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NUCLEAR REGULATORY COMMISSION

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ADVISORY COMMITTEE ON THE MEDICAL USES OF ISOTOPES

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MEETING

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OPEN SESSION

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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

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

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.

SHAEMUS GLEASON (via webcast), Cardinal Health

TRACI HOLLINGSHEAD (via webcast), Avera McKennan

DEEPIKA JALOTA, Bayer HealthCare Pharm.

GARY LUNGER (via webcast), *Unknown Affiliation*

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

PETER LUHRS, Bayer HealthCare Pharm.

ANDREW McKINLEY, American Society of Nuclear Cardiology

JANETTE MERRILL, Society of Nuclear Medicine

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

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

DONNA MOSLEY (via webcast), Fox Chase Cancer Center

MICHAEL PETERS, American College of Radiology

SOBHA PHILLIPS (via webcast), Fox Chase Cancer Center

WILLIE REGITS (via webcast), Cardinal Health

JOE RODGERS, Theragenics

GLORIA ROMANELLI, American College of Radiology

GERHARD SCHULETER, Bayer HealthCare Pharm.

KAREN SHEEHAN (via webcast), Fox Chase Cancer Center

JEFF SIEGEL, Ph.D., Nuclear Physics Enterprises

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

ROSE TALARICO, Bayer HealthCare Pharm.

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

CINDY TOMLINSON, American Society for Radiation Oncology

CHRISTOPHER VASCOE, Bayer HealthCare Pharm.

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

MONA WAHBA, Bayer HealthCare Pharm.

EVAN WESTERN (via webcast), Cardinal Health

GARY E. WILLIAMS, VA NHPP

A-G-E-N-D-A

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

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

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

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

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

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

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

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

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

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

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

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

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

biodistribution studies.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

DR. VOLIOTIS: Yes.

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

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

MEMBER ZANZONICO: Is overall survival.

DR. VOLIOTIS: This was the endpoint based

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

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

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

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

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

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

DR. VOLIOTIS: We have seen none so far.

MEMBER ZANZONICO: None at all.

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

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

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

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

DR. VOLIOTIS: They are captured during the

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

ACTING CHAIR THOMADSEN: Dr. Suleiman?

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

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

therefore used as a primary endpoint.

MEMBER SULEIMAN: So the increase is by 2.8 months?

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

ACTING CHAIR THOMADSEN: Dr. Guiberteau.

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

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

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

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

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

MEMBER GUIBERTEAU: Thank you.

ACTING CHAIR THOMADSEN: Dr. Welsh?

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

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

upcoming studies?

DR. VOLIOTIS: In future studies?

MEMBER WELSH: Yes.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

ACTING CHAIR THOMADSEN: Dr. Welsh.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

ACTING CHAIR THOMADSEN: Thank you. Dr. Suleiman?

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

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

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

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

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

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

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

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

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

ACTING CHAIR THOMADSEN: Dr. Welsh?

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

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

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

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

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

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

radiopharmaceuticals, for example.

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

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

ACTING CHAIR THOMADSEN: Thank you for your comment.

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

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

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

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

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

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

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

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

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

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

DR. VOLIOTIS: For any hospitalization?

MEMBER SUH: Yes.

DR. VOLIOTIS: No, overall not.

ACTING CHAIR THOMADSEN: Dr. Guiberteau.

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

DR. VOLIOTIS: There is no dose titration

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

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

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

MEMBER GUIBERTEAU: Thank you.

ACTING CHAIR THOMADSEN: Dr. Welsh.

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

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

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

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

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

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

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

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

have to review.

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

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

MR. FULLER: Meaning we would require three.

MEMBER WELSH: No.

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

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

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

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

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

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

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

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

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

ACTING CHAIR THOMADSEN: Thank you.

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

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

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

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

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

ACTING CHAIR THOMADSEN: Thank you, Mr.

Fuller.

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

ACTING CHAIR THOMADSEN: Dr. Langhorst.

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

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

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

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

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

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

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

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

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

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

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

ACTING CHAIR THOMADSEN: Dr. Welsh?

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

ACTING CHAIR THOMADSEN: Thank you. Dr. Suleiman?

MEMBER SULEIMAN: Yes, these are more just

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

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

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

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

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

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

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

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

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

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

DR. GERMINO: Chairman?

ACTING CHAIR THOMADSEN: Please identify yourself.

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

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

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

MEMBER SULEIMAN: Thank you very much.

ACTING CHAIR THOMADSEN: Dr. Welsh.

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

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

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

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

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

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

ACTING CHAIR THOMADSEN: Ms. Weil.

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

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

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

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

ACTING CHAIR THOMADSEN: Thank you.

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

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

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

both.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Bayer, as was alluded to at the very end,

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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-

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

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

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

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

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

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

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

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

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

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

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

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

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

ACTING CHAIR THOMADSEN: Dr. Suleiman?

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

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

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

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

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

ACTING CHAIR THOMADSEN: Dr. Palestro.

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

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

Zanzonico?

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

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

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

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

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

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

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

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

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

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

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

ACTING CHAIR THOMADSEN: Dr. Guiberteau?

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

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

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

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

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

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

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

ACTING CHAIR THOMADSEN: And directly into it.

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

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

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

(Laughter)

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

ACTING CHAIR THOMADSEN: They corrected it.

MEMBER MATTMULLER: I'm sorry.

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

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

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

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

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

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

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

radiopharmaceuticals in the past.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

MR. FULLER: Well, this is Mike Fuller and

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

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

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

ACTING CHAIR THOMADSEN: Dr. Langhorst.

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

(Laughter)

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

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

ACTING CHAIR THOMADSEN: Dr. Suleiman?

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

ACTING CHAIR THOMADSEN: Dr. Langhorst.

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

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

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

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

(Laughter)

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

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

ACTING CHAIR THOMADSEN: Okay. Consider it done.

(Laughter)

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

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

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

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

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

ACTING CHAIR THOMADSEN: Not you.

(Laughter)

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

ACTING CHAIR THOMADSEN: I did.

MEMBER GUIBERTEAU: Okay, good.

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

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

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

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

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

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

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

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

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

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

A quick review. In the summer of 2011 two

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

I throw in fluoro- and CT angiography, and

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Why did FDA allow the product back on the

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

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

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

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

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

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

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

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

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

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

Now, I thought about this but I felt I

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

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

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

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

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

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

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

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

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

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

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

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

ACTING CHAIR THOMADSEN: Dr. Van Decker.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

ACTING CHAIR THOMADSEN: Dr. Langhorst.

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

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

MEMBER SULEIMAN: Any change in the label

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

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

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

standard way they would have picked up the breakthrough.

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

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

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

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

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

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

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

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

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

MEMBER LANGHORST: I thank you for my education.

ACTING CHAIR THOMADSEN: Yes, Mr. Mattmuller.

MEMBER MATTMULLER: If I could continue

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

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

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

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

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

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

MEMBER MATTMULLER: In the past I --

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

few of those.

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

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

Now, most of the facilities that were

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

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

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

manufacturer.

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

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

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

licensees into following the package insert.

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

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

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

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

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

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

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

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

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

ACTING CHAIR THOMADSEN: Dr. Van Decker.

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

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

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

(Laughter)

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

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

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

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

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

ACTING CHAIR THOMADSEN: Mr. Mattmuller.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

ACTING CHAIR THOMADSEN: Ms. Weil.

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

particular facility with very high use?

DR. HOWE: I don't know.

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

MEMBER WEIL: Each patient who came back.

MEMBER SULEIMAN: They notified that, yes.

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

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

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

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

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

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

DR. HOWE: Yes, we did.

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

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

MEMBER SULEIMAN: And the other

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

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

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

it's done.

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

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

ACTING CHAIR THOMADSEN: Dr. Langhorst.

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

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

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

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

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

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

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

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

MEMBER LANGHORST: It's the sun.

(Laughter)

ACTING CHAIR THOMADSEN: Mr. Mattmuller.

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

MEMBER WELSH: Dr. Thomadsen?

ACTING CHAIR THOMADSEN: Dr. Welsh.

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

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

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

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

MS. FAIROBENT: Okay, thank you.

ACTING CHAIR THOMADSEN: Mr. Mattmuller.

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

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

DR. HOWE: Two thousand two.

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

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

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

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

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

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

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

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

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

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

ACTING CHAIR THOMADSEN: Thank you, Mr.

Mattmuller. Dr. Van Decker.

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

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

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

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

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

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

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

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

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

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

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

ACTING CHAIR THOMADSEN: Dr. Van Decker.

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

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

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

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

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

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

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

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

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

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

(No response)

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

MS. HOLIDAY: Okay.

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

(No response)

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

backups.

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

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

ACTING CHAIR THOMADSEN: Anybody have a feeling on that?

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

ACTING CHAIR THOMADSEN: I would also prefer September myself.

MEMBER WELSH: I agree.

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

MS. COCKERHAM: Understood, thank you.

MS. HOLIDAY: Thank you.

ACTING CHAIR THOMADSEN: Dr. Welsh?

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

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

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

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

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

MS. HOLIDAY: I believe --

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

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

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

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

MR. EINBERG: After May?

MS. COCKERHAM: Yes.

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

MS. HOLIDAY: Okay.

ACTING CHAIR THOMADSEN: Sounds like it, yes.

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

ACTING CHAIR THOMADSEN: Okay.

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

ACTING CHAIR THOMADSEN: No.

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

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

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

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

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

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