some of us,
21 myself especially, was concerned well, how high were
22 patients contaminated with even more amounts of
23 radiation. We didn't know.

24 So eventually, and I'll try to go into
25 just a little bit of detail here because this still,

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1 we haven't received all of the reports even now, but
2 basically we contacted the Nuclear Regulatory
3 Commission who in turn contacted the states of Nevada
4 and Florida and said their agreement states, so
5 actually they're handling this. And so we shared our
6 concerns with them. We eventually contacted the
7 Centers for Disease Control who, to assist us in what
8 we considered at that time a potential public health
9 emergency because we didn't know. And they eventually
10 worked with about half a dozen states.

11 So, and the state of Nevada within weeks
12 of meeting with us issued a recall for a number of the
13 patients at these two index sites. These were the two
14 clinical sites where the patients had in fact been
15 scanned, and tested I think about -- screened about
16 204 patients.

17 The short -- let me cut to the quick. We
18 had -- patients had been detected at other sites that
19 had strontium-85. Most of the levels were either at
20 breakthrough or just below, and when you considered
21 the uncertainty we're not too concerned about how much
22 they actually received. We knew that, for logistical
23 reasons we knew that there was a lot of delay in
24 counting the patients. Some of these patients weren't
25 looked at till November, so we're talking about in

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1 excess of 10 half-lives for some of these things.

2 We knew, I knew that we would lose the
3 patients that maybe had breakthrough because by the
4 time they got around to being looked at they would
5 have decayed below, but our major thrust was we were
6 concerned about the patients that received very high
7 doses. And I'm convinced that you could see those
8 patients today if you were to find them. So we -- it
9 was a decision and there was a lot of debate about how
10 do we test these patients quickly.

11 There were privacy issues, there was
12 balking, we can't ask the patients to do this. We
13 initiated a regulatory tool we call Post-Marketing
14 Review where we actually establish two clinical trials
15 which involved IRB, Institutional Review Board,
16 approval. And I argued, I internally argued it's going
17 to take a long time. So the patients had to be asked
18 if they wanted to be tested, they were tested and
19 patients who were -- had suspicious levels of
20 radiation were eventually whole body counted. So the
21 logistics were very challenging.

22 Bottom line though, most of the serious
23 levels that we saw were associated with the two index
24 sites. So the company was correct when they felt that
25 most of the problem focused on these two index sites.

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1 But the other question as we were trying to track down
2 the widespread nature of the contamination was why was
3 this failing in the first place.

4 Eventually, and we still don't have all
5 the information in, but eventually at least three
6 patients, at least three patients who had been whole
7 body counted exceeded the 50 millisievert medical
8 event criteria of the NRC. And this didn't include the
9 two index patients, by the way. They came in, the
10 higher one came in with a 49 millisievert criteria.

11 What were our challenges? First was
12 scientific. I mean, I always focus on what do we have
13 some numbers on. The generator issues. What was wrong
14 with the generator? We discussed with the company.
15 They said the sites caused the problem. We agreed. We
16 said if they had been doing breakthrough testing they
17 would have identified that the patients were receiving
18 higher-than-permissible levels of the strontium-82 and
19 -85. But why were these generators failing in the
20 first place? What were the sites doing that caused the
21 generator to fail in the first place? There was the
22 challenge of detecting the strontium in the patients.
23 There's a lot of history and information on strontium-
24 90 which is decades old, but strontium is an element
25 so it's going to behave the same way chemically. But

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1 in terms of detecting the 82 and the 85 this was new
2 territory. And talking with some of the Oak Ridge
3 scientists, some of us feel we missed a real
4 opportunity in not tracking some of these patients in
5 terms of biodistribution and clearance. It would have
6 been very, very useful scientific information as well.

7 And the other challenge that some of us
8 were concerned about from the very beginning and is
9 still an issue that is still very much in the air, and
10 we discussed it a bit in the last session, are the
11 dose calibrator and the infusion system. There were
12 some real logistical challenges. Even before FDA got
13 involved, even before headquarters got involved, our
14 field got involved. The Customs, Border and Homeland
15 Security. I mean, they -- when people talk about they
16 can't detect certain things, they did a phenomenal job
17 here because strontium-82 and -85 is not on your
18 standard book of nuclides. And so they were able to
19 identify it and then report it to our FDA response
20 group in the field who -- and it worked its way up the
21 system. So, considering the patients had been scanned
22 in February and late March or early April, and our
23 field was involved before July and eventually the
24 company met with us in July. So in a matter of a few
25 months the bureaucracy worked although it wasn't

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1 exactly as quick as you would have liked. We had
2 issues with coordinating with the company, with other
3 federal agencies, with the states.

4 And last but clearly very important were
5 regulatory issues. We had different statutes. We were
6 not sure who had which responsibilities. We had
7 different jurisdictions. And so that played into how
8 we responded and why we did what we did.

9 Now, this is a professionally very
10 satisfying but frustrating slide for me because
11 internally we had this discussion. Yes, the radiation
12 doses were much higher than necessary, but were they
13 unsafe? Now, the first line there is your rubidium-82.
14 Using the Bracco package insert, the organ dose table
15 of 23 years ago, the patient, if they receive a 75
16 millicurie dose of rubidium would get about 1.2
17 millisievert. So this is a low dose cardiac imaging
18 procedure.

19 The red is the strontium with the
20 breakthrough. We had documented that at least one
21 patient and eventually a couple more exceeded the 50
22 millisievert, you know, medical event criteria which
23 does not apply to FDA. We were more concerned about
24 the breakthrough limits. I'll get into that. But the
25 question mark was, was there more serious

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1 contamination out there. Was this much more widespread
2 than it was. Also, we had people saying there's never
3 been a problem with this, why has this emerged now,
4 and there are others that said well, maybe we didn't
5 have the Border Patrol testing patients as they come
6 in. So there's a real question out there whether this,
7 you know, this could have been happening
8 intermittently over the years and nobody ever picked
9 it up.

10 I throw in some other cardiac imaging
11 agents just for reference. And you can see the tech-99
12 is about an order of magnitude higher than the
13 properly administered rubidium dose. You hear thallium
14 thrown out a lot because that's considered a higher
15 dose procedure, 41 millisievert. And one of the
16 frustrating things to me was when we met with the
17 company, a colleague, a physicist who's nationally
18 known, you know, made the argument that it's no
19 different than a thallium scan. And I said that's --
20 this is not a discussion about doses from different
21 procedures. I said this product was giving 40 times
22 the labeled dose. This product had a level of impurity
23 that was 100 times greater than was expected. That was
24 our concern.

25 I throw in fluoro- and CT angiography, and

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1 I throw in the occupational limit just for
2 perspective. So, there was some real -- I had no
3 trouble. I've been trained in the ALARA so this was
4 clearly higher than necessary. But we had people
5 saying is this really a safety issue.

6 FDA considered this a drug purity issue
7 and we also realized it was an end user issue. Now,
8 just the numbers. I think last time I may have
9 mentioned these but I didn't have it in the slide. The
10 breakthrough amounts for strontium-85 and -82 should
11 have been 15 microcuries for the 85 and 1.5 for the
12 82. One of the index patients received 7 and 125
13 times the allowable breakthrough. So there was no
14 doubt that there was a problem here. We weren't seeing
15 breakthrough often but why were these patients getting
16 so much higher.

17 And the Nevada testing, and I think Nevada
18 reported it as a medical event criteria. They tested
19 204 patients. We asked them two things as they were
20 lining up the patients to be tested. And one was could
21 we get them to do urinalysis, and they really at that
22 point pulled back on that. And that's a side story
23 that I won't discuss here.

24 But the second thing was could you get
25 your index patient to be scanned with your testing

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1 protocol. We had a walking calibration source, you
2 know. So you talk about calibration but ultimately the
3 individual that was the most important was the index
4 patient who was scanned there who had been sent to Oak
5 Ridge and had actually been now certified. You know,
6 maybe not traceable to NIST but at least traceable to
7 Oak Ridge National Laboratory as a calibration source.
8 He really was the key to the Nevada testing.

9 The other thing that happened at this
10 time, we were not sure whether we could -- how much we
11 could detect in patients. And the state of Nevada to
12 their credit because they moved within weeks of our
13 meeting developed an on-the-fly protocol. They had a
14 survey meter. They actually used an isotope identifier
15 which is the same type of instrumentation that Customs
16 Border uses which does spectral analysis. And after
17 doing some testing and getting some experience they
18 said don't bother with the survey meter, it won't
19 necessarily pick up, but the isotope identifier,
20 because it could tune into the spectra of the nuclide,
21 was far more sensitive.

22 In fact, I'll give you some actual
23 numbers. They had a portal detector that the patients
24 walked through and as we were looking at some of the
25 data, they shared the data with us early. They said

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1 how come that's not being triggered. Remember now,
2 this is what triggered at the Border Patrol whereas
3 with their isotope identifier they were really
4 detecting quite a bit of activity in patients. And I
5 said well, your spectral detector has got a very small
6 window and the signal to noise is pretty high whereas
7 the portal detector had a much broader. And so if you
8 looked at the index patient and if you look at the
9 index patient the portal detector showed that he had a
10 17 percent increase in activity. So if you actually
11 look at the raw data you could see there was an
12 increase. The isotope identifier actually showed that
13 he had 32 times background level.

14 So, later on we got into some
15 disagreements where people thought double background
16 was the standard. I said that's really absurd because
17 it depends on -- I said look at your index patient.
18 He's only seeing 17 percent of background with this
19 set of instrumentation and yet he's being, he's coming
20 through as 32 times background. So don't throw double
21 background as a standard. It really depends on the
22 detector, the geometry, and so on. So these are some
23 details I just wanted to share with you.

24 The effective dose was 49 millisieverts.
25 And I'll show that you can use different dose

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1 coefficients and change those numbers as well. But
2 again, FDA was less concerned with the actual
3 estimated dose. We were concerned about the
4 impurities. But I know that -- I knew that the medical
5 event criteria was important for the NRC or the
6 agreement states.

7 Now, this is what we had presented back in
8 September, 3 or 4 millisieverts from the rubidium
9 scan. Going back to the actual Bracco package insert
10 label that's what you should receive if you undergo in
11 this case a 75 millicurie administered activity.

12 The dose coefficients that were used by
13 the Bracco consultant were ICRP and I think they used
14 OLINDA and so we got an effective dose which is a
15 different metric which most of you are aware of of 4.8
16 millisieverts. And fortunately, and this is now in the
17 new label, and it was kind of surprising to me that I
18 had to insist on it. But this was work that was
19 published in 2010 and 2011 by Senthamizhchelvan -- I
20 hope I pronounced his name right -- and colleagues at
21 Johns Hopkins. The study was funded by Bracco and so
22 they did two nice studies where they actually showed
23 organ doses for resting phase and then another one for
24 distress phase. And so that's now in the new Bracco
25 insert. But depending on which set of dose

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1 coefficients you use you can change the numbers as
2 well. So sometimes when you talk about how you're
3 estimating doses clearly there needs to be some
4 standardization.

5 This question came up several times and I
6 have to admit very pleasantly my supervisor, who's not
7 trained in radiation, said, "Orhan, what if they
8 receive the legal limit of breakthrough? How much
9 radiation would they get?" So it looks like very
10 quickly that -- and we don't know this for a fact, but
11 the yellow is the Bracco package insert organ dose
12 table. And if they get breakthrough limits they'll get
13 about a 50 percent higher dose. I suspect that when
14 they set the breakthrough limits 23 years ago they
15 said let's set it so the patient won't get more than
16 50 percent.

17 The reason it's 58 percent I think is just
18 rounding figures. I think they went with 0.2 and 0.02
19 per millicurie instead of having to say 0.217
20 whatever. And it looks to me that they decided to try
21 to partition the dose equally, though 0.2 and 0.5 are
22 not quite. But I think they decided to allow equal
23 contribution.

24 If you calculate effective dose the whole
25 body dose is 4.8 but the strontium doses are still

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1 about the same quantity but relative to 4.8 are only a
2 15 percent increase. I didn't want to bother you with
3 all the different organs, but if you look at the
4 rubidium table, the kidney receives the highest dose.
5 So with contamination the kidney only gets another 2
6 percent additional dose, 24 millisieverts plus 0.4
7 from those 82 and the 85. If you look at the bone
8 marrow which is the organ that gets the highest dose
9 from the strontium you get a 200 percent increase in
10 dose because from the rubidium you'd only get 1.1 but
11 from the strontiums you get another 2.2, 1.3 plus 0.9.
12 So, when we talk about dose it means different things.

13 I mean, bottom line, these patients were
14 getting much more than they were supposed to. And
15 somebody said well, could FDA change the breakthrough
16 limit? No, we don't change the breakthrough limit.
17 The companies come in, they propose what they're going
18 to do and if they wanted to set this breakthrough
19 limit higher or lower they can do that. So it's not
20 like we can go back and re-tweak them.

21 Now, what was the problem? Some testing
22 was done and it appeared that the critical factor was
23 generator volume. Cumulative volume was a more
24 accurate predictor of breakthrough than time. We've
25 now changed the expiration date from 28 days to 42

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1 days, but we've added volume limit to the label. And
2 the new label reflects this change.

3 Yesterday, when Dr. Welsh was talking
4 about the written directive and how people outside
5 this community don't know what it means. Well, I think
6 it was Donna-Beth who said, "Orhan, FDA people know
7 what a black box warning is, but people in the
8 radiation community may not know what they are." Well,
9 a black box warning, for those of you who aren't
10 aware, is the highest alert level that FDA can impose
11 on a label. Companies usually don't like it on there
12 for -- because people perceive that the drug is more
13 problematic. It doesn't show that the drug is riskier,
14 it just says you need to make sure you follow these
15 instructions. The new label has an FDA black box
16 warning on it.

17 And it all evolves around the expiration
18 of the generator. Time was less of an issue so we've
19 increased the time expiration from 28 to 42 days.
20 We've now added a 17 liter -- when a total volume of
21 17 liters is met you stop using the generator. It has
22 expired. At 14 liters you start conducting
23 breakthrough testing twice daily. This is like your
24 home water cartridge on your refrigerator. After a
25 certain volume it just doesn't work anymore.

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1 They also, Bracco also proposed lowering
2 their breakthrough limit by 50 percent. So the old
3 breakthrough limit was 0.02. And I apologize for using
4 the microcuries but this thing got so confusing at
5 least for me going from breakthrough limits old and
6 new, going to alert limits, going to the different
7 values for strontium-82 and -85, the last thing I want
8 to do was go back and forth between SI and
9 microcuries. So I apologize because I'm a big advocate
10 of SI but in this case I didn't want to waste any more
11 time on that. So, the breakthrough limits went from
12 0.02 to 0.01 for the 82 and 0.2 to 0.1.

13 They have also -- Bracco now has
14 introduced a new concept called alert limits. So they
15 say we want them to pay extra special attention at an
16 even lower volume. So, the reason I -- there was a
17 change in your handout was Donna-Beth caught the fact
18 that I had said one-tenth. It's one-fifth. The new
19 breakthrough limit is one-tenth. The old breakthrough
20 limit is what the point is, it's now 0.002 microcuries
21 per millicurie rubidium-82 and 0.02 for the strontium-
22 85. And Dr. Zanzonico was saying dose calibrators
23 aren't very good down very, very low. Well, you're
24 absolutely correct.

25 Why did FDA allow the product back on the

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1 market? It's a medical product that's used out there.
2 There was concern that we get this back to market as
3 long as it was safe. We felt that the label
4 restrictions were sufficient to ensure the product
5 safety if used properly. We felt there was enough
6 visibility, there was an effort to educate the users.
7 We had a lot of concern within FDA about end user
8 issues, but we also realized they were beyond our
9 jurisdiction. And so that's where we didn't do the
10 things -- we couldn't do the things that maybe we
11 thought were necessary, and we weren't exactly sure
12 what was necessary either.

13 We did question -- I questioned the
14 company personally the very first time we met in terms
15 of the accuracy of their dose calibration infusion
16 system. I've had people from NIST read the label and
17 hey, they're not calibrating this. And so anybody who
18 questions my statements, I would just invite you to
19 read the label three times, because it took me at
20 least that many times to understand it. It was a
21 little bit confusing.

22 I was more concerned about what we're
23 giving patients. And I've argued that actually
24 internally you're all part of large institutions, and
25 you're all advocates for different causes, then you

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1 come out with policy. But I've argued we need to make
2 sure that we know what we're giving patients. And so
3 when they say they're giving 30 or 50 millicuries of
4 rubidium we need to make sure that that's accurate.

5 And I'll share this with the committee.
6 Donna-Beth was focused at that point on the
7 breakthrough. You know, we're sort of covering
8 different extremes of the detector. I was less
9 concerned about it. I was more concerned about what
10 the patient was getting. But clearly the detectability
11 came into play in a more dramatic fashion a little bit
12 later on.

13 FDA is closely monitoring the
14 reintroduction of the product. The company is
15 reporting to us on a regular basis. Even though the
16 product has been reintroduced we are raising more
17 questions as we're getting, observing what's
18 happening. And we expect that things, this is far from
19 over.

20 And one question I pose, I figured it was
21 worth a slide, is if you go through the math -- and
22 it's a little bit of a confusing system. You have a
23 dose calibrator. You're supposed to measure the
24 activity there. And then you -- that's perceived as
25 truth, all right. I think the label says it's

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1 traceable with a cobalt source. That's how it's
2 calibrated, with a cobalt source, even though there
3 are now PET sources out there that are traceable to
4 this. And then the infusion system actually has a
5 separate radiation-measuring device. And they
6 basically take that measurement and relate it to
7 whatever the dose calibrator measurement. So that's
8 the extent of their calibration. They need an infusion
9 system because the product decays away very, very
10 rapidly.

11 And their label says they administer
12 either 30 minimum or maximum 60 millicurie per
13 administration. They'll do two administrations for
14 stress and rest. But the infusion system also will
15 deliver either 50 milliliter minimum or 100 milliliter
16 maximum volume. So, the question right now is can you
17 detect 0.06 microcuries of activity. And the question
18 came up again at the break what's minimum detectable
19 activity.

20 Well, for those of us who've measured
21 radiation you also need to know what's the background
22 level which may vary in a clinic, and how long do you
23 want to count which may affect your statistics. So
24 there's not a simple, you know, answer.

25 Now, I thought about this but I felt I

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1 need to share with you exactly how the strontium is
2 detected. I wish I had some pictures, but basically
3 the things that concern me the most and have been
4 voiced to the company, but the company makes its own
5 decisions and we've allowed them so far. But the label
6 instructions are 23 years old. You couldn't have a
7 multi-channel analyzer in a clinic. But today you've
8 got survey meters that have spectral analytical
9 capabilities which were used at the border to identify
10 the spectra. Not rubidium, not strontium are detected,
11 are validated directly. The activity is measured in
12 this dose calibrator. And so you don't exactly know
13 what the distribution is.

14 One of the things they do is when the
15 company receives the strontium for packing in for the
16 generator the strontium -- strontium-82 is your
17 precursor, is your parent for the rubidium-82, but you
18 get strontium-85 as well. So, at the supplier the
19 producer actually does a measurement and provides them
20 with the -- what's called a strontium 85:82 ratio. And
21 typically it's like -- so it's about 50/50. And the
22 company also has on the label because the strontium-85
23 has a 65-day half-life and the -82 has a 25-day half-
24 life so they differentially decay. And so at any given
25 point you can determine what the ratio is supposed to

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1 be. So, this is important in calculating the different
2 ratios.

3 What they do is they'll take -- they'll
4 measure the activity of the rubidium and then they'll
5 let it wait, they'll let that sample wait for an hour
6 to allow the eluted rubidium to decay away completely,
7 okay? At that point if there's no strontium
8 contamination you should have zero activity in that
9 solution. They measure the activity and they assume
10 that the activity that's been detected is all
11 rubidium-82. And they also assume that that is the
12 same amount of strontium-82 because after 10 minutes
13 once you've eluted the -- once the old rubidium decays
14 away it only takes 10 minutes for the strontium-82 to
15 generate new rubidium-82, and then at that point it's
16 what we call secular equilibrium.

17 At that point, at 10 minutes what is
18 detected in the patients is what you'll detect in a
19 few hours. I mean, they've reached equilibrium. So,
20 they wait a whole hour. And so what they detected in
21 activity they're assuming is rubidium and they're
22 assuming a lot of strontium-82. They then determine
23 the 85 going back to this ratio. So, if anybody's done
24 any radiation measurement or detection you can see
25 where this is not the best method today, 2012.

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1 Many stakeholders are aware of these
2 concerns regarding the accuracy, the detectability of
3 the dose calibrator and the infusion system. We're
4 aware of it. I think FDA is sort of at the point where
5 we have less regulatory authority over this right now
6 than some of the other agencies. Industry, not only
7 Bracco, but I know the dose calibration companies,
8 Biodex, Capintec, they've all been discussing this.
9 You know, we had somebody accuse us, they said how did
10 FDA let this label go out. I said well, we addressed
11 the things we knew were our concern and some of the
12 things we probably need to re-address. This is far,
13 you know, far from over.

14 And I think the clinical sites. We do a
15 lot about qualifying people but it bothers me
16 immensely because some of the stories that have come
17 out. Nevada tested patients but Florida went in
18 because the Florida people told me, hey. They said we
19 have licensed technologists. If they get breakthrough
20 they're supposed to report it to us. So, they
21 immediately went in and shared a year's worth of
22 breakthrough testing from a number of facilities.

23 And you hear stories that they were
24 pushing the millicurie button when they were supposed
25 to be using the microcurie button for testing for the

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1 breakthrough limits. I think any professional who's
2 going to use any equipment, because I do this myself
3 when I encounter something I've never had experience
4 with, I make sure I know how to operate it. I make
5 sure I know what it means. And that's what
6 professional -- that's supposed to be the definition
7 of a professional.

8 So we have sites pushing buttons,
9 believing in the technology. And so they should have
10 been asking what we're measuring, is it correct. So I
11 think there's blame to go around. I wouldn't point it
12 to one group in particular.

13 But I think the thing that bothers me the
14 most in this thing is this term "calibration." We need
15 to make sure when people are doing measurements that
16 they're in fact accurate.

17 Any questions? Or do you want to -- okay.

18 ACTING CHAIR THOMADSEN: Dr. Van Decker.

19 MEMBER VAN DECKER: I have a couple of
20 comments, Orhan. First of all, you know, I think I can
21 speak of everyone practicing nuclear cardiology from a
22 variety of backgrounds that I think we all appreciate
23 the FDA and the NRC's work in this regard.

24 You know, I think that the key goal in
25 anything is knowledge based on root cause, looking by

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1 well-meaning people to try to create betterness for
2 the future and patient access for what a lot of people
3 believe is good technology. And I think that, you
4 know, the thoughtfulness of having done this, you
5 know, with open transparency now over a bunch of
6 months recognizing that getting things back to market
7 if possible is an important piece of the puzzle I
8 think, you know, most people are very, very thankful
9 for. So we want to thank you personally, you've had an
10 interest in this, and everyone else involved for
11 trying to set this right and get everyone on the right
12 path towards doing good here.

13 My second comment would be just a
14 technical one just on a slide basis. While thallium is
15 indeed the highest EDE of a lot of testing procedures
16 I'm not quite convinced by NCRP or ICRP that it is 41,
17 but that's an argument here nor there.

18 I guess my next two comments would just be
19 on future because I look at this not as a -- I look
20 this not so much as a PET spec issue or a radiation
21 issue so much as a generator issue and kind of a
22 device thing, and how we go about dealing with
23 devices, and how we deal with the outputs of devices
24 kind of thing. I think you kind of started all of
25 that. So I find it interesting.

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1 Having spent a career in stress testing
2 patients I learned from my son who hates science that
3 you can stress test banks. So I guess somewhere in all
4 of this when we think about devices we have to think
5 about how we stress test columns and volumes and
6 what's the window of safety when something comes out
7 as far as that column breakthrough goes, and where's
8 windows of safety in devices.

9 And that's not just for this product. I
10 think that this opens the discussion for, you know,
11 all generators that come down the line in any of a
12 variety of different places. And so the question is
13 how do we deal with generators in general as far as
14 getting them through the approval process, monitoring
15 them down the line, making sure people have device-
16 specific concepts of those different generators as
17 they come on and we move out, you know, in a positive
18 manner. So you know, just something to think about.

19 And then the last piece of this is not
20 just a how do you handle a device, you know, how do
21 you stress test it, how do you, you know, look at each
22 one and get it out there on a training basis. But then
23 the last question of the breakthrough question. Just
24 on a concept basis since you said, well you know, the
25 manufacturer kind of comes in with suggested

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1 breakthrough kind of stuff. You know, do we need to be
2 thinking about what percentage of breakthrough to
3 deliver doses appropriate across all generators for
4 all people? Is it an absolute number that really makes
5 the difference? How do we go about trying to sort that
6 out? And do we get to a point in time where we're in
7 the non-measurable piece of it, and if we're in the
8 non-measurable piece of it does that make it a non-
9 useful technology or not depending on where we really
10 think we are number-wise in all of that.

11 But I think that, you know, there's a
12 whole bunch of concepts in here that we could kind of
13 generalize and propagate across a whole variety of
14 different things. And I think that, you know, this
15 thought and this discussion is useful in that regard
16 for getting different viewpoints and moving in
17 positive directions. So I thank you for all of that.

18 MEMBER SULEIMAN: Well, thanks for your
19 feedback. I mean, whether it's unsafe or not, I don't
20 think I know the answer to that. I mean, depending on
21 whom I'm speaking to I argue -- I can argue either
22 side of that argument and I have. But it's a real
23 question. And I did forget to -- those are average or
24 mean numbers. That's why -- but anybody who's done any
25 of this knows that the doses could vary by two- or

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1 threefold or even tenfold for some of those exams that
2 were cited in that. But I decided to take something
3 cited in the literature to be safe.

4 ACTING CHAIR THOMADSEN: Any other
5 questions? Ms. Weil.

6 MEMBER WEIL: You mentioned that several
7 hundred patients were scanned -- were not scanned, PET
8 scanned, but scanned after the PET scan. What
9 percentage of that -- is that of the total number of
10 patients who were -- who used this technology for PET
11 scan?

12 MEMBER SULEIMAN: I don't have a good
13 number for that. I know that Nevada tested 204
14 patients. And using their index patient as a
15 calibration point, okay, I think they sent 90, or they
16 wanted to send 90 but then we gave the patient the
17 option to volunteer. And so they only found three that
18 exceeded the 50 millisievert, but the 90 was selected
19 because we felt that that was above breakthrough.

20 So that's -- now that was the index site
21 and they were the highest volume. And now it wasn't --
22 obviously everything wasn't right, but the highest
23 volume sites are the ones that had the most
24 contaminated patients. And CDC looked at -- I don't
25 have the numbers, but several hundred, about a half a

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1 dozen states. Unfortunately, by the time we
2 implemented this they were looking at them in
3 November. It was just so slow.

4 And I wanted to make a point. I said, you
5 know, I don't want somebody to come back later and say
6 because we didn't see anything meant that they weren't
7 -- that there was no contamination. I said no, I would
8 argue that if you haven't seen anything they weren't
9 seriously contaminated, but we lost that cohort that
10 may in fact have been -- may have in fact received
11 more than breakthrough. But we felt it really wasn't a
12 safety issue, you know, at that point. So I don't know
13 the hard number.

14 MEMBER WEIL: You mentioned that patient
15 privacy issues were a barrier to this. I don't
16 understand why that would be.

17 MEMBER SULEIMAN: Well, it wasn't much. We
18 broke that barrier in 2 days. But somebody, you know,
19 when you started to say we need to -- we work with the
20 company first. And they said well, we can't, it's
21 patient privacy. And they invoked HIPAA. And so we had
22 to get, you know. I mean, we were not in such a
23 regulatory -- I mean, I'm not speaking not just as a
24 regulator but as a consumer. There are so many
25 regulations and you have multiple statutes sometimes

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1 on the same product over years, and all these other
2 laws. I mean, we're pretty much exempt from that. In a
3 situation like that you can go out and do that. We've
4 recalled patients for other products, I know that for
5 a fact.

6 MEMBER WEIL: Absolutely, absolutely. It's
7 a real misuse.

8 MEMBER SULEIMAN: But it was one more thing
9 that you had to drop everything and convince people
10 that no, we have the authority to go ahead and do
11 that.

12 ACTING CHAIR THOMADSEN: Dr. Langhorst.

13 MEMBER LANGHORST: I use these topics and
14 so on to learn so much more about FDA and that helps
15 me so greatly. And I think that having Dr. Suleiman
16 on this committee is just invaluable. And I really
17 appreciate that he is here as one of our colleagues.

18 A question that I have is this is a 23-
19 year-old radiopharmaceutical. Are there -- is there
20 periodic review by the FDA on this, or if a company
21 wants to change something does that trigger a new FDA
22 review of it? And so there's kind of a negative --
23 the company doesn't want to change things because then
24 they have to go through the process again?

25 MEMBER SULEIMAN: Any change in the label

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1 -- I think Dr. Welsh was asking me earlier on with the
2 Alfaradin alpha-emitter. When you do a trial you sort
3 of say these are my goals. We're going for these
4 indications. And you design the trial to meet that.
5 Retrospectively you can't go back necessarily and say
6 oh, we'd like to, you know, cherry-pick or whatever.
7 That's not an absolute, you know. There's lots of
8 things, you know, we can do. But ultimately I think
9 the real decision is is it going to impact on patient
10 care.

11 If a company wants to change a label they
12 have to come back to us. There is periodic review.
13 But this is so interdisciplinary, if the organ dose
14 table has been okayed and nobody has raised a question
15 or if the testing methodology they, you know. So I
16 think that this is -- those of you who talk to me,
17 this has stressed me out a lot and it's stressed out
18 almost everybody else who's been involved. So it's
19 like everybody is exhausted with it. I think everybody
20 wants to get to the same point.

21 But I was falling back on science from day
22 one. You know, when I said this isn't calibrated. You
23 need to come up with a better way. I said this is too
24 complicated. And so I think that's the heart of it. I
25 think if the sites had been doing testing on a

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1 standard way they would have picked up the
2 breakthrough.

3 Can we tell a company what to do? We can
4 tell them what to do but we can't hold them to it
5 necessarily. It depends on what it is. So there's a
6 lot more -- the product was voluntarily recalled. And
7 people say what's that mean. Well, the company, and
8 this is advice for any company. If they've got a
9 problem they should honestly `fess up to it, try to
10 solve it and quit worrying about potential liability
11 because if you're liable, you're -- in other words,
12 the more you don't try to solve the problem the more
13 trouble you get yourself into.

14 And in this case we were never sure if
15 what we were getting from them was filtered through
16 lawyers. You know. And so there wasn't -- Nevada, as
17 soon as they started to test the patients they sent us
18 the information and there was some honest, quick give
19 and take. Everybody was trying to get to the science
20 and figure out, let's get the facts to the surface.
21 So, their intention was honorable.

22 MEMBER LANGHORST: And so if they want to
23 change the way that they recommend that the doses are
24 measured, does that come back to FDA or is that then
25 in an NRC space? Or how does that work?

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1 MEMBER SULEIMAN: Well, let me share what's
2 going on right now, okay? In some of our label that
3 went out -- I'm still not happy with certain parts of
4 it, especially the technical measurement aspects of
5 it.

6 The company was challenged by one of the
7 states and said well, why don't you use like a well
8 counter for measuring the activity. Because that has a
9 crystal and you can more definitively. And from what I
10 heard was the company said well, the FDA has approved
11 this label, it says dose calibrator, so we're
12 precluded from using a well counter.

13 Now, if that's the truth then I've argued
14 internally saying we need to be careful how we word
15 the label so that it doesn't prevent others from using
16 better technology, you know. Either we should use a
17 very simple prescriptive statement that says use a
18 dose calibrator, or use a radiation detection system
19 that will measure the dose accurately to be consistent
20 with NRC standards for traceability and accuracy.

21 If you're detecting which is at the other
22 part of the spectrum you use a detector that'll
23 accurately measure, you know, 0.06 microcuries of
24 activity. If you read the label as currently
25 constituted it really -- it's not prescriptive enough

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1 and it's not general enough. It basically says I think
2 I'm correct so I'm not saying anything that's private.
3 You can read it in the label. Take your dose
4 calibrator reading and divide by 0.548 and that's your
5 number. And I'm saying what's that mean. So I have
6 asked the company where did they come up with the 0.5.

7 I suspect that that 0.548 was a
8 calibration factor based on what they used 23 years
9 ago but somehow during the years when they have
10 updated their label they dropped the make and the
11 model of the dose calibration system. So now they say,
12 you know, use an automobile, you know. Use a dose
13 calibrator. But they're not being any more specific
14 than that. But then they're telling you to take that
15 number and divide by 0.548. It's -- I'm sorry. Unless
16 I'm missing something it makes absolutely no sense to
17 me. And we've discussed this. And so now that others
18 are bringing the same point to them maybe they'll pay
19 attention. They need to get into the 21st century on
20 some of this methodology.

21 MEMBER LANGHORST: I thank you for my
22 education.

23 ACTING CHAIR THOMADSEN: Yes, Mr.
24 Mattmuller.

25 MEMBER MATTMULLER: If I could continue

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1 with my esteemed tablemate's education. In regards to
2 drug product monitoring, once a drug is approved and
3 is out in the market there is continuous monitoring of
4 the product, especially for adverse effects that were
5 unexpected or occur more frequently than was
6 originally described in the package insert. So there
7 are mechanisms out there to collect that data, and
8 then once it reaches a certain point then the FDA does
9 get involved and reevaluate that product. Vioxx is the
10 one drug that comes to mind several years ago where
11 that -- a number of unexpected consequences and cause
12 for a complete reevaluation of the product.

13 The other I guess potential caution I want
14 to put out here is a caution of hindsight. Because
15 this is a 23-year-old product and more than likely the
16 data for all this breakthrough information was
17 probably even generated 10 years before that given the
18 process, the time it takes to go through trials, to
19 get submitted to the FDA, to ultimate approval. And I
20 mean, it wasn't even Bracco, it was Squibb before
21 that. So, I would suggest that 30 years ago this was
22 state of the art breakthrough measurement.

23 So, and I guess I'm trying to stick up for
24 Bracco a little bit here in saying let's not beat them
25 up. I mean, to now it's worked well. I mean, I suspect

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1 if you go back and look at any technology that was
2 established 30 years ago we could find loopholes in
3 it. Thank you.

4 ACTING CHAIR THOMADSEN: Thank you. At this
5 point -- Ms. Weil.

6 MEMBER WEIL: Do we know that it's worked
7 well in the past?

8 MEMBER MATTMULLER: In the past I --

9 MEMBER WEIL: Or you know, is it just that
10 it's never been.

11 MEMBER SULEIMAN: Well, that argument's
12 been -- I mean, we've raised questions on both sides
13 of that. If you're using detecting people at the
14 border as your detector 23 years ago that didn't
15 exist. But on the other hand, if you figure that the
16 root cause was growing beyond the 17 liters this was a
17 much more -- most of the sites from what I found out
18 were lower volume. And when they got to the 28 days.
19 So, but it's not an absolute guarantee that some
20 weren't.

21 Now, the other thing is if you read the
22 label, and this was brought -- you sort of move a step
23 at a time, but I'm looking at the label and it says
24 wait 10 minutes between elutions. And that was to
25 allow for secular equilibrium to be obtained. And I'm

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1 reading, and I'm reading, and nowhere does it say --
2 so that says you can theoretically dose six times an
3 hour times, you know, do the math. So, what I sense is
4 maybe, you know, people saying we can dose this as
5 much as we can and at 28 days we stop.

6 So, the failure to have a 17-liter or a
7 governor or a speed limit or something to say go
8 slower, I'm not exactly sure whether the molybdenum
9 shortage caused people to switch over to the CardioGen
10 or whether reimbursement came into play because it's a
11 PET imaging agent. My CMS colleagues tell me we don't
12 reimburse for the drug, we reimburse for the
13 procedure. So, there must be a number of reasons why,
14 you know, some of the sites were using this more
15 aggressively. But could sites have been -- there's --
16 I don't know the answer.

17 ACTING CHAIR THOMADSEN: Ms. Howe, would
18 you like to give your presentation?

19 DR. HOWE: Orhan's going to be staying
20 because later on when we have questions they may
21 involve both of us.

22 And I'd like to thank Orhan for
23 essentially talking about most of the points on my
24 slide. So, he's gone over the dose to the patients.
25 He's talked about the importance of volume on the

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1 increased potential for breakthrough. He's talked
2 about time as a predictor for increased breakthrough.
3 And also he's alluded to the fact that -- the fact
4 that the facilities may or may not have been doing the
5 tests that they were required to do under NRC
6 requirements and therefore also agreement state
7 requirements is also another major factor. So we have
8 a number of root causes.

9 And I think the most important thing as
10 Orhan pointed out is the fact that these folks were
11 not measuring correctly or every day, didn't cause the
12 generator to breakthrough, it just caused a delay in
13 our ability to -- in their ability to recognize that
14 the generator should not be used anymore.

15 And for a reintroduction we had a public
16 meeting with Bracco that we essentially put out on a
17 webcast to all the agreement states back in February.
18 And at that point they went through their
19 reintroduction process.

20 There were certain key elements that they
21 were going to follow. They were going to provide
22 additional training to all of their sites on how to do
23 breakthrough, on the changes to the package insert
24 which Orhan talked about with the changes in the
25 Bracco breakthrough limits and also the alert limits

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1 and the expiration based on those numbers. And they
2 were going to test the users and the users had to pass
3 a test and then they would get certified to continue
4 to use the rubidium generators.

5 Now, we found out at that meeting that
6 this whole process was taking place and they were
7 busily re-certifying everyone way before the
8 generators were reintroduced into the community. So
9 the question was well, how are you providing the
10 training and how are you testing without having a
11 generator there to demonstrate the breakthrough
12 procedure and go through the radiation measurements,
13 et cetera? And at that point they believed that they
14 could do that purely with PowerPoint slides and
15 information.

16 And I think since then they've recognized
17 that there are still sufficient questions out in the -
18 - in each site that they're sending their
19 representatives to the sites now when the generators
20 are coming to the site so that they can provide some
21 hands-on training and observation.

22 One of the other things that they talked
23 to us about was that they were now going to be
24 monitoring breakthrough from every site. They were
25 going to set up a monitoring system where every day

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1 the site had to provide the breakthrough information
2 to them and they would put it together in a program so
3 that they could see how -- monitor each site and how
4 it was doing. So they would know whether the site was
5 doing the breakthrough, they would know what the
6 values were, they could do this active monitoring.

7 And initially it would be with papers
8 coming in and their inputting data into their computer
9 program, and then later they hoped to put it out as a
10 web-based computer system that people could directly
11 input their data electronically. And they're using
12 that information along with their monthly review.

13 So one of the things that NRC is doing is
14 we didn't have any sites that we knew of that were in
15 excess of breakthrough. And so we've been in a
16 monitoring mode. We've been monitoring what's
17 happening out in Nevada and in Florida for the
18 agreement states and also what FDA is doing because we
19 have a memorandum of understanding with FDA that
20 allows us to share information that may even be
21 proprietary on areas that we both regulate. And so
22 that's been very helpful. So we kind of have the
23 overall view of what's going on.

24 And so the product has been reintroduced.
25 And they're introducing it perhaps a lot faster than

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1 we thought they were going to initially. So they've
2 already gone out to, I don't know the exact numbers,
3 but probably about 100 sites.

4 Now, the next question comes out is to NRC
5 issues. So we decided that this has been up to this
6 point, and when they pulled the product off the market
7 we didn't have any rubidium generators out there so we
8 didn't have ongoing licensing actions and licensing
9 issues. But once the product came back on the market
10 it was going to be important for us to be following up
11 to see the day-to-day use of the product.

12 And when the manufacturer changed the
13 package inserts they introduced a number of new
14 things. One is a new breakthrough limit and that could
15 cause confusion with our NRC licensees. And the
16 package inserts changed from where they were before.
17 So, NRC has decided that it's important for us to put
18 out a generic communication to all of our licensees
19 and explain exactly where the NRC requirements come in
20 with the use of this generator.

21 And so we are developing what we call a
22 Regulatory Issue Summary, a RIS document, and it's
23 going to essentially lay out in a roadmap all of the
24 regulatory areas that we think are important for the
25 rubidium generator. And I can just quickly through a

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1 few of those.

2 We tried to kind of start at the
3 beginning. We didn't start numerically, we started
4 with what we thought was the most important. The first
5 one is 35.200. 35.200 tells you that you can use
6 certain material for imaging and localization which is
7 the product and it says where that material is
8 obtained from. And in that case you can get it from a
9 manufacturer, you can get it from a commercial nuclear
10 pharmacy, you can prepare it in-house. And you can
11 prepare it in-house either under the supervision of an
12 authorized user for 35.200 uses or you can prepare it
13 in-house under the supervision of an authorized
14 nuclear pharmacist if your facility is big enough to
15 have one. So those are the ways that you can obtain
16 it.

17 And because the rubidium has a half-life
18 of 75 seconds you're not going to get rubidium-82 from
19 a commercial nuclear pharmacy or from a manufacturer.
20 You are going to have to prepare the rubidium itself
21 at your site. And so that means it's either going to
22 be prepared under the supervision of an authorized
23 user or under the supervision of an authorized nuclear
24 pharmacist.

25 Now, most of the facilities that were

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1 involved were cardiology practices and stand-alone
2 cardiology practices. So that means very few of these
3 are going to be done under the supervision of an
4 authorized nuclear pharmacist. They're going to be
5 done under the supervision of an authorized user.

6 So the next part of the regulations we
7 thought was important was 35.27. And 35.27 says that
8 if you're preparing a radiopharmaceutical under the
9 supervision of an authorized user or an authorized
10 nuclear pharmacist, that you have to follow their
11 instructions and that you have to be directed on how
12 to do this. So supervision is an important factor
13 because most of the generators are being eluted and
14 the pharmaceuticals are actually being prepared by the
15 technologists. So there may be a few physicians that
16 are doing the elution, but most of it's done with the
17 technologists.

18 So then the next issue is because you're
19 making it yourself you have how to determine dosages.
20 That's 35.63. Since you're making it yourself you have
21 to make the direct measurement. So, the facility has
22 to make the direct measurement and if the facility is
23 making the direct measurement it has to make the
24 direct measurement with an instrument that is
25 calibrated to a nationally recognized standard or the

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1 manufacturer.

2 So we have two possibilities here. One is
3 the rubidium as it's coming off of the generator as
4 being measured at the infusion cart with a radiation
5 detection meter before it is going directly into the
6 patient. And then you've also got your breakthrough
7 limits which are very important, and those you have to
8 measure generally with a dose calibrator. If there's
9 some other device that's better than a dose calibrator
10 that could be used also. So both of those devices need
11 to be calibrated.

12 Now, another part is you've got to possess
13 and use calibrated instruments, so that's 35.60. So
14 I've addressed that a little bit.

15 And then we get to a really important
16 thing, and it's the key to everything. And that's
17 35.7. That's the FDA other federal and state
18 requirements. Back in 1994 we resolved what we call
19 the nuclear pharmacy, the radiopharmacy rulemaking.
20 NRC took away the requirements that we had prior to
21 that time where you had to follow the FDA-approved
22 package inserts when you were preparing
23 radiopharmaceuticals, and that you had to follow the
24 uses of the radiopharmaceuticals that were in the
25 approved package insert. So that we no longer tie our

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1 licensees into following the package insert.

2 And everybody goes well, why did you do
3 that? Well, it ended up we were enforcing a package
4 insert that FDA was not enforcing and was not
5 recognizing the practice of pharmacy in medicine. So
6 we put 35.7 into the regulations that said even though
7 it's no longer an NRC requirement you are not relieved
8 of any responsibilities that may come about because of
9 FDA-approved products or other state and federal
10 regulations that may involve the radioactive drugs or
11 medical devices. And so that's an important point.

12 So even though the manufacturer changed
13 the package insert and -- let's see, I have another
14 part in here I forgot, and that's 35.204. And 35.204
15 is the permissible molybdenum strontium-82 and
16 strontium-85 concentrations. And for NRC that level is
17 in our regulation and it is in -- and Orhan provided
18 the numbers, I think 0.02 for strontium-82 and 0.2 for
19 strontium-85 per millicurie of rubidium-82.

20 So, have we changed that value? And the
21 answer is no. That value is still our regulatory
22 requirement. The package inserts have introduced a new
23 maximum permissible concentration which is one-half of
24 that value. Should our licensees be following that for
25 an expiration date? That's a good practice. It's the

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1 manufacturer's recommendation. It's a good practice.
2 It's not an NRC requirement, okay? So if you were an
3 inspector and going in looking at violations you would
4 not cite a licensee for violating that number.

5 Their action levels. We don't have action
6 levels in the NRC requirements. Those are a
7 manufacturer's recommendation. We think the jury's out
8 on whether it's a good practice because we're
9 concerned about the ability of instrumentation to
10 accurately measure down at that level to measure the
11 action levels. We think that may be beyond the limits
12 of the dose calibrator. So, we have not changed our
13 regulations and at this point we are not intending to
14 change our regulations based on the breakthrough
15 issues.

16 So, that's our RIS. We're going to try to
17 explain to licensees why these particular parts of the
18 regulation pertain to the rubidium/strontium
19 generators. We're also going to add one about -- just
20 to remind people that they can decay in storage. And
21 looking at the manufacturer's instructions they pretty
22 much treat everything that comes through the generator
23 as being totally non-radioactive after an hour. There
24 could be strontium-82 or strontium-85 contamination in
25 the waste vial, in the tubes, et cetera. And so we're

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1 going to remind our licensees that they have decay-in-
2 storage and they need to measure things before they
3 throw them away without regard to the radioactivity.
4 And so that's another reminder. So, the basic focus of
5 our RIS is going to be reminding licensees of the
6 regulatory requirements that we believe are associated
7 with the use of this product. These are not new
8 requirement and they're not new requirements to these
9 types of licensees.

10 Now, the other thing we're going to do is
11 to try to clarify for our inspectors what are exactly
12 -- what the NRC requirements are versus the package
13 insert. So we're once again going to be putting a lot
14 of focus on 35.7 where we no longer require licensees
15 to follow the package inserts.

16 And we're going to try to make it very
17 clear what are factors that would increase the
18 likelihood of breakthrough so that they are sensitized
19 to that, so that they can either be on the lookout for
20 potential licensees that may not be making
21 measurements correctly. And what is an NRC
22 requirement. So that we are not having violations to
23 things that are not NRC requirements. And those are
24 the two actions that we're taking right now for our
25 licensees and for our regions.

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1 ACTING CHAIR THOMADSEN: Dr. Van Decker.

2 MEMBER VAN DECKER: I guess I want to say
3 thank you to you also because I guess these are the
4 two pieces of the issue, right? You know, the device
5 and how we want to treat generators as a whole in the
6 future. And number two, how we understand to use those
7 in the best manner possible for everyone out there and
8 what are the rules and regulations.

9 So in that regard as number one I would
10 say I suspect every professional society represented
11 across this table would be more than happy to amplify
12 your educational process through other mechanisms of
13 communication with membership. We want to get word
14 out, we want everybody to be on the same page of the
15 playbook, and so I'm sure whatever societies are here
16 would tell you we want to be a piece of that. We thank
17 you for offering that up.

18 I guess my second thought on this, once
19 again, is trying to say how can you find generalized
20 lessons to learn for the future. And if you look at,
21 you know, generators as the lifeblood of production of
22 radiopharmaceuticals for the future, you know, we
23 currently have expanded Part 35 open for, well, not
24 open for comment. I'm not sure, Mr. Fuller.

25 (Laughter)

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1 MEMBER VAN DECKER: But you know, and there
2 obviously there is a section on moly generators that
3 were talking about and QC.

4 And you know, you bring up the point about
5 breakthrough limits in rulemaking space and what
6 changes over time. And 2017 being a long way apart,
7 how you deal with rulemaking space with things that
8 are in motion and changing, and you want them updated
9 and done correctly, and yet you also want them to
10 carry some teeth so that the community understands
11 where you are at all points in time.

12 So, I guess as we think this out as far as
13 generators go as a category we should start thinking
14 of not only whether it was a percentage of
15 breakthrough, an absolute breakthrough, but for any
16 different generator or anything else where we put that
17 type of information, how we deal with it as a
18 regulatory piece and as an educational piece for
19 better patient care. I'm sure you are well versed in
20 ways and options of possibly doing all of this, but I
21 think that, you know, some of that has to be part of
22 the process besides just, you know, guidance or
23 appendixes and RIS and everything else we can do to
24 kind of popularize the theories and the thoughts that
25 are going on here.

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1 DR. HOWE: Your point is well taken because
2 we know there are new generators coming out that have
3 different engineering and different abilities to elute
4 products even for molybdenum. There are going to be
5 new molybdenum generators coming out. And so it is an
6 issue because we get complacent with the idea that we
7 have a technetium generator that essentially is the
8 same as it's been since the day one and we have no
9 other generators.

10 And all of a sudden we've got a rubidium
11 generator, but not many people are using it. And now
12 more people are using it. And then we've got other
13 products that will be made with generators. And so I'm
14 not sure how we're going to handle that, but it is a
15 good point, especially in training and experience.

16 ACTING CHAIR THOMADSEN: Mr. Mattmuller.

17 MEMBER MATTMULLER: I have a couple of
18 questions, comments. And just, what Laura asked has
19 been gnawing at me a little bit, and perhaps one way I
20 can answer that is that I do know there's a high-
21 volume cardiology clinic in Kansas City that is very
22 good with rubidium generator. And Orhan, maybe you're
23 familiar with this, but I'm -- in talking to my
24 technologist at my department, and they're in frequent
25 contact with them, they have noticed that -- that if

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1 they use their generator a lot that they start to see
2 breakthrough. So, with the current technology of using
3 dose calibrators it is detectable, it is measurable,
4 so it can be caught if it's done right. And this is a
5 mere site that does things right. So, even though it's
6 30-year-old technology to a certain extent it still
7 works when it's used right.

8 A question for Orhan. In regards to the
9 calibration factors that you're talking about, the
10 dose calibrators, wouldn't that data be, and this
11 probably has to go into the bowels of the FDA to find
12 this, but in the original NDA application wouldn't
13 that data be submitted in there?

14 MEMBER SULEIMAN: I've actually talked to
15 some of our people and what they've looked at says
16 that some of that information is not there, okay? This
17 was 23 years ago.

18 And yes, the test works, okay? It's just
19 that there are some much easier tests today that could
20 make the testing so much easier and the sites' lives
21 easier. I mean, that was -- if they want to continue
22 to use this 23-year-old methodology that's fine, but
23 it's cumbersome, it's problematic and it lends itself
24 to confusion. So why not -- I mean that was my
25 argument with them professionally.

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1 I talked to them after our meeting. I said
2 you need to get this thing into the, you know, it's
3 pretty straightforward, at least to me it seemed
4 pretty straightforward. And I said for calibration
5 you've got a NIST-traceable PET standard. You know,
6 companies are incorporating and selling it all the
7 time. I would calibrate against, you know, I would use
8 that. I wouldn't use cobalt-60, you know.

9 So, it's a case of if you make it simpler
10 and better why wouldn't the sites want to use it? Why
11 wouldn't, you know, the company push that? It would
12 make their product more user-friendly. So, does it
13 work? Yes, but it's just, it's outdated. I mean, we
14 don't use DOS anymore.

15 I have something for Donna-Beth. I don't
16 like absolute numbers in terms of breakthrough because
17 each generator is different. And look at the CardioGen
18 generator. You actually have two breakthrough limits
19 because you've got two different nuclides. So, to use
20 an absolute -- I think it really has to be done on a
21 case-by-case basis. You know, and I defer to the
22 company. You know, their -- and the medical community.
23 They can either follow the label or they can go off-
24 label and do what they want.

25 I think as a -- I'm a very non-

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1 prescriptive regulator, but I'd like -- I think
2 sometimes you need regulation. I would say thou shalt
3 do breakthrough testing and I would back off on
4 necessarily -- leave the details for the specific
5 generator, you know, involved. Because if you come in
6 with a 0.02, well, what's good for moly isn't
7 necessarily good for CardioGen and there may be a
8 different generator or different whatevers.

9 But I think the fact that you have to be
10 doing the testing, I would have opted for make sure
11 that you're measuring the activity given to the
12 patient within a given percentage -- I don't know
13 whether your regs say 5 or 10 percent -- traceable to
14 a national standard, you know. I think -- and then let
15 them fill in the details. I would not, you know, and
16 for the detection you may want two different detection
17 systems for measuring the breakthrough amount versus
18 the other one. So, I'd make a requirement but I
19 wouldn't be so prescriptive that, you know, you don't
20 allow new technology to adapt in the future.

21 DR. HOWE: And Orhan, our calibration
22 requirements are that the instrument be calibrated to
23 a nationally recognized standard or the manufacturer's
24 instructions if there isn't a nationally recognized
25 standard. So we are performance-based in that regard.

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1 We do have specific breakthrough numbers
2 for the moly 99 and the strontium-82, rubidium-82
3 generators because at that point they were the only
4 generators that we were -- that we knew about. So, and
5 we had specific ones for moly. And other values that
6 had been in effect.

7 I would also mention that we're new to the
8 strontium/rubidium generator. We've only been
9 regulating NARM material since about 2007. So this is
10 not something that we have experience with for the
11 last -- since the early eighties. It's fairly new for
12 us. And we're finding out the devil's in the details.

13 And I think to partially answer Laura's
14 question, the way the -- Nevada set up their protocol
15 was that on the index patient day they would go a day
16 before and then the day of the index patient and then
17 each day after that until the generator was no longer
18 used and try to call back their patients. Now, they're
19 in Nevada, they have a snowbird population so their
20 population isn't necessarily there. So in September
21 they're calling back patients that are available and
22 accessible.

23 They also knew that the facility wasn't
24 necessarily doing a breakthrough test every day. Our
25 regulations require that breakthrough tests be done

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1 every day there's patient use and be done before first
2 patient use. So, on the days that there wasn't a
3 breakthrough recorded they decided they had no idea
4 whether a breakthrough happened or not. And so they
5 would bring back the patients on those days. And by
6 bringing back the patients on those days they extended
7 the breakthrough findings from one generator, the
8 index patient, to seven generators.

9 Now, they didn't go back once they got a
10 positive patient and then start collecting data from
11 there to the end of that generator use, but they did
12 identify well in excess of breakthrough limits for
13 individuals that were imaged with seven different
14 generators. So we don't know the total population that
15 was in excess of breakthrough, but we do know that it
16 was a fair number. And they were doing about 20
17 patients per day and I think they were running, we've
18 heard comments like 7 days a week. So they had a very
19 high use.

20 ACTING CHAIR THOMADSEN: Ms. Weil.

21 MEMBER WEIL: So, just to follow up on
22 that. They were calling back patients based on what
23 seems like very reasonable criteria for wanting to
24 look at those patients. But what was the notification
25 process for all patients that were scanned in that

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1 particular facility with very high use?

2 DR. HOWE: I don't know.

3 MEMBER SULEIMAN: I think they said --
4 Nevada handled it under their own authority. I forget
5 what they did. They also worked very closely with the
6 clinical site. And the physicians actually talked with
7 each patient who came back. So they either -- I don't
8 know whether they --

9 MEMBER WEIL: Each patient who came back.

10 MEMBER SULEIMAN: They notified that, yes.

11 DR. HOWE: But the patients that didn't
12 come back are the ones they didn't notify.

13 MEMBER WEIL: The ones they don't notify. A
14 patient decides not to come back, that's one thing.
15 But if nobody is notifying the patient, the patient
16 doesn't realize that what they consented to is not
17 what they got.

18 DR. HOWE: Originally I believe the health
19 department in Nevada wanted to call back all patients.
20 And I think the radiation health group said well,
21 let's do a more focused study. They had no idea what
22 they were going to get. And I think they were -- it
23 was a tremendous effort to measure these 200 patients.
24 I don't know what their thoughts were after that, but
25 I think they really did a huge job.

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1 MEMBER WEIL: This was in Nevada but not in
2 Sarasota. A different story in Sarasota.

3 DR. HOWE: It's a different story in
4 Sarasota. In Sarasota the licensee called back some
5 patients and did their own measurements and found no
6 uptake. Okay? And then later Bracco added the Sarasota
7 site to its protocol that was approved by FDA and
8 identified positive patients. But they were only
9 looking at the day of the index patient. So their
10 protocol was nowhere near as broad as Nevada's.

11 MEMBER SULEIMAN: And their -- this is
12 deeper than you see, okay? But as Nevada was pretty
13 much developing the protocol on the fly and CDC was
14 getting into the act, they pretty much, and I think
15 you guys had input here.

16 DR. HOWE: Yes, we did.

17 MEMBER SULEIMAN: Pretty much modified, and
18 they essentially adopted the Nevada protocol.

19 DR. HOWE: Originally CDC was going to make
20 a different kind of measurement and we said wait a
21 minute, Nevada is working. They are picking up people,
22 they are identifying in excess of breakthrough limits.
23 Why don't you use the Nevada technique and they saw
24 the rationale for that.

25 MEMBER SULEIMAN: And the other

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1 construction is one of those things that I hope is a
2 lesson learned. But I mean, invoking our Post-Market
3 Review regulatory tool for identifying potentially
4 contaminated patients I felt was the wrong strategy
5 because we considered these formal trials. And we had
6 to have, as I said earlier, an IRB approval. By the
7 time -- it took us months to get this on schedule.

8 And there were I think protocols 104 and
9 105. And one was basically focused on the index sites
10 and the other one was focused on sites that were using
11 generators toward the tail end.

12 And somewhere the CDC wanted to conduct
13 this independently and so they did. CDC did testing
14 with the states using the same standard protocol.
15 Nevada did their own thing. They developed the
16 protocol. Bracco did some testing. And halfway through
17 they modified one of their protocols to be consistent
18 with the Nevada protocol. And about a month later I
19 realized that they hadn't modified their other
20 protocol that says let's use a general survey meter to
21 detect the patients first and then look at them in
22 terms of an identifier. When I brought it to their
23 attention I was basically told we've already
24 negotiated this, this is already in -- you can't raise
25 any issues until the trial is finished. I said by then

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1 it's done.

2 So I said as long as they don't make a
3 statement that we haven't seen anybody using this
4 questionable protocol, and then say that what we
5 didn't see implies there was contamination. That's
6 exactly what they did later on where -- and I said the
7 protocol is questionable. I said so the credibility is
8 at issue. It may work, maybe you've seen serious
9 people, but one group of patients that they looked at
10 were done differently than everybody else. So there
11 was a lack of standardization.

12 So at that point I didn't think we felt we
13 had identified the major cause. The serious patients I
14 think were being picked up. It would be more of an
15 academic exercise you know after the fact, but it was
16 a point that I wanted to make sure that people were
17 aware. I said the tests were not done the same way and
18 so it affects the credibility of one of the cohorts of
19 the survey.

20 ACTING CHAIR THOMADSEN: Dr. Langhorst.

21 MEMBER LANGHORST: I have a quick question
22 that may not be able to be answered here, but because
23 the two clinics were in agreement states, and again
24 I'm furthering my education because I've always been
25 an RSO in an NRC-regulated state. Are there lessons

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1 learned here from the agreement state perspective that
2 would help this committee understand this situation
3 for future advice to the NRC? We seem to be missing
4 that perspective that we might have some lessons
5 learned from them.

6 MEMBER BAILEY: I don't have any right
7 here, but yes, I think that would be an important
8 perspective. But it's going to be more in the initial
9 response before -- I mean, there as involvement with
10 FDA, CDC and such, but the trial process is going to
11 be separate to the regulatory body investigating the
12 event, non-event, actions of their licensee.

13 DR. HOWE: And I'd like to add that we're
14 talking primarily about Nevada. What did Florida do?
15 Florida took a slightly different task. By the time
16 Florida was getting involved it was clear that Bracco
17 was going to do the patient measurement for the index
18 site. So, Florida went out and inspected all of its
19 sites to see how its people were performing the test.
20 Now, of course this was after the products were pulled
21 off the market so they weren't able to do live
22 performance monitoring type of thing. But they did go
23 back over records.

24 And so Florida added a very important
25 inspection perspective where they discovered that many

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1 of their sites were not performing the breakthrough
2 test correctly, or they weren't performing it every
3 day. So, Florida gave us a lot of important
4 information about what to expect. Because there's no
5 reason to expect their licensees are any different
6 from anybody else's licensees. And Nevada gave us the
7 patient site. So between the two we got a good view of
8 what was going on.

9 MEMBER SULEIMAN: Now, Florida, early on he
10 says, Orhan, he says if they get breakthrough they're
11 supposed to report it to us. So, the states that
12 actually -- the sites that actually have breakthrough,
13 they went in immediately and they provided some very
14 useful -- they actually went back for a whole year for
15 each site and collected all the breakthrough data.

16 And that provided another insight into the
17 drug delivery system because you would expect the --
18 I'll give you an example. You would expect the
19 activity in a generator would follow a straight line,
20 you know, as it's decaying away. And it wasn't. You'd
21 see inconsistencies. And so I said there's more to
22 this than meets the eye. I said there's something --

23 MEMBER LANGHORST: It's the sun.

24 (Laughter)

25 ACTING CHAIR THOMADSEN: Mr. Mattmuller.

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1 MEMBER MATTMULLER: Mr. Chairman, may I
2 indulge in your patience and present a few additional
3 slides on this topic? Thank you.

4 MEMBER WELSH: Dr. Thomadsen?

5 ACTING CHAIR THOMADSEN: Dr. Welsh.

6 MEMBER WELSH: There's somebody at the
7 microphone behind you.

8 MS. FAIROBENT: Lynne Fairobent with AAPM.
9 Laura, at the CRCPD conference coming up in May, on
10 May 7th there will be a presentation where both the
11 states of Nevada and Florida are also participating.
12 And I'm sure that information could be shared with
13 ACMUI afterwards. And either Darice or I could make
14 sure that that information is provided back to ACMUI
15 if you wish.

16 Then I have a question. Any time frame on
17 when the RIS will be issued on that? You didn't
18 mention a time frame or I didn't hear it.

19 DR. HOWE: I haven't mentioned the time
20 frame because I thought it would be out by now but
21 I've got to go back and do a little bit more work on
22 it. So I can't guarantee when it'll be out but it
23 should be coming soon.

24 MS. FAIROBENT: Okay, thank you.

25 ACTING CHAIR THOMADSEN: Mr. Mattmuller.

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1 MEMBER MATTMULLER: Yes. I'd like to
2 discuss a different viewpoint on an issue that may
3 have contributed to possible causes for this incident
4 with the generator. And you saw the slide yesterday in
5 regards to medical events because some of these
6 patients may or I guess now did exceed the 50
7 millisievert limit. And I'd like to suggest that
8 possibly this issue is training, inadequate training
9 that we have today.

10 So this is the current 35.290 training for
11 localization and imaging studies. A minimum of 80
12 hours for an authorized user. And this figure 80 I
13 believe was set at least back in 1995, maybe before
14 that. But it's been in effect for a number of years.

15 DR. HOWE: Two thousand two.

16 MEMBER MATTMULLER: Two thousand two? Okay.
17 Going back a few years -- I'm sorry. This is the
18 salient paragraph of the 290 where it talks about
19 generator systems eluate, the testing purity and
20 reagent kits.

21 But the question in my mind was does this
22 just really still protect these generators or was this
23 design also to handle the bidding generators. And the
24 last phrase says processing eluate with reagent kits
25 to prepare labeled radioactive drugs. So to me that's

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1 pretty much how we're just really talking about
2 technetium because I don't know of a kit that works
3 with a radiopharmaceutical with a 75-second half-life.
4 So, pharmacists can be fast. We're not that fast.

5 Looking back in the regs, back to '95 or
6 so, this was the relevant paragraph and here it's much
7 more specific to technetium and technetium kits. But
8 there's no mention of PET. Even though the CardioGen-
9 82 generator was available in 1990, but also PET was
10 not under the NRC's purview back then.

11 And again, back to the current paragraph
12 on generators. And I believe, I'm sure I'll be
13 corrected, revised before or in 2002? This is our
14 current regulation. But again I believe this is just
15 really done in focus of technetium generators. Because
16 2005 is when PET came underneath the purview of the
17 NRC.

18 DR. HOWE: But we didn't issue regulations
19 till about 2007.

20 MEMBER MATTMULLER: Okay, right. All right.
21 So, it's consistent. So obviously eluting a rubidium
22 generator is far different than eluting a technetium
23 generator. Perhaps the single greatest difference is
24 that it's eluted directly infused into the patient.
25 And so it's purity is inferred from a breakthrough

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1 test that's performed on the first elution of the day.
2 And that itself doesn't make it a dangerous device,
3 it's just that it puts added focus on the importance
4 of proper breakthrough testing for the generator's
5 eluate.

6 So, on my last slide here I've got PET.
7 And I apologize, this was somewhat done on the fly at
8 the last minute. And perhaps it's more appropriate to
9 say generators, radiopharmaceuticals from all
10 generators, because as has been mentioned this is a
11 relatively new generator. It's technetium. There are
12 different types of technetium generators on the
13 horizon that might make it to the market. There's a
14 gallium-68 PET generator that's on the horizon that
15 hopefully will be approved soon. So it's important to
16 look at all generators.

17 And so, to finalize, have the regs kept
18 pace with contemporary nuclear medicine practices? In
19 '95 it was 80 hours for all practical purposes, just
20 to focus on the technetium generator. And in 2012 it's
21 still 80 hours, but now there's two generators that
22 authorized users need to know about. So, I leave with
23 this thought of have the regulations kept up in
24 regards to training. Thank you.

25 ACTING CHAIR THOMADSEN: Thank you, Mr.

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1 Mattmuller. Dr. Van Decker.

2 MEMBER VAN DECKER: Not to belabor a point,
3 but I'm actually just kind of looking at. But I did
4 want to thank Steve for bringing up what I see as the
5 third piece of the puzzle obviously, right?

6 So, one is, you know, as generators come
7 out as a whole how do we know stress testing-wise
8 they're good. How do we know what breakthrough limits
9 we set and where we go? And then how do we monitor
10 their daily practice down the line. Also, how do we
11 move people from one device in this category to
12 another device?

13 And I would start out by essentially re-
14 emphasizing the fact that you just made at the end,
15 that you know, PET tracers are photon emitters. They
16 are Part 200 isotopes. The radiation protection
17 concepts of dealing with the isotope are no different
18 than the radiation protection concepts of dealing
19 with, you know, spec'd agents.

20 The difference here is obviously the
21 device and how it delivers and how is it different
22 from what's been out there before, especially as it
23 becomes more common in practice and dah dah dah. And
24 you know, I think that as we think this through, and
25 this will probably take a bunch of months here, or at

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1 least a few months, I think that there's lessons to be
2 learned from our colleagues in therapeutics where
3 Gamma Knife is obviously something that comes online
4 and there's a modality where the training concepts are
5 exactly the same. And you know, does it take three
6 cases, does it take industry-sponsored training for a
7 few days or something to get online. I think that
8 those are reasonable things to consider on an overall
9 process of dealing with different generators as they
10 come out. I think that it's obviously something we'll
11 have to think about and kind of work through here. But
12 I think it's a reasonable concept to kind of be
13 bringing up here.

14 ACTING CHAIR THOMADSEN: Thank you very
15 much, Dr. Van Decker. Mr. Mattmuller.

16 MEMBER MATTMULLER: I'm sorry. I failed to
17 add, there's actually the most recent version of my
18 slides was just passed out before my talk, so please
19 pull the old version from your book and just use the
20 most recent version. Otherwise I get in trouble.

21 ACTING CHAIR THOMADSEN: Thank you very
22 much. Are there other comments or questions from the
23 committee? Yes, Dr. Suh.

24 MEMBER SUH: I have a quick question. So,
25 being a Gamma Knife user we use a lot of checklists

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1 ensuring best practices overall. And I'm not that
2 familiar with your space in terms of is that something
3 that's part of the culture in terms of using
4 checklists and best practices overall? Is it pretty
5 uniform if you go from say California, Arizona, New
6 York, how these devices are utilized and what the
7 standards are for monitoring?

8 MEMBER MATTMULLER: Well, I know at our
9 facility it's not necessarily a checklist, but it is
10 something we do. Whether it's a technetium generator
11 for every elution or for the rubidium generator when
12 we were using it that we did it every morning. So, it
13 was just a quality control step that we knew we had to
14 do before we -- we had to verify that the product was
15 safe before we could give it to the patient. So, not
16 necessarily a checklist, but a necessary step.

17 ACTING CHAIR THOMADSEN: Dr. Van Decker.

18 MEMBER VAN DECKER: But I think it's a
19 great concept and I appreciate the thought-sharing.
20 You know, as of January 1st of 2012 all imaging labs
21 in the United States are mandated to be accredited by
22 one of three accrediting agencies.

23 And obviously checklists and good
24 practices of care can be propagated through those
25 types of mechanisms as well as through regulatory

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1 mechanisms based on professionalism and professional
2 sharing of thoughts and ideas. So, you know, it's
3 another concept to be considered.

4 ACTING CHAIR THOMADSEN: Good. Further
5 comments? With that I would like to thank the three
6 panelists informing us on all these aspects. It's very
7 involved. Thank you.

8 And with that I'd like to turn the program
9 over to Sophie or Ashley. Sophie.

10 MS. HOLIDAY: Okay, last presentation of
11 the day. Okay, so we will turn to Tab 14 if you will
12 and please get your calendars out. We are getting
13 ready to plan our fall ACMUI meeting. All right.

14 Many of you recall I sent out a Meeting
15 Wizard application. This is also one of our
16 modifications where we are moving towards the new age
17 and try to make this portion of the meeting less
18 cumbersome for you.

19 So, if we look at our current calendars
20 you will see here on this page that I've highlighted a
21 set of dates that seems to be more favorable for the
22 majority of the committee members. Our first set of
23 dates are September 20th-21st, September 24th-25th,
24 and then if you look at October there's October 18th
25 and 19th.

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1 I will point out that if the committee
2 wishes to meet with the Commission there's a
3 possibility that we will be able to meet with the
4 commission on the October dates if that's what we need
5 to try to push for. But again, this is for your
6 availability and for whichever set of dates that you
7 would like to select. So I guess I would turn it over
8 to you, Dr. Thomadsen, to see if the committee would
9 like to select the 18th and 19th and so forth.

10 ACTING CHAIR THOMADSEN: Okay. The first
11 choice seems to be the 18th and 19th which gives us
12 the options of meeting with the commission if that
13 seems to be what we need to do. Are those dates
14 available for the committee?

15 (No response)

16 ACTING CHAIR THOMADSEN: I think we've got
17 it.

18 MS. HOLIDAY: Okay.

19 ACTING CHAIR THOMADSEN: That would be our
20 first choice then. As a backup, could we look at the
21 September 20 and 21st? Those would be a backup date
22 for the committee.

23 (No response)

24 ACTING CHAIR THOMADSEN: Seeing no
25 objection I think we've got our primary choice and the

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1 backups.

2 MS. HOLIDAY: So everyone is fine with the
3 October 18th and 19th as our first choice and our
4 secondary backup dates as September 20th and 21st.
5 Okay. Seeing no objection I will take note of that.

6 MS. COCKERHAM: This is Ashley. I have a
7 question. If we find out from the Commission well
8 enough in advance that there would not be a meeting
9 would the committee still prefer to meet that late in
10 October, or would your first choice then become
11 September?

12 ACTING CHAIR THOMADSEN: Anybody have a
13 feeling on that?

14 MEMBER ZANZONICO: I would prefer
15 September. I might have a travel in October.

16 ACTING CHAIR THOMADSEN: I would also
17 prefer September myself.

18 MEMBER WELSH: I agree.

19 ACTING CHAIR THOMADSEN: Okay. It sounds
20 like you've hit upon the fulcrum here.

21 MS. COCKERHAM: Understood, thank you.

22 MS. HOLIDAY: Thank you.

23 ACTING CHAIR THOMADSEN: Dr. Welsh?

24 MEMBER WELSH: If we can't meet with the
25 commission and we looked at September 24th and 25th

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1 versus 20th and 21st look like they're open.

2 ACTING CHAIR THOMADSEN: Actually, the
3 25th, the 26th is marked as Yom Kippur but Yom Kippur
4 actually starts on the 25th. I would not be able to
5 make that one.

6 MS. HOLIDAY: Okay. And Dr. Malmud would
7 also be unable to attend that day.

8 MEMBER SULEIMAN: So which is the primary
9 and which is the secondary?

10 MS. HOLIDAY: I believe --

11 ACTING CHAIR THOMADSEN: That's a good
12 question now.

13 MS. HOLIDAY: If we are able to get in with
14 the Commission we will have our first choice as
15 October 18th and 19th with September 20th and 21st as
16 our backup. However, if we are not able to get a
17 meeting with the Commission then our first choice
18 would then switch over to being September 20th and
19 21st with the October dates being your secondary.

20 MR. EINBERG: My question, Sophie, is when
21 will we know from the Commission whether the ACMUI can
22 meet with them? Ashley is coming to the microphone.

23 MS. COCKERHAM: This is Ashley. We should
24 know sometime after May.

25 MR. EINBERG: After May?

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1 MS. COCKERHAM: Yes.

2 MR. EINBERG: So I guess the issue then is
3 can the committee keep both dates available until we
4 hear back.

5 MS. HOLIDAY: Okay.

6 ACTING CHAIR THOMADSEN: Sounds like it,
7 yes.

8 MS. HOLIDAY: Great. And now we will move
9 onto recommendation actions. This will be coming
10 around to you shortly. But as you can see on the
11 screen, our newest recommendation is that the ACMUI
12 approved the electronic subcommittee report on
13 yesterday's portion of the meeting. Are there any
14 questions or comments?

15 ACTING CHAIR THOMADSEN: Okay.

16 MS. HOLIDAY: Okay? We will move on to item
17 number 3. Today, Dr. Thomadsen created a subcommittee
18 to provide a recommendation on licensing for alpha-
19 emitters to include radium-223. The subcommittee will
20 submit its report by June 15th. Subcommittee members
21 include Dr. Zanzonico who is chairing, Dr. Langhorst,
22 Mr. Mattmuller, Dr. Palestro, Dr. Suleiman, Dr.
23 Thomadsen, Dr. Welsh and Ms. Bailey. Your NRC staff
24 resource person will be Ms. Ashley Cockerham. Are
25 there any questions or comments or there?

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1 ACTING CHAIR THOMADSEN: No.

2 MS. HOLIDAY: Okay. Then that closes my
3 portion. I will let you guys know that I will send you
4 out your Form 64's for your travel vouchers as well as
5 your Form 148 which is for your time submission
6 although the pay period does not end until this week
7 comes to a close. So you are not required to submit
8 them right now.

9 Please remove your name tag. Don't take
10 them home with you. And that concludes my portion.

11 ACTING CHAIR THOMADSEN: Thank you very
12 much. Any last comments from the committee or the
13 staff?

14 MR. EINBERG: Just on behalf of the staff
15 I'd like to thank the committee for a very interesting
16 discussion and for very useful advice. I think there
17 was a lot of very good topics and we all discussed
18 here. And so we look forward to meeting again.

19 ACTING CHAIR THOMADSEN: And as always, the
20 committee extends its thanks to the staff for all the
21 services they provided and information and help.
22 Thank you very much. Thank you to the committee. We
23 will be in touch. We stand adjourned.

24 (Whereupon, the foregoing matter went off
25 the record at 12:18 p.m.)

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