Official Transcript of Proceedings

NUCLEAR REGULATORY COMMISSION

Title: Advisory Committee On the Medical Uses of Isotopes

Docket Number: n/a

Location: Teleconference

Date: July 9, 2012

Work Order No.: NRC-1725 Pages 1-44

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NUCLEAR REGULATORY COMMISSION

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ADVISORY COMMITTEE ON THE MEDICAL USES OF ISOTOPES

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TELECONFERENCE

MONDAY, JULY 9, 2012

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The meeting convened telephonically at 11:00 a.m., Leon S. Malmud, M.D., ACMUI Chairman, presiding.

MEMBERS PRESENT:

LEON S. MALMUD, M.D., Chairman

BRUCE R. THOMADSEN, Ph.D., Vice Chairman

DARICE BAILEY

MILTON J. GUIBERTEAU, M.D.

SUSAN M. LANGHORST, Ph.D.

STEVEN MATTMULLER

CHRISTOPHER PALESTRO, M.D.

JOHN SUH, M.D.

WILLIAM VAN DECKER, M.D.

LAURA WEIL

JAMES WELSH, M.D.

PAT ZANZONICO, Ph.D.

NRC HEADQUARTERS STAFF PRESENT:

BRIAN MCDERMOTT, Director, Division of Materials Safety and State Agreements

CHRIS EINBERG, Acting Deputy Director, Division of Materials Safety and State Agreements

JANINE KATANIC, Acting Branch Chief Radioactive Materials Safety Branch

MICHAEL FULLER, Designated Federal Official

ASHLEY COCKERHAM, Alternate Designated Federal Official

SUSAN CHIDAKEL, Office of General Counsel

DONNA BETH HOWE, Medical Radiation Safety Team

RONALD ZELAC, Medical Radiation Safety Team

NRC REGION I:

SANDY GABRIEL

PENNY LANZISERA

NRC REGION III:

CASSANDRA FRAZIER

SARA FORSTER

PUBLIC PARTICIPANTS:

SCOTT BERTETTI, Bayer

DR. COLIN BIGGIN, Algeta

JEFFREY BOVA, Bayer

ROBERT DANSEREAU, NY State Dept of Health

WILLIAM DAVIDSON, University of Pennsylvania

DR. LOTHAR EVERZ, Bayer

LYNNE FAIROBENT, Am Assoc of Physicists in Medicine

DR. JOSE GARCIA-VARGAS, Bayer

MARIA GARRIGAN, Bayer

DR. JOSEPH GERMINO, Bayer

ALAN JACKSON, Henry Ford Hospital

JOHN JACOBUS, National Institutes of Health

DR. DEEPIKA JALOTA, Bayer

Dr. JANAKI KRISHNAMOORTHY, NY State Dept of Health

KAREN LANGLEY, University of Utah

RALPH LIETO, St. Joseph Mercy Hospital

DR. PETER LUEHRS, Bayer

GARY LUNGER, Bayer

KHALID MAMLOUK, Algeta

DR. PIERRE MAPOUYAT, Bayer

JANETTE MERRILL, Society of Nuclear Medicine

DR. ERIK MERTEN, Bayer

MICHAEL PETERS, American College of Radiology

DR. JEFFRY SIEGEL, Nuclear Physics Enterprises

MICHAEL SHEETZ, University of Pittsburgh

DR. MICHAEL TOMBLYN, Moffitt Cancer Center &

Research Institute

CINDY TOMLINSON, American Society for Radiation Oncology

DR. DIMITRIS VOLIOTIS, Bayer

DR. MONA WAHBA, Bayer

GARY WILLIAMS, Veterans Health Administration

MATT WILLIAMSON, Memorial Sloan-Kettering Cancer Center

NANCY YOUNG, Xcenda

JESSIE ZHOU – Bayer

P R O C E E D I N G S

11:01 a.m.

MR. FULLER: Okay. This is Mike Fuller at NRC headquarters. We're going to go ahead and get started.

MALE PARTICIPANT: Good morning, Mike.

MR. FULLER: Okay. As the Designated Federal Official for this meeting, I am pleased to welcome you to this public meeting of the Advisory Committee on the Medical Uses of Isotopes or ACMUI.

My name is Mike Fuller. I am the team leader of the Medical Radiation Safety Team, in the Radioactive Materials Safety Branch, and I have been designated as the federal official for this Advisory Committee in accordance with Title 10, Code of Federal Regulations Part 7.

Present today as the Alternate Designated Federal Official is Ashley Cockerham, the ACMUI coordinator. This is an announced meeting of the Committee. It is being held in accordance with the rules and regulations of the Federal Advisory Committee Act and the Nuclear Regulatory Commission.

The meeting was announced in the June 21st, 2012 edition of the *Federal Register*. This

meeting is being transcribed by the NRC in accordance with the Federal Advisory Committee Act, and in addition, I also want to make everyone aware that this meeting may also be transcribed or recorded by others.

The function of the Committee is to advise the staff on issues and questions that arise on the medical use of radioactive material. The Committee provides counsel to the NRC staff, but does not determine or direct the actual decisions of the NRC staff or the Commission.

The NRC solicits the views of the Committee and values their opinions. I request that whenever possible, the Committee try to reach a consensus on the procedural issues that will be discussed today, but I also recognize that there may be minority or dissenting opinions.

If you have such opinions, please allow them to be read into the record at the appropriate time. At this point, I would like to perform a roll call of the ACMUI members participating today. Dr. Leon Malmud, Chairman.

(No response.)

MR. FULLER: Dr. Bruce Thomadsen, Vice

Chairman.

VICE CHAIRMAN THOMADSEN: Present.

MR. FULLER: Ms. Darice Bailey, Agreement State representative.

MEMBER BAILEY: Present.

MR. FULLER: Dr. Milton Guiberteau, Diagnostic Radiologist.

MEMBER GUIBERTEAU: Present.

MR. FULLER: Dr. Sue Langhorst, Radiation Safety Officer.

MEMBER LANGHORST: Present.

MR. FULLER: Mr. Steve Mattmuller, Nuclear Pharmacist.

MEMBER MATTMULLER: Present.

MR. FULLER: Dr. Christopher Palestro, Nuclear Medicine.

MEMBER PALESTRO: Present.

MR. FULLER: Dr. John Suh, Radiation Oncologist.

MEMBER SUH: Present.

MR. FULLER: Dr. William Van Decker, Nuclear Cardiologist.

MEMBER VAN DECKER: Present.

MR. FULLER: Ms. Laura Weil, Patients'

Rights Advocate.

MEMBER WEIL: Present.

MR. FULLER: Dr. James Welsh, Radiation Oncologist.

MEMBER WELSH: Present.

MR. FULLER: Dr. Pat Zanzonico, Nuclear Medicine Physicist.

MEMBER ZANZONICO: Present.

MR. FULLER: Okay. I would like to state for the record that since we have at least seven members in attendance, a quorum has been established.

I will now ask NRC staff members who are present here in headquarters to identify themselves, and then after that we'll go out to the phones for other NRC staff.

MS. CHIDAKEL: Susan Chidakel, Office of General Counsel.

DR. HOWE: Donna Beth Howe, Medical Radiation Safety Team.

DR. KATANIC: Jeanine Katanic, Acting Branch Chief for the Radioactive Materials Safety Branch.

MR. EINBERG: Chris Einberg, Acting

Deputy Division Director for the Materials Safety and State Agreements Program.

MR. FULLER: Okay. Other headquarters NRC staff that are on the phone please?

MS. COCKERHAM: This is Ashley Cockerham.

MR. McDERMOTT: Brian McDermott, Division of Materials Safety and State Agreements.

MR. FULLER: Brian, could you go ahead and repeat? We had two folks at once.

MR. McDERMOTT: Sorry. Brian McDermott, Director, Division of Materials Safety and State Agreements.

MR. FULLER: And did I hear Ron?

MR. ZELAC: Yes. Ronald Zelac, Medical Radiation Safety Team.

MR. FULLER: Okay. Any other NRC headquarters folks who are on the phone?

(No response.)

MR. FULLER: Okay. I'd like now go to the NRC regions, and ask folks who are participating from the regions. Region I?

MS. GABRIEL: Sandy Gabriel.

MS. LANZISERA: And Penny Lanzisera.

MR. FULLER: Region III?

MS. FRAZIER: Sandy Frazier.

MS. FORSTER: Sara Forster.

MR. FULLER: Region IV?

(No response.)

MR. FULLER: Okay. Do we have anyone else from the Nuclear Regulatory Commission who is participating by phone?

(No response.)

MR. FULLER: Okay. At this point in time, I would like to do a bit of a roll call on folks, individual members of the public who have notified us that they plan to participate.

For some of these names, I want to apologize up front if I do not pronounce them correctly, and for the transcriptionist and for the record, if I do pronounce your name incorrectly, if you will please pronounce it correctly for the record.

First, Brian Abraham, Medical Imaging and Technology Alliance.

(No response.)

MR. FULLER: Scott Bertetti, Bayer.

MR. BERTETTI: Present.

MR. FULLER: Dr. Colin Biggin, Algeta.

DR. BIGGIN: Present.

MR. FULLER: Jeffrey Bova, Bayer.

MR. BOVA: Present.

MR. FULLER: Denise Cannaday, SMT, Incorporated.

(No response.)

MR. FULLER: Peter Currie, Bayer.

(No response.)

MR. FULLER: Robert Dansereau, New York State Department of Health.

MR. DANSEREAU: Present.

MR. FULLER: William Davidson, University of Pennsylvania.

DR. DAVIDSON: Here.

MR. FULLER: Casey Deitrich, CQ Transcriptions.

(No response.)

MR. FULLER: Dr. Lothar Everz, Bayer.

DR. EVERZ: Present.

MR. FULLER: Lynn Fairobent, American Association of Physicists in Medicine.

MS. FAIROBENT: Present.

MR. FULLER: Dr. Jose Garcia-Vargas,

Bayer.

DR. GARCIA-VARGAS: Present.

MR. FULLER: Maria Garrigan, Bayer.

MS. GARRIGAN: Present.

MR. FULLER: Dr. Joseph Germino, Bayer.

DR. GERMINO: Present.

MR. FULLER: Alan Jackson, Henry Ford Hospital.

MR. JACKSON: Present.

MR. FULLER: John Jacobus, National Institutes of Health.

MR. JACOBUS: Present, and the pronunciation is Jacobus.

MR. FULLER: Thank you. Dr. Deepika Jalota, Bayer.

DR. JALOTA: Present.

MR. FULLER: Dr. Janaki Krishnamoorthy, New York State Department of Health.

DR. KRISHNAMOORTHY: Present.

MR. FULLER: Karen Langley, University of Utah.

DR. LANGLEY: Present.

MR. FULLER: Ralph Lieto, St. Joseph Mercy Hospital.

MR. LIETO: Present.

MR. FULLER: Dr. Peter Luehrs, Bayer.

DR. LUEHRS: Present.

MR. FULLER: Gary Lunger, Bayer.

MR. LUNGER: Present.

MR. FULLER: Ragnhild Loberg, Algeta.

(No response.)

MR. FULLER: Dr. Pierre Mapouyat, Bayer.

DR. MAPOUYAT: Present.

MR. FULLER: Andrew McKinley, American Society of Nuclear Cardiology.

(No response.)

MR. FULLER: Ruby Meredith, University of Alabama at Birmingham.

(No response.)

MR. FULLER: Janette Merrill, Society of Nuclear Medicine.

MS. MERRILL: Present.

MR. FULLER: Dr. Erik Merten, Bayer.

DR. MERTEN: Present.

MR. FULLER: Vigdis Reinton, Algeta.

(No response.)

MR. FULLER: Dr. Maria Rivas, Bayer.

(No response.)

MR. FULLER: Joseph Rodgers, Theragenics Corporation.

(No response.)

MR. FULLER: Dr. Gerhard Schlueter, Bayer.

(No response.)

MR. FULLER: Dr. Jeffrey Siegel, Nuclear Physics Enterprises.

DR. SIEGEL: Present.

MR. FULLER: Michael Sheetz, University of Pittsburgh.

DR. SHEETZ: Present.

MR. FULLER: Rose Talarico, Bayer.

(No response.)

MR. FULLER: Dr. John Talian, Bayer.

(No response.)

MR. FULLER: Dr. Michael Tomblyn, Moffitt Cancer Center and Research Institute.

DR. TOMBLYN: Present.

MR. FULLER: Cindy Tomlinson, American Society for Radiation Oncology.

MS. TOMLINSON: Present.

MR. FULLER: Dr. Dimitris Voliotis, Bayer.

DR. VOLIOTIS: Yes, present.

MR. FULLER: Dr. Mona Wahba, Bayer.

DR. WAHBA: Present.

MR. FULLER: Gary Williams, Veterans Health Administration.

MR. WILLIAMS: Present.

MR. FULLER: Matt Williamson, Memorial Sloan Kettering Cancer Center.

MR. WILLIAMSON: Present.

MR. FULLER: Okay. That's all the folks that I'm aware that have notified us that they plan to participate. Are there other members of the public who are on the call?

CHAIRMAN MALMUD: This is a member of the Committee, Dr. Malmud, who joined you while you were taking roll, but I did not wish to interrupt you.

MR. FULLER: Okay, yeah. I was hoping that you had joined us, Dr. Malmud.

CHAIRMAN MALMUD: Yes, I had.

MR. FULLER: Okay. Are there other members of the public who would like to announce themselves?

MR. PETERS: This is Michael Peters,

American College of Radiology.

MS. VOU: This Jessie Zhou from Bayer.

MR. FULLER: I'm sorry, could you repeat that name?

MS. VOU: Jessie Zhou from Bayer.

MR. FULLER: Could you please spell your last name?

MS. VOU: Z-H-O-U.

DR. MAMLOUK: This is Khalid Mamlouk from Algeta. You need me to spell my last name?

MR. FULLER: Could you please?

DR. MAMLOUK: M as in Mary, A as in Apple, M as in Mary, L-O-U-K.

MR. FULLER: Okay, thank you. Anyone else?

(No response.)

MR. FULLER: Okay. Individuals who would like to ask a question or make a comment regarding a specific issue the Committee has discussed should request permission to be recognized by the ACMUI Chairperson, Dr. Leon Malmud. Dr. Malmud at his option may entertain comments or questions from members of the public who are participating with us today. Comments and questions

are usually addressed by the Committee near the end of the meeting, after the Committee has fully discussed the topic.

I would also like to add that the handouts and agenda for this meeting are available on the NRC's public website. As a courtesy to all who are listening to this meeting, and because the meeting is being transcribed, I would also like to ask for all participants to put the phone, put your phone on mute unless you are speaking.

If you do not have a mute button, you may press *6 to mute and unmute the line as needed. Also please remember to note place your phones on hold, as the meeting may be disrupted by background music, if your phone system defaults to music.

Okay. I would like to point -- at this point, I would like to turn the meeting over to Mr. Chris Einberg. He is our Deputy Director for the Division of Materials Safety and State Agreements, and he would like to make a few opening comments.

MEMBER EINBERG: Okay, well thank you Mike. Just a few brief comments. First, I'd like to thank the ACMUI subcommittee for the work and their recommendations for licensing of radium-223 chloride.

Radium-223 chloride represents a first in class alpha-emitting therapeutic radiopharmaceutical and is being considered for use in treatment of skeletal metastases.

Staff will consider the recommendations and make a decision on how radium-223 chloride will be licensed, and at this point, I'd like to turn it back to Mike here.

MR. FULLER: Thank you, Chris. Okay. At this point, I'd like to turn the meeting over to Dr. Leon Malmud, who's the chairman of the ACMUI, and so that the ACMUI can begin. Dr. Malmud.

CHAIRMAN MALMUD: Thank you. The purpose of this meeting is to provide recommendations on licensing of radium-223 chloride, and the subcommittee members who prepared the report, which you have read and have available to you is labeled "Third Draft," dated July 3rd, 2012.

It was prepared by the Committee with Dr. Zanzonico as chair. I would therefore open the discussion by first asking Dr. Zanzonico for any comments that he may have.

MEMBER ZANZONICO: This is Pat Zanzonico. Thank you, Dr. Malmud, and good morning

everyone. I think, I really have nothing to say at this point, beyond what's presented in the summary statement and recommendation of our draft report, and but just to crystallize what we're primarily recommending, and that is that physicians that are already authorized, or authorized users in general, already authorized to use therapeutic radiopharmaceuticals under 35.390 or 35.396, already have, in our opinion, have the requisite education, training and experience to safely and effectively use radium-223 chloride.

As such, licensing of authorized users of radium-223 chloride under 35.390, either category G-3 or G-4, or alternatively 35.396(d)(2) is therefore recommended. We also included a recommendation that the patient- administered activities of the radiopharmaceutical and the residual activity post-administration should be assayed at the end user site, that is at the point of service immediately prior to and after administration of the radiopharmaceutical.

Overall, and other than that, we found the biological and clinical data compelling, in terms of the potential utility of this new agent in advance

castrate-resistant prostate cancer. So I think I'll confine my opening remarks to that, and thank you.

CHAIRMAN MALMUD: Thank you, Dr. Zanzonico. Are there any comments that members of the subcommittee wish to make, in addition to those made by Dr. Zanzonico?

The members of the subcommittee were Darice Bailey, Susan Langhorst, Steven Mattmuller, Chris Palestro, Orhan Suleiman, Bruce Thomadsen and James Welsh.

(No response.)

CHAIRMAN MALMUD: I hear none. Are there comments from members of the public?

DR. JALOTA: Bayer would like to request permission of Dr. Malmud to make a comment.

CHAIRMAN MALMUD: Please do. Please just repeat your name, so that it may be included in the minutes.

DR. JALOTA: My name is Deepika Jalota, and I will be handing it over to Dr. Jeffry Siegel.

DR. SIEGEL: Good morning. I'd like to thank the ACMUI Committee for the subcommittee report, and give my best wishes and regards to Dr. Malmud, Committee chair, and also to Dr. Zanzonico

for the subcommittee chair.

The report recommends that radium-223 dichloride be licensed under 35.300, and asserts that physicians already authorized to use 300 materials pursuant to 390 or 396, have the requisite education, training and experience to safely and effectively use radium-223 with no additional T&E required.

Bayer believes that these recommendations are most consistent with placing radium-223 dichloride in dosage Category 3 in 35.390, since all current Category 3 AUs would not require additional work experience.

If, however, radium-223 dichloride were to be placed in Category 4, additional T&E in the form of at least three cases would likely be required to attain AU status, and has the potential to postpone patient access to treatment.

Therefore, Bayer would respectfully request that radium-223 dichloride be considered as a Category 3 radiopharmaceutical. Would the ACMUI wish to comment on this recommendation?

CHAIRMAN MALMUD: That's a question from Dr. Siegel to the subcommittee members.

MEMBER ZANZONICO: Well, this is Pat

Zanzonico. I'll offer my opinion and other members of the subcommittee certainly can voice theirs. But I would tend to agree. I think that personally, I think Category 3 is the most appropriate licensing category for radium-223 chloride.

So in my opinion, we would agree with that recommendation by Bayer. But again, I would welcome any comments from other members of either the subcommittee or the ACMUI.

CHAIRMAN MALMUD: Thank you, Dr. Zanzonico. Are there other comments? Are there comments from members of the public?

MEMBER LANGHORST: Dr. Malmud, this is Sue Langhorst.

CHAIRMAN MALMUD: Yes, Dr. Langhorst.

MEMBER LANGHORST: Okay, thank you. To me, I've always been confused by Category 3 and Category 4 because of the and/or statement in between the "to" and "the regulation." To me, I believe that what you learn for one parenteral administration is pretty close to what you learn for the other type category of parenteral administration.

So I see no difference between the two, and my understanding of the regulations has always

been that you have either one of those, and typically, we only have isotopes in Category 3.

So I voice my confusion over really what's the difference between three and four, and really if the regulations require that there be cases in each one of those, or there's just three cases needed in the parenteral administration. Thank you.

CHAIRMAN MALMUD: Thank you. Comments regarding Dr. Langhorst's comment of Category 3 versus Category 4?

(No response.)

CHAIRMAN MALMUD: I hear none. Are there other comments from members of the public?

(No response.)

CHAIRMAN MALMUD: So before us is a document which is thorough and prepared by the subcommittee chaired by Dr. Zanzonico, entitled the Subcommittee report on licensing for radium-223 chloride. Quite simply, the proposal is that nuclear physicians and other radiologic physicians who are trained in administration of therapeutic radiopharmaceuticals be granted permission to use this particular agent in the same fashion. Is there any discussion of this proposal?

MEMBER GUIBERTEAU: Dr. Malmud?

CHAIRMAN MALMUD: Yes.

MEMBER GUIBERTEAU: This is Mickey Guiberteau. I'm not a member of the subcommittee. I certainly agree with the report, and I thought it was very well done. I just have an editorial comment which I would like to see addressed, and that is for those who read this document as it will by various individuals with different degrees of experience and expertise with the regulatory processes, in terms of the reference to radium-223 chloride as being -- its status with the FDA, this is referenced a number of times in the report.

Just as an example, in terms of approval and non-approval, there are various forms of approval of radiopharmaceuticals or drugs by the FDA, and I remember in February, when the FDA granted approval to proceed with an expanded access program, or its investigational status, excuse me, there was a great deal of confusion or some initial elation that perhaps it had been approved.

So in line 70 of the report, I think it states very well that it's described as routine, non-investigational clinical use as the positive. But I

think in other parts of the report, in fact, there is reference to it being non-approved, without FDA even being mentioned.

In some areas, it just -- it uses different language. What I would like, since we have an FDA representative and a chairman of the subcommittee who is very familiar with this, that if we could use some uniform language so that those reading it will not --

I think we all know what we mean by this, but it isn't clear necessarily to others what approved and non-approved means, and generally non-approved means for routine clinical use, although the drug is approved for investigational use and now for the expanded access program.

Which means that those that can't enter controlled clinical trials may be treated with this under certain circumstances in a clinical setting. So in any case, I would just offer that as a suggestion, to make this more uniform throughout the document, when we talk about approved and non-approved. Thank you.

CHAIRMAN MALMUD: Thank you, Dr. Guiberteau. Dr. Suleiman is of course with the FDA.

Orhan, would you care to comment on line 70, which I'll quote, which says "Importantly, if approved by the U.S. Food and Drug Administration, it would represent the very first alpha article emitting ray pharmaceutical in routine (non-investigational) clinical use."

MR. FULLER: Dr. Malmud, this is Mike Fuller. Unfortunately, Dr. Suleiman was not able to be with us today.

CHAIRMAN MALMUD: Is there a representative from the FDA with us?

(No response.)

CHAIRMAN MALMUD: If not, Dr. Zanzonico, was this clarified for you any further?

MEMBER ZANZONICO: Pat Zanzonico. Dr. Guiberteau's points are very well taken. It was at Dr. Suleiman's suggestion, who is the FDA representative to the ACMUI, that the status of radium-223 chloride be made clear in our subcommittee report, so that everyone who read it would understand it is not yet approved for routine, that is non-investigational clinical use.

But I also agreed with Dr. Guiberteau that at certain points in the draft report, there's

some jargony language used that may be clear to all of us on the Committee on others, that may not be generally clear. So what I would say at this point is that I and the rest of the subcommittee members will confer with Dr. Suleiman and develope some uniform accurate language that would be clear to anyone reading the report.

So the point is well-taken, and I think we'll address that issue offline with Dr. Suleiman.

CHAIRMAN MALMUD: Thank you, Dr. Zanzonico. May I ask a question just for clarity, since we have a large audience on this call, and that is that if there were to be a patient who fulfilled the clinical requirements currently, could that patient be treated at an institution with a broad license in which there has been experience with parenteral administration of radiopharmaceuticals for therapy? Does anyone know the answer to that question?

MEMBER GUIBERTEAU: Well Dr. Malmud, this is Mickey Guiberteau. I mean I --

CHAIRMAN MALMUD: Please.

MEMBER GUIBERTEAU: Well, in February, the FDA did approve to proceed with an expanded

access program under investigational drugs. Now I'm not an expert in this, and I wish Orhan were on the phone or someone else to address this.

But the language that I believe FDA uses for this is that under certain circumstances, in certain institutions, that if you have seriously ill patients that cannot participate in a controlled clinical trial, that under this program they could be treated. But certainly this does not mean routine clinical use.

But I think it would be, you know, attendant on the subcommittee to get Orhan's input into this, because as I admit, this form of regulation is not in my area of expertise.

CHAIRMAN MALMUD: Thank you. I think that we all understand that it's not ready for routine clinical use yet. My question was should a nuclear physician be made aware of a patient who would benefit from this therapy, though he or she is not part of a protocol, could there be a special "hardship" application of the radiopharmaceutical, and would the radiopharmacy house be allowed to make it available? This is in an interim.

MEMBER GUIBERTEAU: Right.

CHAIRMAN MALMUD: Does anyone from the manufacturer have any insight into this? This question is addressed to the members of the public, who represent the manufacturer, or to Dr. Siegel, who I believe is familiar with the status of the product at the current time.

DR. JALOTA: Hi. This is Bayer. Permission to speak, Dr. Malmud.

CHAIRMAN MALMUD: Please. Introduce yourself.

DR. JALOTA: My name is Deepika Jalota and I represent Bayer. Essentially, the EAP program is an ongoing trial that is under the IND, and it's for investigational use only as far as treating patients, and in order to expand access to patients that qualify under the inclusion/exclusion criteria.

Right now, the drug is under investigational use and can only be administered under a clinical protocol for the ongoing study.

CHAIRMAN MALMUD: Thank you. That clarifies it. Are there any further questions or discussion regarding the report of the subcommittee?

MS. WEIL: Dr. Malmud, this is Laura Weil, Patient's Rights Advocate.

CHAIRMAN MALMUD: Yes.

MEMBER WEIL: Have a question regarding the subcommittee's report at line 111, the section on Radiation Safety and Logistical Considerations. I wonder if, given that this is an outpatient procedure, if there are any concerns -- and it's an alpha-emitter, regarding internal contamination of the public if patients are immediately discharged post-treatment, and within the 36 minute half life for the lead-211.

If there any concern regarding public restrooms, the GI tract excretion of this particular isotope, if there needs to be some regulation regarding sequestering patients for the half hour that would be necessary to reduce that exposure.

CHAIRMAN MALMUD: Thank you for bringing the question forward. Would a representative from Bayer who understands the protocol be able to answer the question?

(No response.)

CHAIRMAN MALMUD: Is there anyone who's able to address the issue.

DR. JALOTA: Yes, if you could please clarify the question again, I'm sorry.

CHAIRMAN MALMUD: The question relates to the public safety, to the safety to the members of the public, who might be exposed to a patient who received the product, particularly in the one hour period after having received the product. Radiation --

MEMBER WEIL: If I might clarify, Dr. Malmud. Specifically, the internal contamination that might be caused by exposure to feces in public restrooms.

CHAIRMAN MALMUD: This is longer than one hour. Okay, go ahead.

MEMBER WEIL: Well no it isn't, but it's the 36 minute half life of the lead-211 that concerns me.

CHAIRMAN MALMUD: Thank you. Is there a physicist with Bayer who wishes to address the question?

MEMBER ZANZONICO: Well, this is Pat Zanzonico. I might offer some comments in addition to anyone from Bayer or anyone else would like to offer.

CHAIRMAN MALMUD: Thank you.

MEMBER ZANZONICO: Certainly, the

external or direct exposure should be minimal. For example, strontium-89 or Metastron, as opposed to say from I-131, where there's a more significant X and gamma ray emission and a more significant external hazard.

I think in terms of the internal hazard, it's important to bear in mind that the administered activities of radium-223 chloride, which are of the order of 100 microcuries for a 70 kilogram standard person in total, what is of magnitude less than one typically is counted certainly for I-131 thyroid disease, or even Metastron, where I believe the standard is four doses or four millicuries or 4,000 microcuries.

So while there's a theoretical contamination hazard, there's really no obvious or significant internalization pathway. I think any accidental trace internal contamination, and this really would be a trace contamination, would be insignificant.

Bayer, for example, provided some calculations or the results of some calculations in a document in response to comments at the time of our last teleconference, presenting some worst case

scenarios in terms of contamination and other means of exposure.

It really would look like given the amounts of activity, that contamination doses really would be insignificant even in worse case scenarios.

CHAIRMAN MALMUD: Thank you. Does that apply also to the radioactive progeny, including the lead-211, which has a half life of 36.1 minutes?

MEMBER ZANZONICO: Yes. Yeah, I believe so, that -- yeah. I would just say yes.

CHAIRMAN MALMUD: Thank you.

MEMBER ZANZONICO: In general terms, my comments would apply to radium-223 and all of its progeny.

CHAIRMAN MALMUD: Thank you. Does that answer the question that was raised?

MEMBER WEIL: Yes, thank you it does. I have just a further request for clarification. Is there any concern re shielding for the gamma emitters that are described as also existing?

CHAIRMAN MALMUD: We'll ask that question to Dr. Zanzonico as well.

MEMBER ZANZONICO: Certainly. Again, I think from a practical point of view, no. We're

talking about a very low abundance in terms of the total energy accompanied with the decay of radium-223 and its progeny, a very low abundance, a very small proportion of that total energy being emitted in the form of X and gamma rays.

And again, given the very low administered activities of radium-223 chloride, which are orders of magnitude below those for even diagnostic radio traces, with much more abundant X and gamma ray emissions, for which there really is no significant shielding problem.

So I think -- I don't foresee any practical difficulties in terms of the X and gamma ray component of radium-223 decay and the decay of is progeny.

CHAIRMAN MALMUD: Thank you, Dr. Zanzonico. Does that address the concern you just raised?

MEMBER WEIL: Yes, thank you.

CHAIRMAN MALMUD: Thank you.

MEMBER LANGHORST: Dr. Malmud, this is Sue Langhorst.

CHAIRMAN MALMUD: Yes, Dr. Langhorst.

MEMBER LANGHORST: Yes. I wanted to add

for Laura's education that the 30 minute half life of one of the daughter products of radium-223, that daughter product will be around as the radium-223 decays. So it doesn't just all go away within 30 minutes. The progeny are existing as the radium is decaying. So I just wanted to let you know that, Laura.

CHAIRMAN MALMUD: Thank you, Dr. Langhorst.

DR. JALOTA: Sorry, Dr. Malmud.

CHAIRMAN MALMUD: Yes.

DR. JALOTA: This is Deepika Jalota. Bayer would like to request permission to speak.

CHAIRMAN MALMUD: Please do.

DR. JALOTA: Erik Merten, would you be able to state Bayer's position?

DR. MERTEN: Sure, thanks. So I have nothing to add content-wise, but I would like to thank Dr. Zanzonico for his remarks on that issue, with regard to public restrooms and shielding. This is exactly the position we have as well, and the only thing that I should add is that the drug has already been applied in a clinical setting more than 1,000 times without any radio safety issue. Thank you.

CHAIRMAN MALMUD: Thank you, Dr. Merten. Are there any other comments from members of the Committee, subcommittee or members of the public?

MEMBER VAN DECKER: Dr. Malmud. Yes. Who's speaking please?

MEMBER VAN DECKER: This is Bill Van Decker. How are you?

CHAIRMAN MALMUD: Fine, thank you.

MEMBER VAN DECKER: I just wanted to say that the subcommittee report was incredibly well thought-out, and I think it is a very reasonably defendable position they put forth. I guess my question is from a general radiation safety perspective, there will be a lot of people reading this as it comes out, and it's kind of in an intermediate stage.

At what point does the NRC see, you know, communication with full stakeholders on a frequently-asked question basis, or on a draft guidance basis or on some information statement basis, you know, through the professional societies or through themselves, trying to get some more of this information to a broader AU population, so that people understand where we are and what this means in

relation to the process and where we're going and that type of stuff?

CHAIRMAN MALMUD: Thank you for the question, Dr. Van Decker. That's addressed to a member of the NRC staff.

MR. FULLER: Yes. This is Mike Fuller with the NRC staff. Dr. Van Decker, the best way that I can answer that question is that once we have a recommendation from the ACMUI, I think that recommendation is part of our process for making a decision.

Once a decision is made, depending on where we come out, we will communicate through the appropriate means. It may be in terms of, you know, posting things to our website and of course communicating with the various professional societies through the normal means.

So again, I guess the answer to your question is that it sort of depends on exactly how we might do it. But the fact that once a decision is made, we will definitely communicate broadly with the folks that would be interested.

CHAIRMAN MALMUD: Thank you, Mike. Thank you. Now at this point, are there any other

comments?

(No response.)

CHAIRMAN MALMUD: Hearing none -- oh, excuse me.

MR. LIETO: This is Ralph. May I make a comment and ask a question?

CHAIRMAN MALMUD: Please, Mr. Lieto.

MR. LIETO: One time was I think to address Sue Langhorst's question earlier about the difference under 300 Category 3 and 4. Probably have to go back into the ACMUI minutes when this Part 35 section was revised, but I think the intent was that four was handle anything, including alpha emitters as well as gamma emitters that were over 150 keV.

So I think it was meant to be sort of a catch-all that did not meet Category 3, and was intentional on having that specific sort of future application. My last comment is that I want to strongly support the subcommittee in its recommendations.

I think they're very well laid out in their licensing considerations, and I really endorse their recommendation on assaying the therapeutic dosage prior to administration.

My question has to do with if the committee has had any consideration or knowledge on the dose calibrator assay specifically, in that I'm assuming the calibration settings are different for glass in the plastic syringe. Are these settings being supplied by the vendor to their knowledge, or maybe Bayer might want to answer this also, or is this something that each site is supposed to develop?

CHAIRMAN MALMUD: Thank you for the question. It appears to be address to Bayer. Does anyone from Bayer wish to address the issue of the dose calibrator vis-a-vis plastic or glass syringes.

DR. JALOTA: This is Deepika Jalota on behalf of Bayer. I'd like to hand it over to Jeff Siegel.

CHAIRMAN MALMUD: Thank you. Dr. Siegel.

DR. SIEGEL: Thank you, Dr. Malmud. NIST has already published a study on dose calibrator use for radium-223 chloride and found that independent of volume and container, that is syringe versus vial, that the dose calibrator can be calibrated using a single vial setting within three percent.

So what Bayer intends to do is to use a NIST-traceable source, so that when they send the material out, this will be, as NIST has agreed, considered a secondary standard, to which the sites can then adjust their dial setting on their dose calibrator, so that they will have a properly assayed activity for radium-223 chloride.

CHAIRMAN MALMUD: Thank you, Dr. Siegel. Did you explain that would be between two and three percent variance?

DR. SIEGEL: Yes, that's what they found. I think the highest percent variance, because they used several different dose calibrator manufacturers, is on the order of three and a half or four percent activity difference.

CHAIRMAN MALMUD: Thank you. Is that referenced in this document?

DR. SIEGEL: I believe it is, Dr. Malmud. It's referenced, I think the last reference in this document.

CHAIRMAN MALMUD: The very last reference. All right. That would be on page --

DR. SIEGEL: That's reference 16, correct.

CHAIRMAN MALMUD: Very good, thank you. So that reference is available for those who wish to confirm that. Any other questions or comments?

MR. FULLER: Dr. Malmud, this is Mike Fuller. Just if I may, it's becoming a little bit difficult to hear everyone because someone is typing very loudly, and it's coming across the entire call. So if whoever's typing could please mute their phones, or perhaps move your keyboard away from the phone, it would be greatly appreciated. Thank you.

CHAIRMAN MALMUD: Thank you for bringing that to our attention. Once again, are there any additional comments?

MR. JACKSON: This is Alan Jackson from Henry Ford Health System, Dr. Malmud, and I'd like to pose a question, and I guess mainly to NRC. This question relates to licensing. Typical broad scope licenses list things like atomic number 3 through 83.

So that would preclude easy adoption of radium-223 for broad scope licenses. That is, we would need to do a license amendment. Has there been any thought by NRC to change common licensing conditions for this case?

CHAIRMAN MALMUD: Thank you for the

question. It's addressed to NRC staff.

MR. FULLER: This is Mike Fuller, and the answer to the question, pretty simply, is no. The question from Henry Ford Hospital is correct. For broad scope licensees, it is typically based upon atomic number and they are typically licensed as atomic number 3 through 83.

So this would not fall under that. So a license amendment would be needed, in order to be authorized for something other than if you need authorization for something other than 3 through 83.

So not to say that at some point in the time in the future we could not consider, but we have received no such request, and the amendment is the only means right now by which someone could be authorized.

CHAIRMAN MALMUD: Thank you for that clarification. I'm certain that the question will arise, and that is for someone who already has -- for an institution that already has a broad license, how long would it take for it to process an amendment request?

MR. FULLER: It should be a fairly routine amendment request. So whatever the regions.

Typically, you know, it would depend on workload and so forth and how many they get and so forth and so on. So it would be hard to say exactly. But it would be a fairly straightforward amendment request.

CHAIRMAN MALMUD: Thank you. Any other questions?

(No response.)

CHAIRMAN MALMUD: Hearing none, it appears that the subcommittee report, first of all, should be complimented for the effort put into it and the final product, and secondly, would someone care to make a motion for approval of the subcommittee report?

MEMBER LANGHORST: This is Sue Langhorst. I so move.

CHAIRMAN MALMUD: Thank you, Dr. Langhorst. Is there a second?

VICE CHAIRMAN THOMADSEN: This is Bruce Thomadsen. I will second.

CHAIRMAN MALMUD: Thank you, Dr. Thomadsen. Thank you for seconding. Any further discussion?

MEMBER MATTMULLER: Yes, Dr. Malmud. This is Steve Mattmuller. Can we vote it as is, or

were we going to rework the FDA approval language a bit first?

CHAIRMAN MALMUD: Thanks for raising the question, Steve. I'm not sure that we can rework the FDA approval language until we have some feedback from the FDA. If we approve it in its current form, it would allow us to amend it with whatever clarification comes forth from the FDA.

On the other hand, if we defer it, we may be delaying forward movement. Whichever the Committee, whichever approach the Committee wishes to take is certainly acceptable to the chairman.

MEMBER GUIBERTEAU: Dr. Malmud?

CHAIRMAN MALMUD: Yes. Who's speaking?

MEMBER GUIBERTEAU: This is Mickey Guiberteau.

CHAIRMAN MALMUD: Yes.

MEMBER GUIBERTEAU: Actually I consider this more editorial than substantive, since it doesn't directly relate to the regulation of radium-223 under the NRC's rules. So you know, I would be comfortable moving forward with an understanding that we would make those changes at another time, when there was more input from those who have expertise in

this area.

CHAIRMAN MALMUD: Dr. Guiberteau, does that mean that you would move this forward now, with anticipation of the changes, or you would hold it back?

MEMBER GUIBERTEAU: No, I'm sorry. That means I think -- I feel that we could move it forward.

CHAIRMAN MALMUD: Thank you, thank you. Any further comments? We have a motion, which has been seconded. All in favor?

(Chorus of ayes.)

CHAIRMAN MALMUD: Are there any opposed?

(No response.)

CHAIRMAN MALMUD: Are there any abstentions?

(No response.)

CHAIRMAN MALMUD: The motion moves forward with unanimity. Is there any other business to be accomplished at this time in this teleconference?

(No response.)

CHAIRMAN MALMUD: I hear none. May I once again thank the subcommittee for a very thorough

report, and particularly Dr. Zanzonico and also may I in parentheses thank Dr. Thomadsen for his chairmanship of the Committee in my absence. I very much appreciate the effort that was put forward.

VICE CHAIRMAN THOMADSEN: This is Bruce Thomadsen, and I'll just say that it's good to have you back.

CHAIRMAN MALMUD: Thank you.

MALE PARTICIPANT: Amen.

CHAIRMAN MALMUD: Thank you very much. It's good to be back, and once again, thank you all for your participation, and we're looking forward to further details from the FDA regarding the questions that were raised, and perhaps the introduction of a very effective therapeutic agent for patients who have otherwise unresponsive metastatic disease from prostate cancer. Thank you all. Is there a motion for adjournment?

MEMBER GUIBERTEAU: So moved. This is Mickey Guiberteau.

CHAIRMAN MALMUD: Thank you, second?

MEMBER ZANZONICO: Seconded, Pat Zanzonico.

CHAIRMAN MALMUD: Thank you. The

meeting is adjourned.

(Whereupon, at 11:54 a.m., the meeting was adjourned.)