Official Transcript of Proceedings

NUCLEAR REGULATORY COMMISSION

Title: Workshop: Enhancing Development of Targeted Alpha Emitting Radiopharmaceuticals, Special Session on Actinium-225

Docket Number: (n/a)

Location: teleconference

Date: Wednesday, September 22, 2021

Work Order No.: NRC-1654 Pages 1-250

QHDO#U1#JURVV#DQG#FR1/#LQF1#
Frxuw#Uhsruwhuv#dqg#Wudqvfulehuv#
4:49#47wk#Vwuhhw/#Q1Z1/#Vxlwh#533#
Zdvklqjwrq/#G1F1##5333<#
+535,#5670776

UNITED STATES OF AMERICA

NUCLEAR REGULATORY COMMISSION

and

FOOD AND DRUG ADMINISTRATION

+ + + + +

WORKSHOP: ENHANCING DEVELOPMENT OF TARGETED ALPHA EMITTING RADIOPHARMACEUTICALS,

SPECIAL SESSION ON ACTINIUM-225

+ + + + +

WEDNESDAY,

SEPTEMBER 22, 2021

+ + + + +

The workshop convened via Video Teleconference, at 9:00 a.m. EDT.

PRESENT:

MARK S. BERGER, MD, Actinium Pharmaceuticals, Inc.

DENIS BERGERON, PhD, National Institute of Standards and Technology

KISH CHAKRABARTI, FDA

DANAE CHRISTODOULOU, PhD, FDA

CATHY CUTLER, PhD, Brookhaven National Laboratory

LISA DIMMICK, NRC

ANTHONY FOTENOS, MD, PhD, FDA

MICHELLE HAMMOND, NRC

KELLEE JAMERSON, NRC

RAVINDRA KASLIWAL, MSc, PhD, FDA

SARAH LOPAS, NRC

LOUIS MARZELLA, MD, PhD, FDA

NEETA PANDIT-TASKAR, MD, Memorial Sloan Kettering Cancer Center

VICTOR PAULUS, Fusion Pharmaceuticals, Inc.

DONIKA PLYKU, PhD, FDA

HALEH SABER, PhD, MS, FDA

MEGAN SHOBER, Wisconsin Radiation Protection Section

RICHARD WAHL, MD, Society of Nuclear Medicine and Molecular Imaging

KEVIN WILLIAMS, NRC

ALSO PRESENT BY RECORDED VIDEO:

MITCHELL ANSCHER, MD, Virginia Commonwealth University

P R O C E E D I N G S

(9:02 a.m.)

MS. DIMMICK: Okay, we're ready to go ahead and get started with today's FDA NRC workshop. So let me kick it off to the introductions. Dr. Marzella, off to you.

DR. MARZELLA: Great, thank you. Thank you, Lisa. Dear colleagues, good morning. My name is Lou Marzella and it's my pleasure to welcome you to our FDA NRC workshop.

Our topic for discussion today is Enhancement of the Development of Targeted Alpha-Emitting Radiopharmaceuticals, and we will place special emphasis on actinium-225.

So important diagnostic and therapeutic uses of radiopharmaceuticals are being realized and more anticipated.

Targeted alpha therapies in oncology is a topic of very active clinical research. So it's very timely that we come together today to discuss this topic.

The objective of the workshop today is to provide an overview of scientific and regulatory considerations for product development.

Our goal is to make clear the path for

making promising new oncology therapies available to patients.

To this end, the workshop will address product quality and preclinical study considerations.

We will then turn to a clinical discussion that will be focused on early phase studies, in particular, the development of dosimetric approaches that are specific to alpha emitters.

And the final session will then be devoted to feedback from some of the industry and academic investigators. We are eager to hear about their experiences and challenges.

I would also at this point like to acknowledge the contributions of several NRC and FDA offices, in particular on the FDA side, the contributions of the Office of Product Quality and the Office of Oncology and the Office of Specialty Medicine.

Recognition is also due to the National Laboratories as well as the National Institute of Standards and Technology.

Finally, I would like to express my gratitude for the participation by the Society for Nuclear Medicine and Molecular Imaging.

Again, welcome. We look forward to a

productive meeting. And at this time, I would like to introduce Kevin Williams of the NRC.

W: Good morning. Hopefully you can see me. I think I can see myself. Good morning and thank you, Dr. Marzella.

On behalf of the U.S. Nuclear Regulatory Commission, I welcome everyone to this FDA NRC workshop.

As stated, my name is Kevin Williams, and I am the Director for the Division of Materials Safety, Security, State, and Tribal Programs in the Office of Nuclear Material Safety and Safeguards at the U.S. Nuclear Regulatory Commission.

The FDA and the NRC continue to demonstrate the ability to effectively coordinate, collaborate, and communicate with stakeholders in the development of smart regulatory approaches for the use of new radiopharmaceuticals and radiological devices.

Last October, the FDA and NRS held an extremely well-coordinated workshop to exchange information on enhancing development of novel technologies.

The goal of the workshop was to leverage knowledge of regulated products and determine opportunities to expedite regulatory use of these novel

technologies.

As a result of that workshop, the FDA and the NRC decided to hold an additional public meeting to discuss targeted alpha emitting radiopharmaceuticals.

I would like to thank the FDA and the NRC staff and the workshop steering committee who have worked diligently to plan and coordinate today's workshop.

I would also like to thank all presenters for their support, substantive experiences by panelists and attendees, including regulatory authorities, scientists, industry, and healthcare professionals with various areas of expertise on advancing targeted alpha emitting radiopharmaceuticals as represented at today's workshop.

Today's workshop provides a forum to exchange information and perspectives on the regulatory framework in compliance of radiation safety of novel technologies amongst all stakeholders, from patients, physicians, pharmacists, nurses, researchers, materials transportation, and diverse medical communities.

Bringing all stakeholders together will

improve the global understanding of the many regulatory and compliance topics associated with radiation safety and novel technologies.

I would like to note that this workshop supports the NRC's mission by ensuring that we effectively leverage opportunities for licensees to use new technologies in accomplishing safety and security for the beneficial use of radioactive material.

I look forward to a great exchange of information today. Thank you for your time and attention.

I will now turn the meeting over to Cathy Cutler for her remarks.

DR. CUTLER: So good morning. It's my honor to introduce Dr. Richard Wahl. He is the Elizabeth E. Mallinckrodt Professor, Chair of the Department of Radiology, Director of the Mallinckrodt Institute of Radiology, and Professor of Radiology and Radiation Oncology at Washington University in St. Louis.

He's additionally the President of the Society of Nuclear Medicine and Molecular Imaging, which is a non-profit scientific and professional organization that promotes the science, technology,

and practical application of nuclear medicine and molecular imaging therapy.

The society represents over 50,000 members in the field, including physicians, technologists, physicists, and pharmacists, with the ultimate goal of improving human health.

Dr. Wahl started as a chemist where he got his BS at Washington University. He went on to do his residency in radiology there, and then went to the University of Michigan where he started as assistant and all the way up to professor, then left for Johns Hopkins University where he was the Henry N. Wagner Professor of Nuclear Medicine.

He has a longstanding interest in nuclear oncology, including extensive studies with FDG and cancer imaging, which contributed to FDG being widely used in cancer imaging and treatment response.

He was the first author of PERCIST criteria for treatment response, and he was the co-inventor of radioimmunotherapy lymphoma with anti-CD radioantibodies, leading to the FDA-approved drugs Bexxar and Zevalin.

He's the co-inventor of precision whole body dosimetry, and has wrote over 480 publications. He has won a number of awards from the de Hevesy Award,

the Berson and Yalow Award, and Pendergrass New Horizons Lecture in RSNA, the Marie Curie Lecture in EANM, and in 2005 was recognized as the Most Influential Radiology Research.

He additionally received the Saul Hertz Award, which is a lifetime achievement award recognizing individuals who have made outstanding contributions to radionuclide therapy.

He has further been elected a member of the National Academy of Medicine.

Today, he's going to talk to us about ongoing work with actinium-225 antibodies in mice and humans, and the title of his talk will be Clinical Evolution of Alpha Particle Radiopharmaceutical Therapy: Focus on Actinium-225. Dr. Wahl? We can't hear you.

MS. LOPAS: You may be muted, Dr. Wahl. I don't know if you muted your cell phone or --

DR. WAHL: Well, my phone --

MS. LOPAS: You're good.

DR. WAHL: Am I audible now?

MS. LOPAS: Yes, you are.

DR. WAHL: Okay. Perhaps you can, let's see, need to be able to --

MS. LOPAS: Do you need Kellee to walk you

through sharing your slides?

DR. WAHL: Let's see. I think, let's see if this works. Well, you're seeing my email, perhaps.

MS. LOPAS: We are, yes.

DR. WAHL: Well, luckily, it's from you. Maybe we best -- okay.

MS. LOPAS: I think just open up your PowerPoint if you have it.

DR. WAHL: It is open. I've just got to get to the other screen.

MS. LOPAS: Okay. Okay, and then just slideshow and you're all set, I think.

DR. WAHL: Okay. Excellent.

MS. LOPAS: Oh, and one more thing. I think we need to see, is it display settings? Maybe click on display settings up there and, very small on my screen, yes, swap presenter view and slideshow.

There you go. Perfect. You're all set.

DR. WAHL: Okay. That was easy. Anyway, let's see if this will behave properly. Here are my disclosures.

I do have some conflicts with some clinical trials and some advising activities.

Like to go over a few things today in the next 29 minutes, just briefly sketch out where we are

with radiopharmaceutical therapy and how we got here, talk about the several randomized trials that have been done with radiopharmaceutical therapy, and then focus on alpha particles and then mainly focus on actinium.

And this is a very rapidly moving field and giving a talk about this and putting in clinical perspective is a little difficult because some of the literature is only published in abstract form and preprint.

So I'm going to include some stuff that is only in abstract but also some preprint stuff just for discussion.

And then we'll briefly discuss some of our challenges going forward.

So I think this group knows what theranostics basically is, but radiotheranostics in particular is pairing a diagnostic agent with a therapeutic radiopharmaceutical.

The diagnostic establishes the presence of a target in general. It can inform whether a patient is eligible for treatment and depending on the specific pairing, it may be able to tell us what radiopharmaceutical, what administered activity to use.

This isn't always the case and it's in

evolution. In some settings, there's no imaging of a therapeutic agent.

If we're doing dosimetry, it's mostly been done by SPECT but some can be done by PET, and we have the issues of radiopharmaceuticals being given as a fixed dose or a patient-specific dose.

As I'll say at the end of the meeting, the end of my talk, the patient as their own dosimeter is really what really matters. What can the patient tolerate? What is safety?

So there's a linkage between dosimetry and outcomes, but with these alphas, it's challenging right now because those signals are quite modest.

So Dr. Cutler mentioned some of my earlier work with my colleagues in I-131 anti-CD20.

I'd like to point out that this was sort of a dual level target. This particular drug, tositumomab, was FDA approved but now is off the market due to low sales, but it had specific targeting to identifiable protein, CD20.

It also had patient-specific precision radiation dosing using a tracer dose of the same radiopharmaceutical.

Of course, this is somewhat similar to how iodine-131 could be used in thyroid cancer, though,

in general, dosimetry wasn't routinely done with I-131, nor is it, and this was built into the therapeutic regimen.

So just as a review for those of you who may not know this history, Bexxar was the commercial name and there was a dosimetric dose of 5 millicuries, and forgive my not using SI, and this was then imaged over three time points of the whole body.

Whole body radiation dose was calculated, then a therapy dose, which was prescribed based on individual patient pharmacokinetics.

And the reason for this is there was significant variability from patient to patient. So what we found to be the maximum tolerated, the appropriate dose at 75 centi-gray in patients who are heavily pretreated, those with rapid clearance would need more radioactivity administered and those with slow clearance would need less.

So this dosimetry can adjust for this and it's a very attractive concept that led to quite an acceptable safety profile with the drug, but it also led to increased complexity of the dosing scheme.

So I would point out, though, that we were able to get this FDA approved in patients who had refractory lymphoma that had failed chemotherapy, but

were also able to advance it based on the good results of refractory patients who were using as the initial therapy for non-Hodgkin's lymphoma, follicular type.

So this movement from a later phase sort of salvage treatment to up front was one thing that this study and this drug did.

And data were published in New England Journals showing outcomes up to 10 years, and in it, half the patients at least were surviving at this point with progression free survival quite common.

And so these were very long duration responses with this I-131 agent.

So what about randomized trials? Well, this drug was used, I-131 tositumomab, in a randomized trial.

These data are shown here. They have matured. And I think it's of interest that when chemotherapy of lymphoma was given and compared to chemotherapy followed by radioimmunotherapy, these later data, the combination of immunotherapy and chemotherapy, was significantly better in terms of profession free survival and 10 years.

However, this overall survival was overlapping in the groups and so this randomized trial did show an advantage of radioimmunotherapy, but it

was a relatively modest one.

Now another trial with ibritumomab tiuxetan, commercial name was Zevalin, these are a little hard to see but I refer you to the JCO in 2008, this was the so-called FIT trial where consolidation was done with yttrium-90 Zevalin, and the top curve is probably the most relevant.

It's progression free survival and we can see a significant difference of a couple of years of the groups that received the radioantibody after chemotherapy versus the group that did not.

And this was a randomized trial. So big differences here, clear activity and improvement of outcomes in lymphoma as measured by PFS.

So those drugs, though effective and shown to have advantage at the randomized trials, are either off the market or not widely used, and sometimes that's the challenge of being early into a field, as there were a number of commercial reasons, business reasons that they weren't successful, I would say.

And here's some data for some other agents. This is an example of a gallium DOTATATE scan in neuroendocrine tumor on the left and a lutetium DOTATATE scan on the right.

And this is a good example of a theranostic

pair. This particular therapy is now widely used.

And this data published by Strosberg in the New England Journal shows that both progression free survival and overall survival in a group of neuroendocrine tumor patients was significantly improved using the lutetium DOTATATE.

So those are strong data that led to regulatory approval.

Here's another one that recently came out. This is a smaller study, but I think intriguing, that in the yttrium-90 microsphere setting in hepatocellular carcinoma that by using personalized dosimetry versus standard dosimetry, longer overall survival was seen.

Now, these are relatively small numbers of patients, but they are intriguing data.

Now, there's a lot of interest in PSMA right now with the recent FDA approval of two diagnostic agents, Gallium and a FANP agent targeting the PSMA molecule.

There's also an antibodies understudy and there will likely be additional discussion of this agent.

But this was a theranostic. Here's an example of a Gallium PSMA scan on the left, and then

lutetium PSMA being used for TheraP.

These have been used, this lutetium PSMA has been used fairly widely in Europe and outside the U.S. and certainly in clinical trials in the U.S., as I'll refer to in a minute.

But a couple of notable randomized trials with a review include the TheraP study that Dr. Hofman led in Australia and New Zealand, where patients were randomized to either chemotherapy agent carbazitaxel or to lutetium-PSMA-617 therapy.

These are castration-resistant prostate cancer patients. And what you see here are waterfall plots, and the red in this case is good, and the PSMA group had, the lutetium-PSMA therapy group had a 66 percent incidence of decline, so 50 percent in PSA, whereas the chemo group in active therapy was less effective.

And in this study, which is in The Lancet, longer PFS was seen in the lutetium-PSMA group. There was less grade three, four toxicity in the lutetium-PSMA group versus chemotherapy.

And there was improved pain control and quality of life in the PSMA group versus chemotherapy. So these are all encouraging findings compared to an active therapy.

Now this trial, which I think most of you are familiar with, but it was very recently published in the New England Journal, is the VISION Trial.

And this trial was a randomized trial of the lutetium-PSMA versus standard of care. And here you see at the top, imaging-based progression free survival, and we see overall survival.

Both are substantially improved versus standard care alone. Standard care wasn't exactly standard, as this was a large, randomized trial and this is a significant improvement in outcome for these groups.

But I would call your attention to the fact that these curves go downhill pretty rapidly. So this, while improving outcomes, is not really curative.

Being able to cure this disease, of course, is our goal, but here we improve it but it's really not cured.

So this, if we know that there's a portfolio of therapeutic agents that are available using the radiopharmaceutical therapies, and obviously not time to review all of them but I'll just highlight that MIBG is one, samarium-153-EDTMP, among others that we don't have the time to discuss.

So what about alpha particles, which I'm

really supposed to talk about, but I wanted to put these in context.

Why are we not curing patients perhaps? Well, one thing to think about is these are data that I think are really informative.

The probability of cure is somewhat related to the energy of the emission of the radioisotope.

So I-131 is a less energetic beta than yttrium-90. And basically, the higher the energy of the beta particle, the more difficult it is for it to kill small clusters of cells or single cells.

And you see on the right here, curability plot which shows that as cell number goes down, you actually, it's harder to cure than if cell number is up.

And that seems odd at first, but that is because what happens, and these are some mathematical data from long ago that we looked at with Ray Raylman, in particular, but if you look at that sphere here, a 1.5-millimeter radius tumor, a lot of the yttrium-90 energy events occur outside of this small tumor.

So a lot of energy is deposited outside the tumor. And this can result in toxicity. If there's all tumor around here, it's great.

So if the tumor is highly heterogeneous, this may be highly hesitated. But or small volumes, you're going to see that most of the events would escape the site of emission.

In this particular paper, we looked at the theoretical effects of a high magnetic field strain the electrons had and came up with something we call magnetically enhanced radionuclide therapy.

And this really hasn't gotten very far because at the time it wasn't possible to build 10 tesla magnets.

However, this is more feasible now. But anyway, using high magnetic fields, you can actually change the behavior of high energy beta emitters and constrain them to a smaller volume.

And the effects differ by isotope. If they're fairly profound, here's an 80 percent improvement in energy deposition with this high energy beta emitter, the effects with the low energy emitter, such as iodine, are only about 20 percent.

But the thought here was both how do we keep the energy in the tumor and cure these small foci?

Well, the obvious answer was alpha emitters, but we at that time didn't really have access to those, although I would point out that Marie Curie

and her colleagues actually put radium into patients probably almost 100 years ago, without precedent.

Anyway, the alpha emitters have the advantage of high linear energy transfer, half-lives, as we'll see compatible with therapy, versatile chemistry, and improving availability.

So we're going to focus on actinium, but there are a number under investigation. Clearly, not enough time to discuss all of them.

And basically, the alpha emission of the helium nucleus is very toxic, very potent, and it is able to kill cells with irreparable DNA damage.

The electrons take more event and allow more DNA repair. So these alpha particles are bigger, deposit a lot of energy, and the one thing I would say is that since the energy travels such a short distance, if the radiopharmaceutical doesn't reach the tumor, if there's heterogeneity, profound heterogeneity delivery, then they may be insufficient.

So here this is shown schematically the alpha particles with the short range and beta particles with a considerably longer range.

Alpha is also our less subject oxygenation effect, and that, at least in practice, at least potentially, be better in hypoxic tumors, although the

tumor would actually have to be reviewed sufficiently that the alpha emitter would reach it.

But here highlighted are some alpha emitters that have been attracting attention. Given the time, we're going to talk about actinium-225.

And I point out that the half-life is almost 10 days, which is well matched to that of an antibody, intact antibody.

Bismuth-213 received a lot of interest earlier due to its availability in the generator system.

And I think one of the key issues is how quickly does the carrier molecule localize in the tumor?

Small molecules can localize very rapidly, but intact antibodies can be very slow. My opinion is that in general, the therapeutic should have a half-life equivalent or longer than the localizing molecule.

If an antibody localizes slowly, the radiopharmaceutical will not, will mainly deliver its radiation off target.

There are exceptions to this. If the tumor is highly accessible, such as in the blood or intraarterial or perhaps intracavitary, intrapleural,

those situations that shorter lived alpha emitters may be well fashioned to the biological of localization of larger molecules.

Just a little bit on Bismuth-213. It can be used to treat tumors. We've used this a bit in animal models.

And I'm going to show you this briefly, but this only works well when given intravenously and the tumor has been given by an intravenous route.

And here are some comparisons between Bismuth-213 rituximab, yttrium-90 rituximab, and I-131 tositumomab.

I could show you here that initially, those cells clear when you give them intravenously, and then the animals are treated, and we see the controls have rapid regrowth.

The high energy beta emitter doesn't do as well in the system as the low energy beta or the Bismuth-213 rituximab.

And this is optical imaging, where the cells have a reporter gene and we see that there really is a difference, depending on the isotope attached.

And in this particular study, both I-131 tositumomab and bismuth-213 rituximab were capable to cure.

It is an unusual model in that the cells were given IV and just moved to mature. So you can see, the ones on the left didn't work very well for this low tumor volume situation.

These animals were followed quite a long time ago. Here are some of the growth curves. We see even with this short half-life of Bismuth-213, there was a therapeutic advantage.

So the cards were stacked against them but it was sufficient. And here are survival data, showing that the agent was effective.

Short lived isotopes, relatively alphas like astatine-211, can also be effective in disseminated models.

Now, back to what I'm really supposed to be talking about, alpha emitters, I think we all know that there's one other randomized trial that led to a drug approval, and that's for radium dichloride.

And these are the data on radium dichloride, which is an available agent for treating skeletal metastases.

So radium 223 prolonged survival for 11 months to essentially 15 months. And that is now an available agent for survival and palliation of bone decay.

So actinium, huge growth in interest in alpha particle literature. This is what I found on PubMed.

Actinium has had a really rapid growth. You see on the bottom middle, and actinium-225, specifically as well.

So there's been this explosive growth. And there are 32 known isotopes of actinium, from actinium-205 to 236, and there's also seven isomers.

But the main ones that I think we're interested in are the actinium-225 and actinium-227, which can be a contaminant.

This is the main decay scheme here, and we see that actinium decays to francium and then to astatine, bismuth, and then thallium.

But as a result, there are emissions of alpha particles, and this slide from George Sgouros shows that these alpha particles have somewhat different energy, but all have a relatively short range in terms of their energy deposition.

So these are animated and hopefully this slide works correctly. But you have actinium, francium, astatine, and the bismuth related alpha emissions.

But there's sort of a, not all alphas are

exactly created equally, but they are very similar.

And Dr. Cutler I think will speak more about actinium supply. I'd say currently there's a great effort on going worldwide and right now it's still a little hard to get if you're an investigator.

And there have been concerns about actinium availability. And one of the, these are a couple things that Dr. Sgouros was kind enough to lend to me.

So one of the concerns always is, is there actinium-227, and as I said, that long half-life could be a concern in terms of radiation safety or dose, or at least we'll discuss it.

Now, how do you get actinium onto a peptide or an antibody? Well, one of the nice things about actinium is it will chelate into DOTA, which is widely used.

But the efficiency of chelation is relatively slow. So heating is essential. So here's a good efficiency, but this had to be heated to 95 degrees. That's pretty bad for antibodies.

So with antibodies, the efficiency of labeling is sometimes less. There's a two-step and a one-step method.

And there's been a lot of interest in

having a more rapid method in getting radioactivity into the chelates on antibodies in a single step.

The advantage of rapid labeling would be less radiolysis and less wasted actinium. So this is an area of great interest.

If actinium's not well chelated, and these are some, this is three actiniums that was injected that we've done, it'll go to the liver and spleen, and you don't want that.

This very nice review by Dr. Wilson on some of the different ways to label. There's a lot of chelators that are being looked at.

I'll highlight a few of these. Obviously, a great deal of research interest. Some work well. In our own settings, we've been using it, DOTA, and have found that it works quite well for labeling anti-CD20, and that it localizes to tumors very similar to the localization we've seen with zirconium ofatumumab.

So that's interesting that these two potentially could be paired. So what about the clinical data?

Well, there's not as much published as one might like, but I'd like to say that early data, with actinium-225 anti-CD33 was done, and I believe this

will be discussed later today, but this, I had a chance to use this in a leukemia patient back when I was in Baltimore, and this has been a topic of interest and I look forward to an update from the commercial provider on this topic.

Why don't we just move ahead here? There's a couple of areas where there's been progress. One is, although there's very little published, this is an example of a 25-actinium DOTATOC.

And here's a partial remission in a patient reported by Richard Baum and colleagues. So this is a clinical example.

We see a significant uptake and a diminished tumor size.

And there's an abstract that was in the Journal of Nuclear Medicine this year from India, and unfortunately, it's not published yet, but I refer to it because it's a lot of patient. That is very interesting.

Eighty-two patients were treated with a median of five actinium-225 DOTATATE cycles. And in this group, only about a third of the patients were lutetium progressors.

Some of them had not received prior peptide radionuclide therapy, and 30 percent had stable days.

And they went up to nine cycles. So this is very interesting, very preliminary. In their experience, their median progression free survival was 24 months, and they had very little toxicity.

So it's early data. It's abstract data. But very interesting and promising.

The other area of substantial interest where there's more data, including a recent meta-analysis that I'll highlight, deals with actinium PSMA targeting.

And this particular case from South Africa got a lot of attention and we see a patient being treated with actinium-225 PSMA 617, showing a visually or a significant remission of tumors.

Here, we see from the Journal of Nuclear Medicine, a study where a patient was treated and had a significant decline in tumor burden as measured by PSMA PET.

These patients who were studied had a substantial decline in PSA and a significant number in an early case of study.

In that paper from the Journal of Nuclear Medicine 2017, the dose escalation that was done in Heidelberg showed what it looked like was the balance between dose and toxicity.

So here they escalated on body weight and administered activity, and they found responses to be more common at the higher radioactivity dose, but the toxicity to become unacceptable due to xerostomia at that dose.

So this was an effort to do dose finding and I believe that the 100 I think is what they were settling on.

There have been several studies, this one recently recorded in the European Journal of Urology, where the PSA response to lutetium was compared to the PSMA therapy.

But on the left here is the PSMA actinium therapy where there was a substantial degree of activity in this therapy in patients who had been treated.

However, we do see, and we look at the graph here, that these are the overall survival after starting therapy.

The median progress-free survival was three and a half months. And the overall survival was 7.7 months. So this was, these patients have mass relief.

And in this group from, this was recent, as I said, in European Urology, those patients who had

bulky liver disease did even less well.

So while active, these patients' disease did eventually typically win, unfortunately.

And this is a swimmer plot and it shows the different therapies with the red being actinium-225 PSMA.

And what we see is that the patients were not under therapy too long with actinium PSA relative to their earlier therapy.

This isn't surprising, but I think it puts in place visually what the time course is in patients who are treated for prostate cancer and for this therapy as being integrated late, and it's a very difficult clinical situation.

Now, this literally just came out in the last couple of weeks, and I think it's worth reviewing.

This is a meta-analysis of actinium-225 PSMA therapy in metastatic castration-resistant prostate cancer.

And these may be hard to see, but this is now available online in the Journal of Nuclear Medicine.

They looked at nine studies with actinium PSMA PET, and these are the forest plots of the therapeutic response.

We see that a greater than 50 percent decline in PSA is not uncommon, and some decline in PSA is very common.

The other thing we saw in terms of toxicities is xerostomia to be quite common, although quite variable as well among these studies, and anemia, leukocytopenia, and thrombocytopenia to occur, but relatively infrequently.

So the summary of this meta-analysis, and I think it's worth a look, because it's the largest report on this divergent group of actinium PSMA studies in the literature, is that a 50 percent decline in PSA was seen in 61 percent of patients.

Eighty-four percent of patients had a decline in PSA. Mean progress-free survival was nine months. Mean overall survival was 12 months.

Again, this was a highly diverse group of patients. Xerostomia was seen in two-thirds of the patients, but severe anemia, leukopenia, and thrombocytopenia were relatively infrequent.

So this is probably the largest report we have.

So here's the graphical abstract showing the good by chemical response in almost two-thirds and solidary dysfunction in about two-thirds as well.

So in the last few minutes, I'd like to just highlight, here's some clinical trials that are listed on clinicaltrials.gov.

This was a few days ago when I put this together. The diverse range, and I would refer you to those, but there clearly are trials that are using actinium-225, one of which is using francium as a theranostic care.

What about quantitation? I know there will be more discussion about this. There's a lot of interesting quantitative SPECT.

As stated in this article, the time is now. And I think we're getting much better at it. There are detectable photons.

The francium decay and the bismuth decay both have some gamma emissions. However, and in principle, you should be able to tell them apart.

And just recall that if the francium is loose, if it goes somewhere else, though, it would be interesting to tell them apart, although the argument is with PSMA that these are internalized and are basically colocalized.

It is, at least in principle, possible to image actinium PMSA. This is from the literature. But you see on the left, gallium PSMA, and this is from India, shows the very modest uptake one can detect here.

And interestingly, they used three photopeak. But we see these are very low count images.

And I think given these low counts, and we see how many dots there are outside of the patient, that there's a lot of issues about background correction and other challenges.

Again, I refer you to this in Clinical Nuclear Medicine. There's another case example of imaging with actinium PSMA.

There's a high uptake in the kidneys in this particular instance, and the kidneys could be visualized.

But I would point out that some of the dosimetry that have been obtained were PSMAs that have included extrapolations expecting that lutetium predicts actinium, and that is how the group at Heidelberg did it.

This is, I would caution you, I only found this at a pre-print server, so it's not yet published. I found it a little interesting that there were -- this is energy spectrum for the paper.

This is from Hopkins, Dr. Liapi and her colleagues. But you see three photopeaks here. The low energy one I think is probably not the relevant one.

But these two, they were trying to separate francium from the other decay. And so here, they're trying to show the difference between francium and bismuth.

They do look the same here, and I would just say that this is an area of substantial interest

and investigation.

MS. DIMMICK: Dr. Wahl, we're out of time.

DR. WAHL: Okay, I got two slides left, I think.

MS. DIMMICK: Okay, thanks.

DR. WAHL: Yes. I would say that this paper is just accepted for publication. Dr. Benabdallah, Dr. Thorek, Dr. Jha and others from WashU have been using a low count approach to reconstruction for quantifying low count SPECT studies including radium and thorium and actinium.

And this has some promise, but we still are limited on the counts. These data, again, suggest that this low count method is more accurate.

The variance from traditional methods is much less.

So I'd say that there are cautions on dosimetry in the Clemens Kratochwil paper. They described a case that, quote, exclusively illustrates methodological limitations of dosimetry, and warns about a critical reliance on dosimetry as a dose limiting organ, saying basically that the patient as the dosimeter may be the most appropriate approach as dosimetry improves.

So I guess I'd like to summarize. Thanks

for your attention. Covered a lot of ground here. I look forward to the other talks.

But both the randomized trials show the benefit of radiopharmaceutical therapies, cures are elusive, actinium is very attractive as a general alpha emitting agent, and supply, as it improves, will be very helpful.

The data with NET targetings are limited, are quite encouraging. The dosimetry and end results with the PSMA are also encouraging.

New approaches to low count dosimetry are promising but I'd say not yet fully validated. There are many opportunities ahead for actinium therapies with or without a theranostic cure.

Thank you very much for your attention. I'd like to really thank Dr. Thorek, Jha, Longtine, Abou, and others for their contribution. That's it.

MS. DIMMICK: Okay. Thank you, Dr. Wahl. And we do have some questions for you that we'd like to just address at the end of session two in that Q and A session.

DR. WAHL: Sure. Are you able to reclaim control of the screen, or do I have to --

MS. DIMMICK: You can stop sharing and then Danae Christodoulou will take over from here.

DR. WAHL: Yes, thank you.

DR. CHRISTODOULOU: Good morning. Can everyone hear me okay?

MS. DIMMICK: Yes, your audio is fine.

DR. CHRISTODOULOU: Welcome to Session Two, Novel Radiopharmaceuticals: Standards Development, Product Quality Considerations, Supply and Demand.

I'm Danae Christodoulou. I'm a Branch Chief of the Office of Pharmaceutical Quality of the Office of New Drug Products at the FDA, supporting diagnostic and therapeutic radiopharmaceuticals.

I'm also an inorganic chemist by training. Graduated from the University of Michigan.

The first speaker in our session is my colleague at the FDA, Dr. Ravi Kasliwal, and it's my pleasure to introduce him.

He has been instrumental in many FDA committees as well as USP, developing standards, different guidances, and assessing very complex radiopharmaceutical, diagnostic, and radiotherapeutic radiopharmaceuticals at the FDA over the years. Ravi?

DR KASLIWAL: Can you hear me now?

MS. DIMMICK: Yes, your audio is good.

DR KASLIWAL: Okay, and you can see my

slides, I hope?

MS. DIMMICK: Yes.

DR KASLIWAL: Okay. Good morning. My name is Ravi Kasliwal and I'm, as Danae mentioned, I'm a CMC expert in the Office of New Drug Products and the Office of Pharmaceutical Quality at CDER/FDA.

So at FDA, we believe that a quality product of any kind should consistently meet the expectations of users, and drugs are no different.

Patients expect safe and effective medicine and with every dose they take, and therefore pharmaceutical quality, assuring that every dose is safe and effective, free of contamination and defects.

This is what gives patients confidence in their next dose of medicine.

In this presentation, I will go over how the CMC information for a radiopharmaceutical product may be organized and regulatory application, how information concerning the radionuclide can be provided, and I will use actinium-225 as an example, how one may approach the issue of controlling and reporting radionuclidic impurities, particularly long-lived radionuclidic impurities.

I would also like to clarify some of the aspects of radionuclidic impurity that is used in the

quality control of particularly actinium-225 radiopharmaceuticals.

I will briefly go over qualification of the radiolabeling process, particularly when the impurity amount continuously increases.

And finally, I would like to emphasize the importance of establishing non-radioactive reference standards responding to radioactive drug, particularly in case of small bond cure, which is critical for structure characterization and confirming the radiochemical identity.

I would like to also emphasize importance of establishing NIST reference standards for actinium-225.

So in this audience, everybody probably knows that the requirement or required form for submitting information and application is the Common Technical Document.

Now, CTD was working with the idea that you have a drug substance which is tested and released, and then it's formulated in the drug product, which is then tested and released as a final product.

We all know that radiopharmaceuticals, for radiopharmaceutical manufacturing is a little bit different, where the radioactive drug substance is

generally not isolate data. It forms in situ during the drug product manufacture.

Therefore, we recommend that you consider following when organizing your work. You should have a drug substance section.

For example, for biomolecule, if it's a monoclonal antibody type product, you should have a drug substance section for the bult chelate containing molecules, for example DOTA-linked monoclonal antibody or any other chelator linked to small monoclonal antibody to describe manufacturing and controls.

You should have drug substance section for the radioactive material described in manufacturing and control.

You should have a drug substance section for the radioactive drug. This section should be used to describe the nomenclature, structure, general properties, and structural characterization, reference standard, and any other relevant information about the drug molecule.

The radioactive drug forms see that each of the manufacturing and product controls can be incorporated in the drug products section.

Now, in some cases, you may need a drug product section for a vialed chelate containing

product.

Some of you are doing that. It's such a point of use. This section should describe the manufactured vialed product along with manufacturing product quality controls for the vial.

And finally, you should have a drug product section for the radioactive drug product that is a product that is to be marketed for use or used in investigational studies.

And obviously, any information may be referenced to other NDA, BLA, or type-II DLF.

Now, let's have a high-level look at production of actinium-225, and Dr. Cutler will probably describe this in much more detail.

Actinium-225 broadly can be produced either by actinium-225 generator or by proton bombardment of thallium-232.

Now, advantage of generator produced actinium-225 is that the product is free of other actinium isotopes, but the issue is that there is only a limited amount of material available by itself.

So the Department of Energy has been looking at other ways to produce actinium-225, which has led to accelerator produced material.

The advantage of accelerator production

method that can produce relatively large amount of actinium-225 to meet the needs, but the major issue is the product contains other actinium isotopes, including the actinium-227 as impurity.

Now, actinium-227 has a half-life of 21.8 years, and when you compare its half-life to 10-day half-life of actinium-225, the relative amount of actinium-227 would keep on increasing with time, both in actinium nitrate raw material and in the actinium radiopharmaceutical itself until the end of shelf life.

So now as a drug product manufacturer, you must establish material control for actinium-225 raw material.

So towards that end, you would need to establish specifications for actinium raw material, for example, actinium nitrate.

So in establishing classification of impurity and quality would suggest that you consider specifications for appearance. That is the material received without apparent defects.

There's classifications for radiochemical identities, classifications for radiochemical purity, radionuclidic identity, radionuclidic purity, specifications for impurities, such as radionuclidic, radioisotope impurities, actinium-227 or any other

contaminating relevant radionuclides.

And there may be some other non-radioactive elemental impurities that may interfere with the radiolabeling process.

The results from the lot may be accepted from the actual analytical results for the lot provided in qualified supplier COA.

You will, however, still need your specifications and your own analytical letters for each of the best attributes.

Now, actinium-227 is an undesired impurity. It does not contribute to efficacy and could have safety implications.

Therefore, its amount in the product must be kept as low as possible. Towards that end, all possible approaches to reducing the impurity content in the patient, such as rapid production methods, reducing hold times for actinium nitrate, and for the radiolabeled product, and limiting the drug product shelf life, should be explored and implemented.

Now, with respect to actinium nitrate raw material, you should establish limits for actinium-227 at the time of acceptance of this material from supplier.

And for supply for releasing it for

production, as I discussed on the previous slide, you should establish actinium-227 limit that will not be exceeded when actinium raw material is actually used in your manufacturing process, radiolabeling process.

So you should establish a maximum hold time or use period for actinium raw material.

With respect to controlling actinium-227 impurity in the final drug product itself, you will need to establish limit for actinium-227 related impurity in the drug product as a specified impurity.

You will need to provide justification for the proposed impurity limit. Now, this justification may be based on studies that show the actinium-227 related impurity will not be retained in the body on a long-term basis.

To show that, these studies might include mass balance studies, basically confirming to show that what goes in comes out and it's not retained on a long-term basis, in vitro stability studies using physiological conditions to show that actinium does not come off the chelate, and the physiological conditions, different people use different speculates.

And justification should also consider that actinium-227 impurities, a proposed limit will not significantly adversely affect dosimetry of the

intended actinium-225 product.

And my colleagues will go over these aspects more in detail in later presentations.

I would like to caution that introduction of new radionuclidic impurity may require reevaluation of the drug product radionuclide impurity quantitation method.

This is particularly so when you're going from generator produced actinium-225 to accelerator produced actinium-225.

It may also necessitate implementing of a new analytical method that can quantitate actinium-227 in a drug product.

Now, if you're changing the source of actinium-225 during an investigational study, say from generator to accelerator produced actinium-225, you would need to submit an IND amendment prior to implementing this change.

Now towards that end, we know that you have met the raw material specifications, that is actinium nitrate specifications, to account for new radionuclidic impurities, to establish use period for actinium nitrate, establish validated hold times, as discussed in previous times.

You should revise the drug product

specifications to include a justified limit of actinium-227 related impurities.

You should change the affected analytical method. You should requalify the manufacturing process, that's radiolabeling process for accelerator produced actinium-225, and I will talk about that a little bit later.

And you should provide data verification batches and assess impact on drug product shelf life.

Now, I want to take a slide to emphasize that FDA expects that the finished product will be manufactured in the CGMP manufacturing facility and be sent to the clinical site or to the user of the drug product as a ready to use product.

Radiotherapeutic products generally should not be designed as kick products. Also, I want to clarify that the regulations in 21 CFR 211 are that CGMP regulations for therapeutic radiopharmaceuticals.

Now, I would like to go over some of the quality tests that are performed on actinium-225 radiopharmaceuticals.

First, let's consider how the identity of the radioactive drug might be established. As part of the control of quality, in addition to ensuring the

radionuclides in the correct desired radionuclide, it is also necessary that the radioactivity in the correct chemical form.

And there may be various approaches to establish the correct identity and confirming it at the time of quality control test.

The actinium-225 radioactivity is conjugated to various different molecules. They can be large volume biomolecules or small molecules, and the approach may be different.

Now, radiochemical identity must be an ambiguously established as part of the structure characterization of radioactive drug substance.

Just characterization of precursor is not sufficient. You take the precursor radiolabel and the process molecular structure changes.

So in addition to assuring that the new structural aspect of the molecule, you must ensure that the integrity of the molecular structure is characterized and the precursor is not altered during the radiolabeling and purification process.

Towards that end, we recommend, as far as small molecules are concerned, that you assess possible de-establishing a non-radioactive reference standard.

Using an element that has similar

chemistry to actinium-225, some kind of surrogate standard, and some people have used lanthanum as a surrogate element.

The identity should be established, and the identity should be established using the reference standard, and then using two orthogonal methods having different operating principles.

Finally, once the radiochemical identity is established, the retain release method must be specific for the radiochemical, but that is to be able to distinguish between the intended molecule and related structures that may potentially form.

And you can assess this by stress stability studies.

With respect to radiochemical curing methods, the methods should in the test study give you the percentage of radioactivity that is associated with the radioactive drug molecule.

A method that simply separates unbound actinium-225 from bound actinium-225 cannot be assumed to be a valid radiochemical purity determination method.

You cannot assume that the bound activity is in the desired chemical form, or the activity is from a single molecular entity. You have to prove and

confirm that as part of your validation exercise.

Now, besides unbound actinium-225, the method must be capable of separating ligand, for example, peptide, and potentially potential structure related radioactive impurities.

Ligand degradation should be evaluated during stress stability studies and determined to determine potential degradation pathways that may occur as part of the manufacture or may occur during a store of instability.

Also, as I mentioned, we recommend that you evaluate possible using a surrogate reference standard with fully characterized structure to established chromatographic profile of the drug molecule.

We highly recommend using an HPLC-based method or a combination of HPLC or TLC method for confirming the radiochemical purity as relates to stability.

The radiochemical purity method must be stability indicated. In fact, all methods that are used as stability assessment should be stability indicating.

Now, regarding quantitating and reporting a radionuclidic impurity, there are two aspects,

radionuclidic impurity and specific radionuclidic impurities.

With respect to radionuclidic impurity, the acceptance criteria should be specified to one decimal point at least, and you should provide justification to describe how the proposed acceptance criteria was derived.

In addition to radionuclidic impurity, specific radionuclidic impurities of concern should also be included in the drug product specifications.

In the application, both in drug substance and drug product sections, an assessment of all potential impurities should be discussed, and mitigation and control procedures should be implemented.

With respect to analytical methods, you must have a validated analytical regulatory method. The method should be able to quantitate the individual impurities to provide an accurate result on total radionuclidic impurity.

If a single method is not able to do so, different methods may be needed, particularly when impurities have different radiation emission properties.

Now, three general comments concerning the

radioanalytical method used, concerning the radioanalytical methods used, specifically with actinium-225 radiopharmaceuticals.

For actinium-225, generally methods use detection of gamma emission from actinium-225 decay products, as you saw in the previous presentation from francium-221, from bismuth-212, to actinium activity.

Now, for accurate results, actinium-225 and its decay products must be in secular equilibrium so that the gamma emission information can be extrapolated to actinium-225 activity.

Method description in the submissions must include the hold periods for the drug product samples and during analysis as appropriate.

You must describe how the hold periods were established. This description also be provided to justify the hold period and how the accuracy of actinium-225 measurement is assured.

Actinium-225 is an alpha emitter, and I mentioned that the radioactivity as a method using a dose calibrator may rely on gamma emission from its decay products.

In the submission, describe how the accuracy and reliability of the radioactive dose is assured.

What are the aspects that must be controlled to assure accuracy and reliability of the measured dose?

And also discuss in detail how the method was derived. With respect to radiolabeling procedure methods, you would need to qualify both the generator produced and the accelerator produced actinium-225 in the manufacturing process.

So we suggest that you use highest radioactivity amount to be used during radiolabeling, and if its accelerator produced actinium-225, it should contain maximum amount of actinium-227 impurity.

I just want to emphasize that an accelerator product, much more actinium-227 atoms will be present relative to actinium-225 atom at the time of radiolabeling.

So the ligand to radioactivity stoichiometry may be different for accelerator product relative to the generator product. Something to keep that in mind.

Both fresh and aged actinium nitrate preparation should be qualified, and you will need to provide data to support the hold periods for both actinium nitrate and actinium-225 radiopharmaceutical.

Finally, we strongly recommend that the radiopharmaceutical manufacture coordination with NIST to develop actinium-225 reference standard material urgently, in a timely manner.

This reference standard is really needed to establish dose calibrator settings for use in commercial marketplace.

It assures that the material dose has been accurately measured. I also want to caution that this should be done gently as there is a risk with all that the dose that you're measuring in clinical trials is equivalent to what will be available in the commercial marketplace.

Now with that, actinium-225 radiopharmaceutical in general, as Dr. Wahl mentioned, is a rapidly developing area.

I hope I have described to you some of the regulatory issues that we face relative to actinium-225 radiopharmaceuticals.

With that, I will conclude my presentation and thank you for your attention.

DR. CHRISTODOULOU: Thank you, Ravi, for that very comprehensive presentation. Our next speaker is Dr. Cathy Cutler, the Director of the Medical Isotope Research Production and Development Group at

Brookhaven.

Cathy and her group operate the LINAC Isotope Producer at Brookhaven, and they are currently evaluating the accelerator production of actinium-225.

Cathy brings 28 years of experience in the development and evaluation of radiopharmaceuticals, and Cathy, the floor is yours.

DR. CUTLER: Thank you. Can you see the screen okay?

MS. DIMMICK: Yes, we can.

DR. CUTLER: Okay. So thank you. So I'm going to be talking about the high energy accelerator production of actinium from the Department of Energy.

And although I'm from Brookhaven National Laboratory, this is really a tri-laboratory effort that involves Brookhaven National Laboratory, Los Alamos, and Oak Ridge National Laboratory.

And Dan Stracener of Oak Ridge is actually the project manager. And I believe Eva Birnbaum and Roy Copping, who are also involved in this, are on this call.

This really takes a team of scientists at each of the labs to make this happen, so I just want to acknowledge that and that it's a multi-disciplinary team carrying this out.

So I'm going to talk a little bit about the perspective of actinium-225. It's really nice to be speaking today because actinium and other alpha emitters have been studied for actually quite some time.

And although interest is growing recently, it's really only that we're now getting the tools in place to help actually support these applications.

So it's good to actually see the applications being developed and moving forward. I'll talk to you about the accelerator production of actinium-225, and if you just watched Kellee's talk, what you realize is what's really needed is a robust, consistent supply of actinium-225 that can be used to really support drug development.

The Department of Energy has been developing Drug Master File, which has been submitted for this, and we've continued engagement with the FDA and with our customers and users so that we can understand their issues and improve as we go along to make sure that we're meeting their needs.

Based on that, we are undergoing improvements so that we can meet their needs by increasing the frequency of production and also bringing on alternate backup production routes that

are being pursued.

So I probably don't need to overly go over this, but alpha emitters have been of interest because they deliver a very high dose in a short range, which mimics the toxicity.

And basically, they've been observed in clinical trials to result in complete responses when patients really have not responded to other treatments.

A major challenge has always been the limited availability, which is what the Department of Energy has stepped in to try to address.

So as we pointed out, actinium-225 has been available typically from a thorium-229 generator. Thorium is the parent that decays and then the actinium is separated via a call separation.

The advantage of this is that it's free of other actinium isotopes and it provides a clean form of actinium-225.

The disadvantage is that thorium-229 is limited, which thereby limits the amount of actinium-225 that's available, particularly for applications in clinical trials.

Based on this, the Department of Energy realized going forward that the amount of material from the generator was not going to meet the demand, so they

started looking at other routes of providing actinium-225.

So in looking at the amounts that were needed, the need for GMP, the need for year-round production, they focused on the high energy accelerator production of actinium-225.

And as pointed out, the advantage of this is that it can produce large amounts, allowing us to put curie quantities into inventory.

But the disadvantage is that you do produce the actinium-227 with the half-life of 21.8 years.

Additionally, realizing that the demand for this is growing, Department of Energy is looking at other routes.

So in originally deciding the route of production to be pursued, some criteria was set up, and one is that it was understanding that as this is going to be used in clinical trials to support drug development, what we really needed was a sufficient supply to support year-round.

Additionally, you need to be, as based on the slide you saw previously, robust, consistent supply that would support drug development.

Then we needed to have robust, established specifications that would support clinical evaluations

and that we needed documented GMP production.

So actinium-225, as been pointed out, can be used in two ways. It can be used on its own, has a 9.9 half-life, and can be used with small molecules up to antibodies, and administer about 2 to 5 curies per patient kilogram based on the molecule of interest.

It can also be used as a generator form to provide the shorter-lived bismuth-213, which can be supplied in 1 millicurie per patient kilogram.

A number of different organizations have pointed out the interest in using this but the fact that there was just not enough to really support the robust clinical trials that were needed for evaluating the applications that were being brought forward.

Actinium-225 was originally in the U.S. developed by Oak Ridge National Laboratory, in which they extracted the thorium-229 and then used that as the parent to supply the actinium-225.

They've been supplying the actinium from this route since 1997. They've supplied over 10 curies and over 2,000 packages.

They perform about 13 campaigns per year and supply approximately a curie of actinium-225.

Now, what you can see is the graph on the bottom that shows the amount of material that is

available, what has been actually shipped out, and then red is the number of shipments that have been made.

And what you can see is that there's been a significant increase in the number of shipments that have gone out, and the challenge is, is that this generator material is now overprescribed.

So the Department of Energy realized that this was coming, and that's why they started looking at alternate methods of supplying actinium to support the demand.

And based on that, what they looked at was forming the Tri-Lab Effort, and this was to look at using high-energy accelerators to radiate thorium-232 in a spallation reaction to produce the actinium-225.

So this Tri-Lab Effort consists of Oak Ridge, based on their over 25 years of experience and knowledge in isolating actinium-225 from a variety of different waste to help develop the chemistry for this.

Los Alamos has been running the Isotope Production Facility and has a high energy accelerator that does 100 MeV in energy, and Brookhaven National Laboratory that has an accelerator that can deliver 66 up to 200 MeV and 165 micrograms.

Los Alamos and Brookhaven have worked for years supplying isotopes and implementing GMP to supply

those to meet the requirements of the FDA.

So all of these elements were critical for bringing this team together to meet the elements for supplying a robust supply of actinium-225.

Now, as mentioned previously, one of the challenges with these high energy accelerator production of thorium-232 is the co-production of actinium-227 that has a half-life of 21.8 years.

And in this slide, what you can see is the ratio of the actinium-227 to actinium-225 produced in regards to proton energy.

So you can see that at 100 is about its highest and it drops down as the energy is increased.

They have been radiating targets now since about 2014, and we very well understand the implications of the radiation conditions on the production of the actinium-227 and how to moderate them to maintain that level as low as possible.

The challenges with the actinium-227 is, is not necessarily unique to actinium-225. There are other isotopes, such as samarium-153, lutetium-177, and even technetium that have long-lived impurities that need to be addressed.

So the long-lived impurity actinium-227, the Tri-Lab has been working on methods to maintain

this level.

The actinium is provided as the radiochemical actinium nitrate. We have established specifications including a limit on the actinium-227 impurity that is present.

We monitor this routinely to ensure the levels are maintained and consistent, which is necessary for our end users who are using this product.

Now, in the beginning, the DOE understood that it was important to understand the actinium-227 and the possible impacts, so they actually funded an FOA where they brought in experts to evaluate applicants that came in to look at the 227.

Based on that, there were three awards that were given to people to look at the dosimetry and the toxicity of the 227 and look at the impacts.

Here you're seeing a user meeting. The Department of Energy has regular meetings where it meets with its end users to understand their needs so that we can use those to inform the process going forward, to ensure that we're making products that will meet their needs.

So one of the grants that was funded was a grant to Kate Dadachova. At the time, she was at the Albert Einstein College of Medicine, and she did

a study looking at free actinium-227 and chelated, looking at the radiation dosimetry and toxicity.

And she published those results in a 2018 special issue of Current Radiopharmaceuticals. In this, she worked with Darrell Fisher, who is well known for his work on terbium dosimetry, and they looked at the dosimetry and toxicity.

And the conclusion or data demonstrates that accelerator produced actinium-225 is suitable for the development of pre-clinical and clinical radionuclide therapy.

A second award was given to Jeff Norenberg, who at the time was working at the University of New Mexico.

Jeff has had a long history in looking at alpha emitters and being actually one of the leaders in bringing up alpha emitters.

So he looked at the comparison between the actinium-225 from the cow material to that from the accelerator material.

And in those results, his conclusion that there was clinically, it was insignificant, the differences between the dose that was obtained from the cow material and the material from the accelerator.

Now, additionally, we've been interested

in looking at the direct labeling efficiencies, and this was brought up in the previous talk.

And we have done comparisons of the cow material with the accelerator material using the most gold standard ligands that are used, which is DOTA, and we have not seen any differences in the labeling efficiencies between the two materials. And this has been done over time.

Additionally, we've had external evaluators compare the use of the accelerator produced actinium-225 material as a source material for bismuth generator performance.

And there was no differences noticed in this materials. And as I showed you in the previous slides, the impact of the actinium-227 content evaluated previously, it has been demonstrated to be small.

There are still challenges that remain with the 227. One of those is with the facility licensing that is required, in which those receiving the material need to have decommissioning funding plans and funds on hand to handle this.

And we have been in discussions with the NRC to see if there's a path forward, and maybe to look at this as they did for gallium 68 and germanium 68,

or possibly as they're handling for lutetium.

In the U.S., it's not clear that patient waste, if there will be an issue. Over in Europe, there is an issue in which they have to store the waste to decay.

Now the Department of Energy ordered to support the use of the accelerator material did submit a Drug Master File.

Oak Ridge National Laboratory submitted this file based on the material that is radiated at the Brookhaven and Los Alamos and shipped to Oak Ridge for processing and then sent out the door

So this Drug Master File contains all the information regarding the radiations, the target material, and the conditions that we use for the radiation, the parameters, as well as the facility at issue for processing that, the composition of the final radioisotope solution, and the specifications for that material, and the container closer. The Drug Master File at Oak Ridge was submitted in 2019 for the accelerator produced material, and a certificate of analysis was developed.

It actually goes out, which this is the acceptance criteria and the rest results.

Oak Ridge has further submitted a Drug

Master File for their cow material in December of 2020.

Brookhaven National Laboratory is getting ready to set up processing facilities in the next year and will be submitting their own DMF in support of this material.

So in continuing efforts going forward to increase the availability of actinium-225, and our continuing discussions going on with customers, one of the things that we're working on is increasing the frequency of the batches of actinium that we make.

And so towards the later part of 2022, we'll be going to production twice a month of actinium-225 to supply that and to get it into trials.

It may not be apparent, but when you're radiating these targets and scaling up, there are technical and logistical challenges that we need to ensure that the product continues to be consistent and reliable.

And we have been working on addressing those to ensure that the product that we make will be consistent from this level up to the curie level.

Additionally, we've been working on continuing improvement of shipping capabilities. We want to ensure that we can ship the targets and the material between the labs to we're sure that we have

redundancy in the radiation as well as in production.

There are investments going on at Brookhaven in which we are bringing up a hot cell, which we're in the next year planning to bring up for processing the actinium-225 so that we will have two processing sites.

In the future, Los Alamos is working on bringing up a site there so that we will have redundancy in the processing capability.

And through all of this, we continue to work with our users of this material so that we can understand what their needs are as they scale up to ensure that we are meeting their demand.

Now, as the demand for this has seemed to grow and expand, it's understood that there's going to be a requirement for multiple sources of the material.

So there are other routes that the Department of Energy is looking at. One is at Argonne National Laboratory, where they're investigating the electron reaction production on radium-226 to produce radium-225 as a generator approach for actinium-225.

At Brookhaven, we're looking at using a low energy cyclotron for radiating radium-226 to provide actinium similar to what's provided from the

generator.

And Oak Ridge is looking at a radiation of radium to produce the parent thorium-229. So these routes are under development and we expect them to come up over the next few years.

So in summary, the Tri-Lab Effort was brought together to bring up production of actinium-225 to produce a significant amount so that it could actually support the applications of getting these products into clinical trials.

The product is available and we have made multiple shipments to end users. Currently, we've distributed over 440 millicuries of the produced actinium-225.

We are working with our end users as they prepare to support them as they go into phase one trials.

The actinium-227 content, we are monitoring it. And studies that we have supported have indicated the impact is insignificant.

Now, this is something that each of the users should be evaluating for themselves to really understand what the impact is.

We are continuing to work on scaling up the isotope and basically increasing the frequency of

production so we can help support the end users' use of this to support the applications.

And then finally, if you have any questions, you can go to isotopes.gov, or if you want pricing or anything like, this is a good place to start.

And on that, I thank you for your attendance.

DR. CUTLER: Thank you, Cathy, for the great presentation, and also thank you to the National Labs for their great contributions in being the supplier of actinium-225 in the very important supply chain of this medical isotope.

The next speaker is Dr. Denis Bergeron. He is a research chemist at NIST in the Radiation Physics Division and joined the Nuclear Medicine Project in 2008 and is very actively involved in the development of standard for medically important radionuclides.

Denis is very active in the international metrology community, serves in various committees, is well published, and Editor in Chief of Applied Radiation and Isotopes and has received very prestigious awards. Denis?

DR. BERGERON: Thank you. So I hope my slides are up and you can see my mouse.

MS. DIMMICK: You are good, Denis.

DR. BERGERON: Great, thank you. So, yes, I'm Denis Bergeron from the National Institute of Standards and Technology and I'm thrilled to be here for this exciting session today. Thank you.

And I'll be talking about realizing the becquerel for actinium-225, going over sort of a current landscape and the road to a new National Activity Standard in the United States.

So the U.S. Constitution is an enlightening document, whereas the guys who wrote it knew a lot about the importance of measurements and commons.

And so the U.S. Constitution, in Article I, Section 8, gives Congress the power to fix the standard of weights and measurement.

And they have passed that responsibility onto NIST. In my case, we're responsible for standards for activity.

I think when end users think about activity measurements, what they really want is a button on the radionuclide calibrator so they can push the button, read the activity, and be done.

We're mostly responsible for all of the chemistry, physics, and everything that goes on behind

that button.

So end users do activity measurements in two main ways. I think one is with these radionuclide calibrators.

These are reentrant well-type ionization chambers that will turn a current produced in the gas into activity on the readout using some sort of calibration factor.

It's either represented with a dial setting number or a button with setting.

And then we have gamma-ray spectrometry. So this is achieved with high purity germanium systems commonly or often used well-type sodium iodide found to stay popular in clinical studies.

In that case, instead of a button, what you need is an absolute gamma ray emission constant. That also comes back to us.

So the activity list defines the Becquerel. The becquerel is the SI-derived unit. It's defined in terms of decays per second of radionuclide.

And I'll note now, and then never say curie again, the list at the top, but one millicurie is 37 megabecquerels.

So the physical standards that we develop

at NIST are the basis for activity calibrations everywhere.

Standardizations are based on measurements with primary methods where primary means some sort of internally consistent self-calibrating approach, and I'll talk about one of those in particular.

So the absolute activity standards developed at NIST and other metrology institutions around the world are the basis for radionuclide calibrator calibrations, and are the basis for absolute gamma ray emission probabilities.

If you want to define the becquerel, the first part of that is defining what decays for a particular radionuclide.

Today, we're talking about actinium-225. And the decay scheme is complex. We've got 52 percent of decays go directly to the ground state of francium-221, and then the other 48 percent we've got to contend with is split from 47 excited states in francium-221 with all the attendant gamma ray emissions and a lot of complex states we have to contend with, just to say what the decay actinium-225 output is.

And that's part of the definition that's going to be the per second, just the measurement, just

counting the decays.

We have a lot of different methods for doing this and they've got to be selected to be appropriate to the decay types that we're measuring, and we need good efficiency models that correct for all the miscounts that are going on with our measurement scheme.

The next part of the definition is this parenthetical aside of a radionuclide. And I like to point out here that the A, the Article A, is really important.

If you want to account for radionuclidic impurities, including breakthrough parents, so this is the thorium-229 breakthrough that came through on thallium-225, or the actinium-227 impurity that we've heard so much about already.

Those don't count. Any contributions from those in our measurements don't contribute to the becquerel of actinium-225.

So if you account for all of that, and then on the flipside of these decay chain nuclides, we have to account for the progeny, solving the date nitration to make sure we know what the expected ratios for each and every member of the decay chain look like and what they're contributing to our evidence.

We had a lot of recent experience developing activity standards for alpha emitters. We sort of started the modern part of it anyway in 2005 when, at the direction of the FDA, a company approached us to development measurement standards for radium chloride.

And we've heard this story a little bit from Dr. Wahl this morning. But the success of this first date class alpha therapeutic, we've seen a lot of demand for activity standards for other alpha emitters with therapeutic attention.

Now, I'll just comment here that to us, the Xofigo, and we don't endorse commercial products, but the lithium chloride is a great case study because the company came to us, we developed activity standards, and now participates in a NIST mega assurance program.

That means that they are able to establish NIST-traceability of their activity measurements.

And in fact, every new site receives a NIST-traceable calibration service with their first shipment.

So actinium-225 has some unique measurement challenges, but as I mentioned, we're looking at a lot of alpha emitters and lutetium nuclides

lately, so these unique challenges are unique but in a familiar way.

In particular, we have to deal with the equilibration period which I hinted at earlier. I'll talk a little bit about the challenges from some of the short-lived progeny of polonium-213, and then of course breakthrough of impurities also can be a challenge in measuring a bit of a certain standard.

So first we have this ingrowth period, two days after separation, actinium-225 gets to 99.99 percent of equilibrium.

And we can watch how the different progeny grow in solving the date equation, which this changes if you have any breakthrough of thorium-229, which effectively that means that we're dealing with supported, or some fraction of supported actinium-225 and the ratios that we calculate all change.

At NIST, we want to be doing measurements after we've achieved equilibrium so that we don't have to account for rapidly changing contributions from the daughters and the other methods.

The short-lived progeny introduce a challenge for some of our measurements. In this case here, we have astatine-217 with a 32-millisecond half-life and polonium-213 with a 3.7-microsecond

half-life.

And it's easiest to describe I think looking here in a lot of our measurements, like a liquid scintillation-based measurement that I'll talk about in just a minute, we're going to catch most of the bismuth-213 decay events, which means that we're starting instrumental dead time on that trigger.

Polonium-213 will then most often decay during that dead time so we don't see it, but bismuth-213 is a beta emitter.

We're going to miss some of those events. In that case, we will definitely see the polonium-213.

So the simplest model is to treat the bismuth polonium pair there of having counting efficiency equal to one.

That's how it's done and I'll talk more about what that means in a moment. But there are a lot of corrections to be done in terms of we have to consider with our instrumental dead time and decays of daughter nuclides that have proved their waste time.

So the method that I want to talk about is a primary method based on liquid scintillation points.

It's called the Triple-to-Double Coincidence Ratio, or TDCR method of liquid

scintillation.

So it is liquid scintillation. They put a sample into an organic cocktail to have a four-ply detector with high energy betas or alpha emissions.

They get very high counting efficiency where I'm talking about efficiency in terms of counts per decay.

So we use a three detector system where we can count events that happen in coincidence that are observed by either two or three of the photomultiplier tubes.

And we can write down a simple equation that says we count for a while and the number of triples events over the number of doubles events that we count is actually a measure of the counting efficiency for triples events over the counting efficiency for doubles events.

That sounds like a lot but it's, as you can see, written down it's a fairly simple equation.

And then we do a little trick. We vary the efficiency that we use to count. And the simplest way to do this is to take our liquid scintillation vial and effectively put sunglasses on it, neutral density gray filters that will knock out some of the optical photons generated in the liquid scintillation

cocktail.

So we reduce the count efficiency with the measure of a few different points. Then the simplest way to look at it is we can build a little curve that looks something like this.

And as we look at our data, we see that as the TDCR increase, the number of doubles counts that we've measured increases.

It can extrapolate out to where this ratio, this Triple-to-Double Coincidence Ratio is a 1.

That means that the triples efficiency and doubles efficiency are the same. The only way that happens is if we're counting perfect efficiency, which means that our observed count here is actually the decay rate.

So we have a measure of the activity that's not relying on any calibration methods. It's all internally calibrated in between.

In practice, things get a little bit more complicated, but we have good models for the complicated parts.

One of those good models is described by Karsten Kossert and Grau Carles in this Applied Radiation and Isotopes paper. It's in 2010.

It's a MICELLE2 model. Here, I'm showing

it applied to a recent alpha emitter that we looked at, radium-224, where because of the decay chain and the various contributions, we've got about 5.65 counts per radium-224 decay.

For actinium-225, Karsten Kossert, who I just mentioned on the previous slide, comes up again.

They recently, the PTB, sister lab in Germany, performed a primary measurement actinium-225 activity.

They wrote down the efficiency equation. It looked something like this. In the interest of time, I won't go through it and all of the terms.

I'll just say what we can draw from this is that we need reliable calculations for the data LS efficiencies if we're going to do this experiment.

Also, we need precise half-lives for the equilibrium coefficients and for the corrections that I mentioned earlier, and we need a precise knowledge of our system's dead plan.

Preferably, we need the ability to vary our system's dead time and how we should do this measurement.

Just talking for a moment more about the recent PTB standardization for actinium-225 activity, you can see that they achieved their really remarkably

good standard combined uncertainty, the TDCR emissions, by 0.16 percent on their activity.

They also used their standards to calibration ionization chambers of PTB, which means that they can then measure incoming solutions relatively easily, and that means that in the future, a comparison of activity standards applied to a comparison between NIST and the PTB would be possible without the PTB having to review the entire formula. It's going to make measurement better.

So the measurement science is only part of the story. When we achieve a primarily realization of the becquerel emissions, our stakeholders really care more about how that standard is disseminated, how it gets out the door.

And what they also really care about is how their measurements become traceable to that standard.

So in order to perform calibrations and link them to our primary methods where we need very precise links between incoming very high activity concentration solution and the very low level sources that we use for our primary counting techniques.

We achieve that with gravimetric dilutions that take us from very high activity concentration to

workable low activity concentrations, and in the middle somewhere we have limp sources that we can use to calibrate the types of instruments that are of interest to our end users.

On this slide, it's very busy but I'm not expecting much to be absorbed. This is a typical dilution scheme.

I looked them up in one of our standard experiences where we come from a master solution incoming from the manufacturer, perform a series of dilutions, creating a lot of counting sources for various primary methods, and those are then linked to (audio interference) performed in the ionization chambers.

We check all of the gravimetric mounts with radiometric mounts using all standard methods and generalities in our laboratory.

In the case of the radium-224 activity standard, we performed multiple experiments and compared across different methods.

The TDCR method that I talked about, coincidence kind of thing, that's the thing that comes up the activity from a different approach.

Efficiency tracing, we were able to use ionization chamber measurement in our labs to compare

across experiments with our same benchmark.

And we were also able to calibrate sort of a well-type and compare the results there with the Monte Carlo results, which you use on the decay data.

The activity standard in this case paired a model centered uncertainty less than 0.5 percent, and has disseminated the ionization chamber factors decayed then.

In fact, in this instance, we found discrepancy with our high purity germanium detectors that resulted in a revision to the absolute emission in terms of for the main gamma ray in radium-224 that might impact gamma spectrometry both methods' results.

So what does an activity standard look like for a stakeholder, for a customer? When someone comes to us and we perform one of these experiments, we oftentimes are asked to deliver a NIST calibrated reference source at the end so that local instruments can be calibrated in the user's lab.

We provide guidance on clinical calibrations, in particularly a benchmark regularly applied calibrator settings.

And we also have to look a lot at geometry and composition-dependence. With these radiopharmaceuticals, we often see exotic geometries

and exotic chemical theorems related to various microparticles or complex biomolecules.

And sometimes that can affect baseline of response in different ways, what we're looking at or not.

We typically publish the results of our measurement campaigns, and those publications often include a review and an update of the nuclear decay data.

The question that is asked of me most often is, okay, how long does it take to do a primary standard and how much does it cost?

Of course, the very unsatisfying answer is it varies quite a lot, but here's an attempt at typical.

If we have a primary standard in place, the calibrations will often be completed in a week or two, with the caveat that that's once work starts, and sometimes the lead times coming up to that can be pretty long.

If we have to develop a new primary activity standard, things tend to take longer. In a couple of recent cases we had standardization pinpoints down in 6 to 10 months.

And again that is once work starts, and

the lead times can sometimes get very long, especially in this COVID era when everybody's trying to (audio interference) there is a backlog (audio interference).

So the other part of this is how much NIST is required to recover our costs. So it can vary quite a bit.

In a few recent standardizations, customers have billed $60,000 to $150,000 per result of a primary standard.

With that, I'd like to thank the entire NIST Nuclear Medicine Project Team, including Brian Zimmerman, Jeff Cessna, Ryan Fitzgerald, Leticia Pibida, Lizbeth Laureano-Perez, Ron Colle, and I welcome any questions.

DR. CHRISTODOULOU: Thank you, Denis, for that excellent presentation. And we will move now in Sessions II panel session.

And we will take first the two questions that came from Dr. Wahl. So, Sarah, go ahead and read the questions for Dr. Wahl.

MS. LOPAS: Okay, the first question, Dr. Wahl, we have for you is why are alphas less subject to the oxygenation effect?

DR. WAHL: Others are perhaps more qualified to answer than me, but fundamentally, the

alpha can cause damage directly to the nucleus if it's in close proximity due to the power of the helium nucleus.

A lot of the effects of beta emitters are mediated through oxygen radicals and secondary events that are generated that are more prevalent during conditions of oxygenation.

And it's just basically the mechanism of the cell kill, being more direct with alphas.

MS. LOPAS: Okay. And then Danae, I have two other questions here. So one says, Dr. Wahl, can you please discuss progress being made to prevent xerostomia?

I apologize if I pronounce that wrong, X-E-R-O stomia, with the use of actinium-225?

DR. WAHL: I'm not sure I can address it authoritatively, but it's a very interesting area because at least my read in the literature, and this is not my work in any way, the amount of PSMA in the salivary glands is not as high as what one might expect, not as high as one would expect to cause high uptake.

Further, the antibody-based agents don't have as high uptake in the salivary glands, so there may be an uptake mechanism, probably is an uptake mechanism, that isn't necessarily PSA targeted.

It could be due to other physicochemical effects. So. I know that there have been a variety of approaches, cooling of the salivary glands.

There are some efforts I am aware of where people are trying to modify the PSA targeting molecule to have less off target accumulation in the salivary glands.

But as I indicated clearly, xerostomia's a real issue and has to be addressed.

So I'd say it's an active area of research, and, I mean, there have been approaches with steroid injections into the salivary glands among other things.

But at this point, it's still I think an unsolved challenge.

MS. LOPAS: Okay, and then here's your final question. How do you interpret the meta-analysis data, given that the dosing is patient weight based rather than tumor burden based, with the respective treatment affecting toxicity?

One would imagine that if the toxicity will depend on the tumor burden where patients with higher tumor burden would have a tumor sync affect away from the normal dose tissues, for example, salivary glands.

DR. WAHL: Yes. I think it needs further study. I mean, in my read of the meta-analyses, tumor

burden. I don't think was extensively studied.

It wasn't in the Journal of Nuclear Medicine article. We certainly saw patients who had less favorable outcomes who had higher tumor burdens, such as liver lesions, but I think it's a reasonable variant for a study, and I think more information is needed.

In fact, well, between the time I made my slides and today, I believe that there's another meta-analysis that just came out from the India literature looking at the same papers.

It seems like, anyway, but worth further study. It may be you're right, it would need to be studied systematically with a measurement of tumor burden. So it's a good question.

DR. CHRISTODOULOU: Thank you, Dr. Wahl. And thank you, Sarah. I have some questions now for our panelists. So I will start with Dr. Kasliwal.

And the first question I have is, can a precursor be used as a surrogate reference standard for the small molecule radioactive dark substance?

And go ahead, Ravi.

DR KASLIWAL: Yes, not without qualifying the circulated reference standard molecule. When chelate forms, you will notice a shift in retention

time, and you can establish a precursor in the chelated molecule, some kind of a relative retention time, relationship, and then you may be able to use precursor as a standard on a routine basis, but you will have to establish that as part of your evaluation exercise.

DR. CHRISTODOULOU: Thanks, Ravi, and actually, for metal complexes, what we have practiced so far is that we are requested the development of a reference standard that includes the natural form of the metal ion.

And we had a lot of success with Gallium and some with ritisium. We understand that the actinium-225 is a much more challenging case, but this has been our practices so far.

The second question, Ravi, that I have for you is, is it sufficient to have specifications for radionuclidic purity, or does one also need specifications for individual radionuclidic purities?

DR KASLIWAL: Yes, I mean, so, if the product has long-lived radionuclidic impurities, such as actinium-227, or if the impurity can potentially affect radiation dose to the patient, or if it's in a relevant routinely encountered impurity, for those radionuclidic impurities, you should have a specified individual radionuclidic specified limits.

As one of my slides did indicate, radionuclidic impurity is that, but your individual radionuclides, depending on what it is, you may need specifications for that.

DR. CHRISTODOULOU: Thanks, Ravi, and also, I'd like to add that we always consult with toxicology when it comes to individual specified impurities.

I think the next question you have already answered in your slides, but perhaps you can remind us. This came from the audience.

And is radiochemical purity tested by TLC efficient for release of that product?

DR KASLIWAL: Yes, and I saw in the chat there was a related question, because in HPLC there's a flow to detector and it may not have the sufficient equilibrium time to have the secular equilibrium established by the time detection occurs, subsequent to separation.

I understand that, but it's highly unlikely that TLC can provide a complete picture. I mean, it's a good method to see what is bound and unbound, but it may not be specific enough to tell you whether a bound activity is a single desired molecule or molecule plus impurities or other degradation

products.

So let me just consider the actinium-225 radiolabeled antibodies. TLC won't tell you whether you found high molecule gray aggregates or low molecule impurities in that. So you will need a separate method.

Same way in the small molecules. So we recommend that you have a combination of methods. TLC gives you a complete picture of the radioactivity, what is bound versus unbound.

But you can have an HPLC method that will tell you something about the molecule, whether it's still intact or it's degradated.

Obviously, you may choose an appropriate detector if maybe a mass base did occur to assess the degradation of your other part of the molecule besides radioactivity.

DR. CHRISTODOULOU: Thanks, Ravi, and actually, one point that we have been asked about a lot is what about the end users, at the end user's release?

So in some cases, TLC is appropriate, as Ravi pointed out. It has to be previously compared with the HPLC or other suitable method with suitable detector.

But if we have the data already in an application and then at the end user's side, we can have TLC measurements.

And I think that's reflected in the package insert for Netspot.

The next question I think you already responded to. That came from the audience, too. Testing requirements for product quality.

So I think it's probably best if we move to some other questions that came in for our other speakers and then we can take this at the end if we have time.

So the next question that I have is for Denis. And the question is, radiopharmaceuticals have very short half-lives.

How can a pharmaceutical country ship a traceable calibration source to end users? Go ahead, Denis.

DR. BERGERON: So radiopharmaceutical companies can establish traceability for their measurements through measurement assurance program or through calibration services that NIST offers.

The example would be with radium-223, where the measurement assurance program involves annual submission of a sample from a company to our

labs so that local calibrations for radio pharmacies are compared with the missed activity.

And that way, they're able to maintain traceability over years and years and continue to ship samples to end users that has NIST traceability.

DR. CHRISTODOULOU: Thanks, Denis. The other question is that if NIST has an activity standard for actinium-225, does this mean that there is also standard for its progeny? For example, astatine-217, bismuth-213, et cetera.

DR. BERGERON: Yes, that's an interesting issue that comes up a lot. And the short answer would be no, and it's because of how you have to solve the Bateman equation and the difference between unsupported and supported nuclides.

So in the case of actinium-225, we would have a specific ratio of the progeny that arises at equilibrium, whereas actinium-225 is not present, then the ratios between bismuth-213 and its progeny will look different.

So the measurement and the ability to do the measurements is all put in place by the development of one standard, but the actual standard itself and the, in particular the ionization chamber responses, are different between those two.

And so we have to consider that carefully, and it's not simply a matter of subtracting the contributions from one. It's a matter of considering the ratios of everything that's from a Bateman equation.

DR. CHRISTODOULOU: Thanks, Denis. And from what I understand about the NIST timelines, it sounds that if we have a prospective application to the FDA, the development of a NIST reference standard should be, of course it would be more timely if we start this ahead of submitting of the application.

But yes, during, you used Xofigo example, that happened concurrently with the FDA new cycle that these conversations need to happen and start before we're ready to bring some of these very important medical isotopes to market.

The next questions are for Cathy that I have. And the question is, given the production of a product could be of multiple size, will there be any impact on the quality of the product?

DR. CUTLER: Yes, so the DOE plans to have production of actinium at multiple sites, and they will have a Drug Master File for each site.

But the specifications for the product will be the same of the product that's produced at those

different sites, so the quality will be the same.

DR. CHRISTODOULOU: Okay, so that also touches on FDA comparability analysis. So the expectation is that an applicant should have consistent acceptance criteria and develop specifications for actinium-225 that they're getting from different sites.

And could you also tell us what is the projected availability of actinium-225 by the National Labs or from the accelerator program?

DR. CUTLER: Yes, so we, currently we've been supplying material every four to six weeks. We're moving toward supplying it once a month.

And then as we move into the latter part of 2022, we're working at supplying it every two weeks and actually put into inventory.

DR. CHRISTODOULOU: Thank you very much. And so I'm going to turn it to Sarah to read some of the other questions that came in throughout the session, because I am having some issues with my chat box on my device. So, Sarah, please go ahead.

MS. LOPAS: Okay. Let me know, Danae, if you got this one. Let's see. What just came in here? I apologize if we already read this one.

Any thoughts on mechanisms of resistance

of PSMA alpha and beta agents?

DR. CHRISTODOULOU: Okay, is this a clinical question? Perhaps we can take it in --

DR KASLIWAL: In the afternoon session.

DR. CHRISTODOULOU: -- in the afternoon session. So we'll skip that, Sarah. Go ahead.

MS. LOPAS: Yes, I'm going to highlight that one. All right. Let's see. Have there been any INDs started with accelerator produced actinium-225?

DR. CHRISTODOULOU: I'm going to ask Cathy to respond to this question. I think she already mentioned it in her slides, because the FDA cannot tell you what applications we have in house.

DR. CUTLER: What I can tell you is that we're working with people who we know are interested, but I'm kind of stuck in the same situation as the FDA in which I'm not at liberty to really discuss it much more than that. Sorry.

DR. CHRISTODOULOU: Thank you, Cathy.

MS. LOPAS: Okay. So this one is for Ravi. It says, can you please expand on the reluctance to have radiotherapies as kit products? Is this an area to explore, possibly expand access, and help with impurity removal potentially?

DR KASLIWAL: Well, in part, that is. You

heard in different talks that radiolabeling conditions may be harsh and alpha emitter, there could be degradative labeling, there could be degradations.

And the purification, it's a complex procedure, not to mention the eventual measurement of the dose and reliability of the dose.

So at this time, we're highly encouraging people to manufacture ready-to-use product, and then they can control all these different aspects to avoid product variability from place to place.

MS. LOPAS: Okay. All right. Thanks, Ravi. The next question I have here, it was discussed that radiochemical purity must be established.

Is accelerator produced actinium-225 tested for organic contaminants? If so, what technique is used and what are their permissible limits?

DR KASLIWAL: Maybe Cathy can answer that.

DR. CUTLER: Yes. So we currently do not test for organic impurities. I will say that we have somewhat evaluated the process to determine if there are organic impurities using total organic content to evaluate what we see as we go through the process.

But we don't have like a routine test that we report on for that.

DR. CHRISTODOULOU: And again, when we have the production of the final drug product, the radiolabeled drug substance and drug product, that's where we actually are looking for chemical impurities and organic impurities, not in the actual inorganic isotope, per se. Thanks, Cathy.

DR KASLIWAL: Right. So as part of your overall product manufacturing program, you should be doing a risk assessment.

Contribution of different impurities from different raw materials and what is the risk to the eventual product and what, considering all of the manufacturing and purification and other process that you go through.

So to me, it would seem like the organic contribution would be relatively low if at all from actinium nitrate.

MS. LOPAS: Okay, we have another question here. This is for Denis. Could you comment on standards for thorium-227, which is not in secular equilibrium with radium-223?

DR. BERGERON: Absolutely. That's a good question, and I saw that some of our colleagues from the National Physical Laboratory in the U.K. are on the call as well, and they have some recent experience

with this.

We have not in the U.S. started yet, but we are getting close and in the planning phases at the moment.

I think with thorium-227 and other similar cases where you're not measuring equilibrium, is that the time evolution of the ratios of the radionuclides that emit from must be considered very carefully.

In order to do any of this, you have to have a really well defined and well-known separation time, and you have to have a really good knowledge of the efficiency of the separation, at the separation time.

And then every calibration factor and everything else that you're looking at will be time dependent, and you have to define a very specific window in which the calibration factors that you're developing are applicable.

For example, a look up table where you say it's this long since separation, so this is what I'm building.

It's a complicated case but it can definitely be done, and it's interesting in the metrologist's perspectives. It's exciting and fun stuff, the method.

MS. LOPAS: Okay. The next question we have here is presenters have indicated the concerns regarding actinium-227 contaminant in accelerator produced actinium-225 has been mitigated.

Can more details be provided regarding this? And has the FDA provided input to this progress?

DR. CHRISTODOULOU: Sarah, can you repeat the question, please?

MS. LOPAS: Yes. Presenters have indicated that concerns regarding actinium-227 contaminants in accelerator produced actinium-225 have been mitigated. Can more detail be provided regarding this? And has the FDA provided input to this progress?

DR. CHRISTODOULOU: Right. So in the context of INDs, we can actually provide multidisciplinary input for this effort of impurities.

So as Cathy mentioned, the isotope production usually resides in Drug Master Files. These are referenced by applications, either investigational new drugs or the marketing applications, the NDAs, the BLAs and so on, or ANDAs.

And during that process, we have opportunities to provide interdisciplinary input. And I don't know if Ravi would like to add anything to this?

DR KASLIWAL: Okay, let me put it, I think the question is trying to get at that actinium-227, this is my interpretation of the question, that the levels of actinium-227 have been found to be okay, and whether FDA has had any input in that.

There was also another question within the chat, which I will take it up with this, is FDA prepared to provide an upper limit for actinium-227 that can be presented in a finished drug product?

So FDA is not prepared to provide an arbitrary limit, and we work on the scientific data driven basis.

Now, if you go stepwise, if actinium-227 is present in however amount, what each drug product, the issue will be different.

Actinium-227 will also chelate to your ligand, okay? It's unlikely that it will chemically behave any differently than actinium-225.

So it's biodistribution, it's removal from the body, all of these factors are taken into consideration when an impurity limit is decided upon, okay?

So just arbitrary some limit for all drug product, it does not make sense. Maybe because it doesn't contribute to efficacy, we would like to have

it as low as reasonably possible, but eventually it will depend on drug to drug.

Some drug products, it goes in very rapid clearance and may not be an issue in terms of dosimetry, there's no retention of that.

The other drug products, because it's chelated with the molecule and if the drug molecule internalizes into the cell, maybe you have retention.

So the issue may be different. We cannot come up with a one limit on a scientific basis.

DR. CHRISTODOULOU: Yes, and we're going to hear some more this afternoon in the afternoon session about contributions of actinium-227 to dosimetry and so on.

And like I said, we do carve out multidisciplinary migrations. At this time, we can just say that it's going to be a specification for a particular drug product, and that's the best we can do. Thanks.

Sarah, do you have any more questions?

MS. LOPAS: I think this might be the last question. Lisa, I didn't know if you wanted to take any more questions or if you wanted to take a break for lunch?

DR. CHRISTODOULOU: How close to the

30-minute mark are we?

MS. DIMMICK: Since Session Two started five minutes late, we are now at the 30-minute mark. So we did do a 30-minute Q&A session.

So we'll go ahead and take our break. It's kind of an early lunch, but it's the way that the agenda worked out.

So we will restart at noon with Session Three. Panelists, you should be back on and ready to go at 11:55.

And the speakers and panelists from Session Two and Three, if there were any questions in the chat that you can answer and want to respond to, go ahead and take that opportunity.

They just won't be read aloud into the record, and we are having this whole workshop transcribed, and that was the reason for reading the questions in the chat and providing the responses.

But certainly, speakers, if there are any questions from the chat that you can answer, that would be fine.

DR. CHRISTODOULOU: Thank you, Lisa.

MS. DIMMICK: Okay

DR. CHRISTODOULOU: Thank you so much for a productive Session Two.

MS. DIMMICK: Okay, and we'll see everyone at noon.

(Whereupon, the above-entitled matter went off the record at 11:22 a.m. and resumed at 12:01 p.m.)

DR. MARZELLA: Well, dear colleagues, we are ready to resume, and we are, this afternoon, moving from product quality considerations and from an overview of the clinical significance and importance of these products to the preclinical considerations for product development as well as early phase clinical development.

So welcome to session three then focused primarily on preclinical and clinical considerations for development of novel radiopharmaceuticals. And to lead us off, I would like to introduce Dr. Haleh Saber who is the deputy director for FDA's Division of Hematology Oncology Toxicology within the Office of Oncologic Diseases in CDER.

Dr. Saber is a recognized expert with considerable industry and regulatory experience. She was the lead author for a seminal guidance for industry on non-clinical studies for therapeutic radiopharmaceuticals. She's an expert in making determinations of first-in-human dose selection

studies which is really critical to get these studies off the ground in optimal fashion.

And we welcome hearing Dr. Saber's remarks on alpha-emitting therapeutic radiopharmaceuticals, non-clinical studies prior to initiation of a human study with focus on dose selection and impact of impurities. Dr. Saber.

DR. SABER: Good afternoon. Thank you, Lou, for the introduction. So first of all, can you hear me well?

MS. DIMMICK: Yes. Your audio is good, Dr. Saber.

DR. SABER: Okay, thank you very much. My talk is on non-clinical recommendations for radiopharmaceuticals prior to initiating a human study, talk a little bit about alpha-emitting radiopharmaceuticals -- it's not advancing. How do I advance this? The slide is not -- oh, okay. Sorry.

So I'll talk about non-clinical recommendations prior to initiation of first-in-human studies, and first-in-human dose selection. Both these topics are covered in our guidance that was finalized in 2019. Then talk a little bit bout alpha-emitting radiopharmaceuticals, and particularly around actinium-225 and maybe a little bit about

actinium-227 as an impurity.

Prior to initiation of the first-in-human study for an investigational product, you need to submit an IND to the FDA for review. And in terms of non-clinical studies, that will be submitted to your IND, you will need results of pharmacology studies. These are proof of concept studies.

So if you're going after a certain type of cancer, then you will have studies, in vitro and in vivo, to show activity against that tumor type. You'll have binding data, affinity data, et cetera. But pharmacology studies could be also used to gain certain safety information. For instance, they can be used to define an MTD, maximum tolerated dose, of the radiation in animals.

Your IND will also contain data on safety pharmacology of a drug. These are toxicities of your radiopharmaceutical to the CNS, cardiovascular, and respiratory systems. And oncology standalone studies are usually not needed, but assessments will be needed, and these could be done through biodistribution studies as well as general toxicology studies.

So the biodistribution study is done with the radiopharmaceutical, and obviously, where the radiation goes is where the toxicities go. So if the

distribution shows that your radiopharmaceutical is distributed in the CNS, for instance, that could tell us about adverse events that can happen in the CNS.

General toxicology study is done with a cold pharmaceutical, and that can have incorporated measures to have an assessment of CNS, cardiovascular, respiratory effects, and I'll talk a little bit more in detail about biodistribution studies in my slides because general toxicology studies are -- of the cold pharmaceutical is covered in other guidances such as ICH S9.

Your IND will contain results of animal biodistribution studies. Again, these are studies that will help us first-in-human dose selection for the human dosimetry. They're also used in assessing toxicities from the radiation.

And again, based on the distribution of the radiation and the knowledge of organ-specific radiation toxicities, you can put a risk assessment together that you will include in your IND with the potential toxicities from the radiation from your radiopharmaceutical. And these studies can also have toxicity endpoints incorporated in it such as clinical observation, body weight, clinical pathology.

Your IND will also contain results of a toxicology study. These will assess ligand-related effects. In our guidance, when we say ligand, we are referring to the chelating agent or the targeting moiety, the antibody or the difference. A toxicology study with the radiopharmaceutical is usually not needed because as I mentioned earlier, the biodistribution study could be used to assess radiation-induced toxicities.

Again, a little bit more on biodistribution studies. These are usually done in a single animal species with a single dose administration, then you look at activity over time in the animals, also called the time-integrated activity or accumulated activity, which is really the total number of transitions.

And these data in the animals can be used to estimate the same values in humans, and the total transitions in human can be used to obtain the estimated absorbed doses in human organs. Sorry, how do I go back? Okay. That's all right.

So what I wanted to say and I went too fast, is that you'll do the animal study and this estimate in the animals will be used to have the total transitions in the human organs, and then you use those

to get the absorbed doses in human organs which is then used to come up with an appropriate dose for human dosimetry.

You heard this morning about use of theranostic pairs. Theranostic pairs are biocompatible pairs of radionuclides that have a comparable PK in animals and humans in terms of distribution and half-life.

Here's an example of when a theranostic pair could be used. Here, in this example in this slide, I have an investigational product for use in cancer that has yttrium-90, and the animal studies are done with the yttrium-90 containing product. However, we know that this is not suitable for imaging in human dosimetry. As a result you can you use a theranostic pain in humans for the human dosimetry which is, in this case, indium-111 containing products.

Animal-biodistribution studies provide estimates at best. They can under-predict effects in humans. So the total number of transitions in the organs of animals may not necessarily be identical to what you expect to see in humans. For instance, if the biological product, the biological component of the radiopharmaceutical results in the formation of

antibody and results in a high clearance in the animals, you might have reduced number of transitions in the organs of the animals.

For that reason, we emphasize in the guidance that when you have data in humans that are relevant to the use of your product, you can rely on that or use that information, and based on that, the animal studies could be abbreviated. And also the first-in-human dose could be based on relevant clinical data as opposed to the non-clinical data.

Here is an example of an abbreviated non-clinical program. Let's say that you have an IND for a radiopharmaceutical that binds to the CD20 antigen on the surface of B cell, and this is labeled with iodine-131. And this is the product that I'm showing on the top right of this slide. And now a few years later, you have a different antibody that also binds to CD20 and also contains iodine-131.

In this case, you do not need to repeat your biodistribution studies in the animals. The data that you have in humans in this case would be relevant to select an appropriate dose of the investigational product to conduct a human

dosimetry, or depending on the data available, to even select an appropriate human therapeutic dose.

For first-in-human dose selection, you need to consider two different items. One would be the mass dose, that is the dose of the cold pharmaceutical. And again, in my talk, I'm spending a little bit of time on the radiation dose and biodistribution because the mass dose is covered in other guidances. In oncology we use ICH S9. So just follow ICH S9 in terms of the appropriate dose of the cold pharmaceutical.

When it comes to the radiation dose, again, we rely on animal-biodistribution studies assuming that there is no relevant clinical data. And that will provide us with estimated absorbed radiation doses in human organs, then these doses are compared to the threshold of tolerance in human organs from the radiation. And for organ tolerance in patients, you can use the articles on external beams as a starting point, and apply an appropriate RBE. And for alpha-emitting radiopharmaceutical, we recommend an RBE of five.

Again, we heard this morning about the advantages of alpha-emitting radiopharmaceuticals. They have some advantages and disadvantages, pros and

cons as summarized on this slide. The advantage is that it's a high-potency product, and it causes DNA double strand break, high LET, high RBE.

And if it's taken up quickly by the tumor, and if it's retained in the tumor for an appropriate period of time, then injury to the healthy tissues would be low. And also, these could be suitable for small tumor size and micro-metastases.

On the flip side, because of the short range, the radiation dose could be non-uniform in the tumor. There are challenges associated with imaging and dosimetry for these products. And also after the emission, the daughter nuclides can separate and redistribute. And particularly, if the distribution into a tumor takes a long time, then that is more likely to cause damage to healthy organs and tissues.

So there are certain properties that would be essential when coming up with an alpha-emitting radiopharmaceutical. One is the ligand property, one that I mentioned just now. Two, it's important for the product to be taken up quickly by the tumor, and for a specific period of time to be retained in the tumor in order to reduce the chance of daughters separating and redistributing.

The physical half-life is important. You

don't want it to be too long or too short. If the half-life is too short, then that will cause issues with the potency from the time of manufacturing to the time of this being delivered and given to patients could result in reduction in the activity and potency of the product.

And on other hand, if the half-life is too long, it can cause patient safety issues in addition to other potential issues such as environmental exposures.

Imaging capabilities is also important whether availability of theranostic pair for your alpha-emitting radiopharmaceutical, or having elements in the decay chain that could be imaged.

And the first three bullet points on this slide summarizes what I've come across in the INDs for alpha-emitting radiopharmaceuticals and the techniques used for biodistribution or dosimetry. One that is used is dissecting the organs of the animals, and counting and doing the -- counting the radioactivity, one has been the theranostic strategy, but also uses imageable signals in a decay chain.

I came across some papers -- so the last bullet here is just additional detection methods that have been described in the articles, and I thought you

might find these useful.

The question came up why actinium-225. In the last few years there has been increased amount of interest -- increasing interest in the use of actinium-225 in radiopharmaceutical, and we were interested to know what is resulting in this much increase in the use of actinium-225.

So one thing is probably availability of clinical data with actinium-225, and maybe also because we have clinical data with bismuth-213. And usually when publications become available, not just with radiopharmaceuticals, with any product or class of drug in general, my observation is that when the INDs are submitted, and then sponsors publish their data, and then other sponsors out there read these articles and they are encouraged to use the same class of products, or the same radionuclide, but also its advantage to the sponsors because now they use these articles to design their own non-clinical and clinical programs.

So I did a brief search back in June to see the publications. I used different key words that combine actinium with clinical or with cancer, and as you can see, except for the last part, this was done in June, so the last year, this year -- it does not represent the entire year -- you see the increasing

number of publications on actinium-225.

And that, again, might explain the more data become available, then the sponsors thinking about using alpha particles, now they are perhaps encouraged to use actinium-225.

So, again, why actinium-225. So the first one is what I think is the reason actinium-225 being used, non-clinical and clinical data being available. But also searched into application to see what the sponsors are saying why they are using actinium-225.

And among the discussion points were the half-life being optimal or they were able to do dosimetry and the optimal energy of it was discussed. And a few other points, but briefly, the two bullet points half-life and ability to dosimetry was discussed in several applications.

Here's a case study from an IND that used actinium-225 in their radiopharmaceutical. The strategy that they took was that using indium-111 as the theranostic pair, this sponsor had another IND that contained indium-111. They had conducted non-clinical studies, and they had conducted clinical studies.

And they had some clinical data, human dosimetry data with indium-111 product. And again,

the ligand is the same in the two products. They also presented some dosimetry data in the animals that was consistent with the clinical data that they obtained with the indium-111.

So for this particular IND, the review team, instead of using the animal data to select the first-in-human dose, they rely on the theranostic pair and the data in human from indium-111, and the dose was selected based on clinical data.

Because of high demand in actinium-225, we've noticed that there has been a shortage, and thus, there has been attempt in coming up with different methods to increase the supply of actinium-225. And one of these methods that has been described earlier today is the accelerator-produced actinium-225.

And it will result in the co-production of actinium-227, that has a long half-life of 21.8 years. These two cannot be separated from each other, and the concerns are -- various concerns such as patient level, environmental safe handling. But the focus of this talk is on patient level, what our team reviews is data as related to patient-level safety. And so that's what I will be talking in the next couple of slides.

DR. MARZELLA: Dr. Saber, if I may, a

reminder that we're coming close to end of the time allotted. Thank you.

DR. SABER: Okay. I think I have two slides only. Thank you. In case if your product contains actinium-227, then we do want to see the stability of your product. It's important to show that actinium-227 stays with the ligand such that the elimination is through biological elimination consistent with the effective half-life.

When you do the biodistribution dosimetry in the animals, you need to take into account both components, the actinium-227 and 225, and other decays. So this is when you start with an accelerated-produced actinium-225. However, if you have already conducted non-clinical studies, or you have conducted some patient study with the generator-produced actinium, and now you're switching to the accelerator-produced product, what information do you need.

Again, the stability is important. You need to show the stability of the product. The modeling approach could be used with a worst-case scenario. If actinium-227 separates and redistributes, what would be the worst case scenario and the dose from it -- absorbed dose from it? And an abbreviated animal dosimetry mass balance can help

to make sure that actinium-227 is released -- is excreted from the body.

And if you have any questions, these are all product-specific. If you have any questions, you can always ask for a meeting. And that's the end of my presentation.

DR. MARZELLA: Thank you, Haleh, for the very informative presentation. We will then move on to the next topic which will be a presentation by Dr. Mitchell Anscher. Mitch, is the medical officer in the division of oncology who is now retired and couldn't join us. So we will have a recorded presentation.

Just as a brief introduction, Mitch has a long and distinguished academic career in radiation oncology. The most recent at the MD Anderson Cancer Center where he was genitourinary section chief, and before that, he was at Virginia Commonwealth U where he shared the Department of Radiation Oncology. So we look forward to the presentation. Mitch will give the recorded presentation focusing on safety assessments in early phase clinical trials of radiopharmaceuticals.

DR. ANSCHER: Hi, I'm Mitch Anscher.

MS. LOPAS: Okay, everybody, just if this is showing up small on your screen, there's a couple

of things you can do. The little controls on the bottom right-hand next to like the progress, the time bar of this, you could press that. I think it's kind of view full screen. That'll help make it a little bit bigger. And then you can also press expand view.

So first you have to do view full screen, and then expand view, and that'll help make these slides, this video a little bit bigger. But that's it. Thanks, Kellee.

DR. ANSCHER: -- medical officer at the Food and Drug Administration. And I would like to thank the organizers for the opportunity to talk about challenges to safety assessments in early phase clinical trials for radiopharmaceuticals. Next slide please. I have nothing to disclose. Next slide please.

Radiopharmaceuticals offer several potential advantages over external beam radiation. They may be more targeted, thus, delivering a high-dose to the tumor while sparing normal tissues. Similarly, the lower energy charged particles typically employed in these therapies offer rapid dose fall-off, thus preferentially treating tumor over normal tissue.

Some particles emit gamma rays in the decay process, and thus, may offer the opportunity to combine

imaging with therapy. However, in reality, the targets may not be 100 percent tumor specific. For example, prostrate specific membrane antigen, a potential target in patients with metastatic prostate cancer, is also found in the kidney, small bowel, salivary, and lachrymal glands. So off-target toxicity may be an issue.

Depending on the isotope used, the depth of penetration may not be ideal for the clinical situation. Unfortunately, many agents used for therapy cannot be directly imaged, and a related an isotope with decay characteristics more suitable for imaging may need to be used to select patients for therapy.

Because the agents are administered internally and usually bound to carrier proteins, they must be evaluated like drugs. Information about how the agent is distributed, metabolized, and excreted becomes critical for determining dose and dosimetry which is different from external beam and sealed brachytherapy sources which are not circulated or metabolized. Next slide please.

Dosimetry for radiopharmaceuticals presents unique challenges compared to external beam radiation, some of which are listed here.

Particularly challenging are assumptions of uniform distribution of the product throughout the target when, in fact, this is not often the case as we will see shortly.

Also, each isotope has a different half-life which means the rate of dose delivery varies between products. And this may impact on the biological effectiveness of the product.

Finally, accumulating evidence suggests the tolerance doses for radiopharmaceuticals are not the same as for external beam radiation, and are likely to vary by isotope. Much work needs to be done in this area in order to optimize the use of radiopharmaceuticals. Next slide please.

This figure illustrates the impact of the four Rs of radiobiology, repair, repopulation, redistribution, and re-oxygenation on cell kill. And also how ionization density can overcome some of these factors.

The curve at the far left labeled HDR for high dose rate illustrates the cell kill expected from a high dose rate exposure such as external beam radiation. As the dose rate is lowered, other factors come into play which may either increase or decrease the killing of tumor in normal tissue cells.

For example, a lower dose rate allows for repair of sub-lethal DNA damage in cell proliferation or repopulation which will increase the surviving fraction. On the other hand, at low-dose rate, cells may redistribute into a more radiosensitive phase of the cell cycle leading to decreased cell survival.

In general, the lower the dose rate, the less cell kill is achieved per unit of dose. Thus lower dose rate therapies would require higher total doses to achieve effects of higher dose rate therapies.

The curve on the right illustrates the importance of oxygen to radiation sensitivity. Oxygen is the most effective radiation sensitizer known with well-oxygenated cells being about three times more likely to be killed than hypoxic cells by the same dose of radiation. This is known as the oxygen-enhancement ratio, or OER.

The curve on the lower right illustrates two of the advantages of alpha-particles. Notice that the curve is straight. The bend in the early portion of the other curves occurs as a result of repair of sub-lethal DNA damages at lower doses or lower dose rates. Next slide please.

The reason that alpha particles seem to be immune to the effects of the four Rs lies in the

difference in the physics of energy distribution. Alpha particles deposit their energy and tissue over a much shorter distance than do photons, protons, or beta particles. Thus, alpha particles are referred to as high-linear energy transfer or high LET radiation. And the others are referred to as low LET radiation.

The consequence of high LET is that most of the energy deposition results in DNA double strand breaks, which are not repaired and lead directly to cell death.

In contrast, the interaction of low LET radiations in tissue are less likely to result in irreparable DNA damage, and more likely to result in the production of free radicals leading to cell death by other mechanisms which are more easily overcome by normal biologic repair processes.

Thus, alpha particles are a radiologic killing machine, but unfortunately, they do not distinguish between normal tissues and tumor cells in this process. Their very short path length in tissue, however, offers the potential advantage of confining their killing effect more within the tumor than may be possible with other types of radiation. Next slide please.

When prescribing radiation, radiation oncologists will estimate the probability of tumor control and the probability of normal tissue injury. The ratio of tumor control probability to normal tissue complication probability is referred to as the therapeutic ratio.

Estimates of these probabilities are based on population-derived data and are not precisely known a priority for an individual patient. We continue to define our knowledge of TCP and NTCP through ongoing research, but in order to do so, precise estimates of doses delivered to both tumor and normal tissue are critical. Next slide please.

In most drug studies, dose-limiting toxicities are determined after a relatively short observation period, generally 30 days. However, for radiation therapies, the toxicities that usually drive prescribing practices are late-occurring toxicities which we refer to as late effects. By convention, late effects are those that persist beyond 90 days from the end of therapy or begin more than 90 days after therapy.

There are few effective therapies for late radiation effects at the present time, so the approach taken is prevention. This requires accurate knowledge of dose distributions and doses delivered to normal

tissues in order to accurately define tolerance doses and prevent the development of late effects.

There are some exceptions to this rule, however, when acute responding tissues can dominate the picture. The most sensitive normal tissue is the bone marrow, and low doses to large volumes may lead to permanent marrow failure. The effects may be detected within the first week of treatment if large amounts of bone marrow is irradiated.

With external beam radiation, the problem is avoided by limiting the volume of marrow treated. With systemic radiation, it is not possible to limit the volume of marrow irradiated, so this problem must be avoided by limiting the dose to the marrow. Next slide please.

Many factors influence the therapeutic ratio. These include patient-specific factors that might make an individual more or less likely to suffer a complication from radiation with a normal tissue complication probability. In tumor-related factors that impact on the likelihood of controlling the cancer or the tumor control probability. Next slide please.

Unfortunately, few of these factors are under our direct control. We can try to get patients to stop smoking during treatment and to avoid taking

substances that might interfere with the efficacy of the therapy. The one thing over which we have total control are the radiation treatment factors, but only if we have accurate information about dosimetry. Next slide please.

Admittedly, the state of our understanding of dose-volume guidelines, even after over a hundred years of treating cancer with external beam radiation, is imperfect. Probably the biggest reason for this situation is that these guidelines have been derived mostly from retrospective analyses in which complications have most likely been underreported.

Fortunately, more studies are addressing these issues and our knowledge base is improving. However, more work is needed to define risk at the individual patient level which will require a knowledge not only of the dosimetry, but also an individual patient's biological risk profile. And we're a long way from being able to determine that with accuracy. Next slide please.

The next two slides will compare the differences in dose distribution between external beam radiation treatments and systemic radiation therapy. This slide demonstrates the ability to deliver external radiation to complex geometries precisely,

and to achieve both the desired tumor coverage and protection of normal tissues. It also demonstrates the relative predictability of the pre-defined dose gradient distributions.

The figure on the left demonstrates a dose map. The thick turquoise red and blue lines represent prescription dose lines. In this example, everything between the turquoise and red lines is getting a dose of at least 45 gray, everything between the red and blue lines is getting at least 75 gray, and everything inside the blue line is getting at 100 gray.

The figure on the right is a cartoon representing how the dose to the stomach was kept to a safe level. The green area represents a safety zone placed around the stomach to be sure that no more than 45 gray was delivered to this organ. On the left, you can see that the turquoise line touches the wall of the stomach, the contents of which is a dense white area. Next slide please.

This figure demonstrates that in contrast to external beam radiation, the dose distribution of systemic radiation is dependent on blood flow to the tumor which is distinctly non-uniform. This dose has a large area -- or this tumor has a large area in the center shown at the top which would not be expected

to have a viable blood supply referred to as the necrotic center.

This is confirmed by the images at the bottom in which the bright area represents distribution of Y-90, and the dark region represents absence of isotope distribution. If one calculates the dose based on the assumption of uniform distribution, and then calculates the dose based on the actual distribution of Y-90, the dose determinations vary significantly.

However, because of the low penetration in tissues of the particle radiation relative to external beam photons, the dose distribution to the surrounding non-tumor containing liver may be lower than with external beam radiation if no radioisotope is injected into the blood supply to the remaining liver. This is a good thing as you will see in the next figure. Next slide please.

If one goes back to our concept of therapeutic ratio, these figures illustrate both the need to individualize dosimetry for this treatment and the difference between the dose desired to the tumor versus normal liver. In both figures, you can see that the probability of effect, either dose, or tumor response, or liver injury increase with increasing

dose.

But the desired doses to achieve a high probability of tumor response and a low probability of liver injury are vastly different. To prevent severe liver injury, the dose to the uninvolved liver must be much lower than the dose to the tumor. Next slide please.

Since our conference is on actinium, let me focus more on issues directly related to alpha-emitters. To date, the only alpha-emitter approved for human use is radium-223 for selected patients with metastatic prostate cancer affecting only the bone. In this situation, radium is not bound to a carrier protein, but rather is directly administered intravenously.

Once in the circulation, it substitutes for calcium and is taken up in bone in regions of increased bone remodeling such as that found at the site of metastatic disease.

The lower two bullet points are not issues specific to alpha-emitters or even to radiopharmaceuticals. These reflect general principles of early phase drug development which apply across the board. The final line on the slide, however, is a key question unique to the study of

radiotherapeutics, either externally or internally administered. Next slide please.

The use of carrier proteins molecules provide an opportunity to target systemic radiation to tumors preferentially, but probably not exclusively. Thus, as part of the evaluation of a radiopharmaceutical, it is important to determine where in the body, besides in the tumor, is the target protein found, and how the carrier protein is handled by the body. This information will provide insight into potential toxicities, both acute and late, due to off-target irradiation. Next slide please.

What have we learned about adverse event occurrence from studies to date of radiopharmaceuticals? First, for systemically administered agents, bone marrow toxicity seems to be a common occurrence. This is not surprising due to the extreme radio-sensitivity of the bone marrow. It tends to occurs which each treatment and tends to determine the maximum individual dose of the dosing interval.

Other acute toxicities seem to be more dependent on the distribution of binding of the carrier protein in normal tissues. For example, the target protein prostate-specific membrane antigen is also

found in salivary glands. So dry mouth is a common occurrence in trials of radiopharmaceuticals bound to proteins targeting PSMA.

Early phase trials are designed to capture and manage these types of adverse events as the goal of these studies is often to determine the maximum tolerated dose and the optimal dosing intervals. In order to accomplish these goals, the trials must be able to identify dose limiting toxicities. Next slide.

Our biggest knowledge gap remains in the area of late toxicity. Remember, these are the adverse events that generally drive prescribing practices for radiation therapy be it localized or systemic. The reason for this practice, is that most late toxicities are permanent, irreversible, and as yet, there are often no effective treatments to effect the underlying pathophysiology.

As radiopharmaceuticals assume a larger role in the management of some cancers, it will be important to strike a balance between the need for more effective therapies for diseases with a poor outcome with the need to define these risks before trying to use these therapies in patients with a better prognosis, and thus, a potentially less favorable

risk/benefit ratio. Next slide please.

Finally, what are the trial design challenges we face as the number of trials of systemic radionuclides continues to increase? We've touched on the issue of dose-limiting toxicities.

What is the ideal observation period to define dose limiting toxicities for systemic radionuclides? Is it the standard 30 days, or should it be based on the half-life of the isotope? What role does biodistribution play in this assessment as this information may provide clues about off-target toxicities to anticipate?

Should patients be observed for just one cycle, or should adverse events be assessed for all cycles since radiation effects are cumulative and ultimately, we want to detect not just acute toxicities, but also late toxicities? This will probably require a continuous reassessment of adverse events as they develop over time to refine determination of tolerance doses.

And phased therapies become indicated earlier in the course of the disease, imaging to select patients will become impractical since micro-metastatic deposits cannot be imaged. In this situation, dosing may have to be based purely on normal

tissue tolerance. For this approach, we will need better information about organ-specific tolerance doses. Next slide please.

So in summary, an increasing number of radiopharmaceuticals are being studied in patients with advanced cancers. Owing to the unique method of delivering radiation, these agents hold great promise for the future. The safe and effective prescribing of these agents will require not only a knowledge of their short-term side effects, but also a better understanding of the long term risk associated with their use.

Long-term, preferably lifelong, follow up of patients enrolled in prospective trials will be the only way to accurately determine the risk of late complications and truly establish organ specific tolerance doses. That concludes my presentation, and thank you very much for your attention.

DR. MARZELLA: I think we are ready now to move to the next topics of our session, and we are going to shift now more squarely our focus on dosimetry. And I would like to invite next Dr. Donika Plyku to come to the podium.

Dr. Plyku is a nuclear medical physicist and a senior staff fellow in the FDA's Division of

Imaging and Radiation Medicine. She leads a research team that focuses on evaluation of regulatory requirements related to radiation dosimetry. And she is a consultant to various offices at FDA for diagnostic as well as therapeutic radiopharmaceuticals.

Dr. Plyku has considerable research and clinical experience in dosimetry at the Johns Hopkins Hospital as well as the Washington Hospital Center. So Dr. Plyku will talk to us about dosimetry for radiopharmaceutical therapy. Donika. You may be muted.

DR. PLYKU: Okay, just --

MS. LOPAS: Dr. Plyku, just -- we are seeing your slides, just not in slide show view. Whatever you had before, they were in slide show view, so.

DR. PLYKU: Right. Yeah.

MS. LOPAS: There you go. Now we see them, and we hear you.

DR. PLYKU: Can you hear me?

MS. LOPAS: We can, yes.

DR. PLYKU: Okay, great. Okay. Good afternoon, everyone. I'm Donika Plyku, medical physicist at the Division of Imaging and Radiation Medicine, Center for Drug Evaluation and Research at

the FDA. Today I'll talk about dosimetry for radiopharmaceuticals therapy. This is now kind of my talk.

MS. LOPAS: Can I just ask that you --

DR. PLYKU: Yes.

MS. LOPAS: -- speak up a little bit? You're just a little bit quite. I apologize. If you could just get a little closer to your speaker, that'd be great. Thank you so much. Or your microphone, thank you.

DR. PLYKU: Yes. Sure. This now kind of my talk, I will talk -- I will discuss radiopharmaceutical therapy in comparison to other treatment modalities that are used for metastatic cancer. And then I will describe the MIRD formalism for internal radiation dosimetry. And dosimetry for RPT including challenges and considerations for -- with alpha-emitters.

So radiopharmaceutical therapy is a treatment modality that targets disseminated or metastatic cancer, and the radiation is delivered internally using radiopharmaceuticals. And that accumulate physiologically or bind to specific cancer cells.

So the radiopharmaceutical is generally

formed by a combination of radionuclide with a biologically active pharmacophore or a targeting molecule. And the two are chemically labeled, and the targeting molecule will bind to specific cancer cells, or a specific target in the body.

The radionuclide component or the radiation-emitting isotope determines the imaging and/or therapeutic properties of the radiopharmaceutical depending on the predominate emission types. And the imaging properties allow external detection of the emitted radiation. Also, these radionuclide component can also confer desired localization properties such as in the case of radioiodine.

The chemical structure of the pharmaceutical component on the other hand determines the biological properties of the radiopharmaceutical, acts as a carrier for the radionuclide component, and determines localization and biodistribution.

So RPT is a form of targeted therapy where radiation is delivered systemically and local regionally similar to chemotherapy and biologically-targeted therapy. However, unlike external beam radiation therapy, there is no direct control on where the agent goes and accumulates. So

essential questions for RPT are where does that concentrate, and for how long? And what type of radiation is being emitted?

The first question can be addressed by performing pre-clinical biodistribution and/or pre-clinical or clinical imaging studies. One can implement imaging as a theranostic approach, or using a theranostic approach where the surrogate imaging agent is used to provide target distribution and project for therapeutic imaging agent. Or one can image therapeutic agent itself. The type of radiation that is being emitted depends on the radionuclide.

So let's look more closely at the radionuclide component, and it is important to distinguish between the physics and the radiobiological properties of the emissions that are important for therapy, and that is beta and alpha particles.

So the two differ substantially in terms of the path length prevalent in tissue, and also in terms of the amount of energy deposited locally which is the linear energy transfer. And, in fact, the LET is an important quantity that can be used to differentiate between them. And also it is important when we consider the different radiobiological

effectiveness of alpha particles in comparison to beta particles.

So beta particles are electrons elementary particles that are sparsely ionizing. The path length in tissue is a few millimeters, and many tracks are required for cell kill. And the DNA damage in this case can still be repaired.

However, alpha particles are heavy helium nuclei that are densely ionizing, have a very short path length in tissue, so micron range. And a very high LET, so densely ionizing. A few tracks can kill cells, and the DNA damage in this case is irreparable.

Photons with appropriate energy emissions are important for imaging. So the table shows examples of beta and alpha emitters. So far there are many low LET and beta emitters that have been approved and be approved for use clinically. In contrast, there is only one alpha emitter, that is radium-223, that is approved for treatment of metastatic prostate cancer.

However, the good news is that there are many therapeutic agents, including alpha emitters, that are now under development and this table shows a surge in clinical trials -- the number of trials for specific isotopes shown here, both at low LET and high LET emitters. And more details are available in this

reference.

So why do we need to perform radiation dosimetry? Well, we need a measure to predict potential toxicity, efficacy, and risk associated with exposure to radiation. And the relevant end points in the contest of therapy are toxicity and efficacy as opposed to cancer or other health risks that are stochastic effects and that are relevant in the diagnostic realm.

So the important quantity here is the calculation of absorbed dose which is the amount of energy absorbed per unit mass in target organ in tissue. And this is the most closely related quantity to the biological effect associated with exposure to radiation. And with optimal dosing for RPT, one aims to achieve good tumor response within the constraint of normal organ toxicity.

Next I want to continue discussing the MIRD formalism for internal radiation dosimetry and this is basically the global scheme of nuclide dosimetry. And the absorbed dose -- to calculate the absorbed dose to target organ, one needs to have a measurement or measurement of a number of disintegrations, decays in source organs, or in the organs that have shown accumulation of the agent that was administered.

So the first factor in this equation, it is the number of disintegrations in the source organ, and then this is multiplied with the energy released per disintegration. And then with the other factor is the fraction that is absorbed in the target organ. So the total amount of energy in the target organ that is delivered to the target organ is then divided by the mass of the target organ to obtain absorbed dose. So let's look at how this is done.

To obtain the time-activity data pharmacokinetic data that are needed for dosimetry calculations, this can be derived generally from animal studies as was described previously by my colleague, and these are usually performed for the submission of an IND. Here larger animals, the PK data can be obtained via imaging, and smaller number of animals may be sufficient.

For smaller animals, one has to perform biodistribution studies where organs are harvested at certain time points post-injection, and radioactivity is counted. And then used to characterize the time activity curve in animals, and then extrapolate to time activity in human organs to obtain estimated absorbed dose to human organs. Another way is clinical imaging, and this is usually performed in case one, two, or three

of the approval of an NDA, involves imaging and also other measurements in humans.

The MIRD absorbed-fraction methodology that is based on imaging starts with the acquisition of serial quantitative images. And then one defines the regions of interest. And for each region of interest, one can characterize the time activity curves, fit and integrate to obtain the accumulated or the time-integrated activity coefficients, and the so-called residence times. And this is the first term in the equation.

And once we have obtained the residence time in the human organs, either projecting from pre-clinical studies or direct measurements in humans, we can use the MIRD equation to obtain observed dose.

And to simplify this calculation, the MIRD committee of the Society of Nuclear Medicine came up with the so-called S values. They incorporate properties of the radionuclide that are shown here by the delta symbol, and also organ anatomy and organ mass.

And S values are generated using Monte Carlo based reference human anatomy or human phantoms. And an earlier model that was used for this calculation is shown here. However, more sophisticated models have also been developed.

So the absorbed dose of the target organ is then the sum of the product terms of the activity measured in the source organ with an S value from source to target organ -- different source to target organ combinations. Coming right to this scheme, this calculation can then be performed manually or using a software.

So what I've described so far, this is the MIRD absorbed fraction methodology, and that is primarily developed to address or to provide dosimetry estimates for risk evaluation of diagnostic radiopharmaceuticals. Here the end points are cancer or other health risks that are stochastic effects in comparison to the deterministic effects that are relevant in therapy. And the calculation is based on reference anatomy where it is specific to the patient, so this is representative of a population.

Because reference models and reference anatomies are used, the tumor dosimetry cannot be directly handled within the formalism. However, one can estimate tumor doses assuming spherical shapes and calculating the -- only the self-dose, not accounting for other contributions.

This is an activity-based calculation using model S-values. However, it is important that

in the context of that therapy, one can actually modify the organ mass in the calculation to reflect the organ mass of specific patient, and this can be derived from volumes that have been drawn on patient's CT images. One of the standard tools that are used for this calculation allows for this modification.

On the other hand, voxelized techniques that have been derived in the context of external beam radiation therapy or dosimetry for external beam radiation therapy have also been adapted for radiopharmaceutical therapy. And the endpoints here are, again, organ toxicity, efficacy, and tumor response which are deterministic effects.

The calculation is a patient specific dosimetry calculation that is appropriate for RPT because the calculation is done using patient specific anatomy. And in this calculation method, one can actually derive dose rate information, and then model voxel level energy deposition for actual patient anatomy. And starting with dose rate, one can actually incorporate radiobiology in this methodology. And the table shows several software packages that have obtained FDA clearance.

Next, I want to continue discussing alpha emitters, and there are several criteria that can be

considered in the selection of an alpha emitter for therapy. And with respect to the nuclear characteristics, the radionuclide should have a long half-life to allow for production, transport, radiochemistry as well as administration and uptake. However, short enough to avoid toxicity and waste.

And there should be a large fraction of alpha emissions per decay to increase the probability for self-heal. And high-energy photon emissions are advantageous because they can allow imaging even for alpha emitters. And other considerations include purity, and chemical properties, and cost of production as was discussed previously.

So a potential alpha emitters for therapeutic use are shown here. The first one that was used clinically is bismuth-213. That was labeled to anti-leukemia antibody. The first one to obtain FDA clearance, so it's radium-223 for metastatic prostate cancer. And the radium-223 has four alpha emissions, and a long half-life.

Similar to radium-223, actinium-225 has also four-met high energy alpha particles for decay, and this is easily chelated to DOTA and other chelating agents. It has a long half-life, and it is available from Oak Ridge and other sources that have been also

recently used for the production, and it's currently being used in a variety of pre-clinical and clinical trials.

So I want to discuss dosimetry for alpha emitters, and special challenges regarding alpha emitter dosimetry. The MIRD formalism has been adapted for alpha emitters. Here to absorb those estimates depend on the PK fate of unstable daughters. So one has to consider all daughters in the decay process, and also half -lives, specific half-lives.

Given the recall energy of the daughter radionuclides can be thousands of times larger than the chemical bond -- than the chemical bonds, the alpha decay may close the daughter product to become unconjugated from the radiopharmaceutical. And this is concerning because one has to basically estimate different scenarios of daughters either becoming free and accumulating in different organs, in other organs. For example, bismuth-213 accumulating in the kidneys.

And also, scenario software, these remain conjugated. If imaging is not possible, then one can use biokinetic modeling to obtain time-activity curves. Several techniques have

been -- or are being developed for imaging alpha emitters, and some abstracts are shown here on this slide.

So it is important to mention and to consider the difference in LET between alpha and beta emitters. And again, this actually effects the radiobiological effectiveness of the alpha emitters, and the so-called RBE value is different for -- is higher for alpha emitters because of this.

RBE is defined as the absorbed dose that can -- it's calculated as the absorbed dose of a reference radiation required to produce a biological effect divided by the absorbed dose of the test radiation. And this is an experimentally determined value defined for a particular biological effect, and for a particular system or tissue type. So RBE depends on absorbed dose, biological endpoint, and tissue type.

Because human studies using alpha emitters have yet to be analyzed for deterministic effects, the RBE value is not well-defined for alpha emitters. However, an RBE value of five has been recommended by consensus for projecting possible deterministic biological effects associated with an estimated alpha particle absorbed dose with respect to external beam radiation.

The other point of consideration is the short-range of the alpha emitters. So a few -- I mean microarrays are a few millimeters. And this is three to four cell diameters. So basically the dosimetry method should account for both organ-level and micro-scale distributions due to the short range of the alpha particles.

The organ level dosimetry can be, again, done by patient imaging. However, micro-scale dosimetry requires a combination of both whole organ measurements with pre-clinical measurements, and also modeling of the microstructures of particular organs that are critical organs.

The RBE value, and also micro dosimetry can also be incorporated in the context of the MIRD methodology, and an RBE-weighted dose value can be calculated for a particular alpha emitter.

So to summarize, radiopharmaceutical therapy is a systemic and targeted treatment modality for disseminated cancers. Dosimetry for RPT has its roots in the formalism established by the MIRD committee to assess additional ways for the diagnostic radiopharmaceuticals. A more appropriate dosimetry scheme for RPT involves a more patient-specific approach, voxelized

calculations and tumor dosimetry.

Dosimetry for alpha emitters includes other special considerations such as the RBE value and microscale dosimetry. And pre-clinical and clinical dosimetry studies in general are essential for the development of new radiopharmaceuticals for RPT. Thank you.

DR. MARZELLA: Thank you, Dr. Plyku, for that very nice presentation. And we turn now to Dr. Kish Chakrabarti who will complete our session. Dr. Chakrabarti has a long record of achievement at FDA where he's currently a senior expert scientist. He has made very seminal contributions to mammography and breast tomosynthesis.

Dr. Chakrabarti is a fellow of the American Association of Physicists in Medicine. So we're very pleased to have the benefit of his expertise. Dr. Chakrabarti will speak on dosimetry (audio interference) and a note of caution about the potential risks of extravasation from alpha therapeutics. Dr. Chakrabarti, the forum is yours.

DR. CHAKRABARTI: Thank you, Louis, for the introduction. Let's see if we can share

this. It looks like I had to share. Is it --

MS. LOPAS: And I think you are sharing -- because we're seeing your WebEx application screen, so if you can maybe bring your PowerPoint up.

DR. CHAKRABARTI: Okay. That's what I'm trying to do. Is it working?

MS. LOPAS: Not yet. It's a little slow on our end though, so it could be a delay. There we go, I think something's coming up now. Nope, we're not seeing it yet. And, Kish, let us know if you would just prefer Kellee to share your slides because she could do that as well.

DR. CHAKRABARTI: I am -- it's not going through, is it?

MS. LOPAS: No, we're not seeing it.

DR. CHAKRABARTI: The one that you had?

MS. LOPAS: I am not -- I think we got a -- I'm not sure if we got a revised version of your slides most recently, but we do have those. I think we got revised --

DR. CHAKRABARTI: Yeah, yeah. If you have the revised version, that should do.

MS. LOPAS: Yeah. Kellee, are you able to pull those up?

MS. JAMERSON: Sure.

DR. CHAKRABARTI: Well, so it tells me that you are sharing, so I got to stop share, right?

MS. LOPAS: Yep, that's right. Kellee will pull them up. Look good, Kish?

DR. CHAKRABARTI: Perfect. That's good.

MS. LOPAS: All right. She's going to -- she'll do the slide show and we'll be all set.

DR. CHAKRABARTI: Thank you so much. So far you have heard the last few speakers discuss some alpha emitters in general. I am going to talk about dosimetry of alpha emitter, that is the only sole approved alpha emitter. Slide please. I don't think I can move. Okay. It's radium-223 dichloride, it's a castration-resisting in prostate cancer in patients with bone metastasis. And that's the FDA approved alpha emitter so far for diagnosis or therapy.

Part of my talk will be discuss the dose calculation that is based on the internal report that is provided to FDA, biokinetics by Glenn Flux, and dosimetry by Sgouros. I will strictly follow the outline of the dosimetry that is provided to us.

There are several papers where I think both of these people and their group after this radium-223 approved by FDA, there are papers coming up and there micro-dosimetry has been included, but I am strictly following what we have, and that would be the outline of the dose measurements.

They talk about very little extravasation from the alpha emitters. By the way, this is a bad time to speak because it's lunch time, and you already have three speakers before me. So next slide please. And I hope I will not make this too boring because if some of you are dosing, I don't want to interrupt your sleep.

It's something I heard in one of the meetings that I was giving at -- I was listening, not giving a talk. There's a guy who told me -- the guy -- the speaker is not only boring, he's loud because he could not sleep. So this is not the right time for give a presentation is lunch and then three speakers before me. But I'll try my best.

So going back to radium-223, this has a very complicated decay which involves three alphas, two betas -- I'm sorry, five alphas and three betas, and of course, associated gamma with

it. However, most of the decay expressed first disintegration from radium to radon, and you see that that takes 1,143 days and the rest of the decays are in minutes and second till it reaches late as a stable element. Next slide please.

Okay. So it starts with radium, as you'll see there's an alpha and there's a gamma, the alpha and gamma. These gammas provide a clue, this provides imaging, and that is what is taken up to calculate the dose. The dose measurement for alpha is not -- it's a very cumbersome process. And there is no direct way because you cannot emit alpha in vivo. Okay. And that's a big handicap with alpha emitters.

Hopefully, the way it is advancing and the way the interest is developing, we'll get more information directly from the alpha particle, but right now it's a secondary way of getting the dose. So here it is as I mentioned, that there is decays with gamma and beta, and then finally is a stable lid. Next slide please.

So radium-223 is a bone-seeking alpha emitter. It's a natural bone-seeking alpha emitter with high energy transfer which is LET of 80 keV per micrometer. And its range is less than

100 micrometers. So if you multiple by total hundred by 80, you get about eight to the sixth -- 10 to the sixth, point 8, 10 to the sixth. So that's it in terms of meV, that's the energy that is provided.

Also which verified alpha, three electron, 18 photons. And out of those, two are gamma and six x-ray emissions in the process. Next slide please.

So it moves very clearly, and it's clearly quickly from the blood. And about 61 percent is taken up by skeleton which is why this is very effective for bone-seeking and for metastasis in the bone. So, once again, within this process, it takes about four hours, and 61 percent is taken up in the skeleton. Next slide please.

So the whole idea that I am putting it finally is to get the absorbed dose in different organs. Although, the belief is if it is alpha, it remains within a very short distance, but there are other gamma and beta, and this can migrate to other organs.

So we will show you the average organ dose in the nearby area and the toxicity level.

That's the whole idea of this dose calculation. That's why it's the safety of the system. So safety and effectiveness, or efficacy, we're going to discuss the safety part based on the results that they've provided.

There are 20 -- as I said, there are about 20 meV of which 95 percent are alpha emissions, and 3.2 percent are beta, and less than 2 percent of the gamma emission. So this results in a very low signal from gamma which present challenges for quantitative imagery, but it is the alpha which provides -- I'm sorry, it is the gamma, even though that's a very low, nevertheless, it provides the individual biodistribution studies and that results the dose.

Emitting characteristic are three peaks, and that is a probability of 1 percent with 10 photons. And optimal energy windows that is set at 82, 154, and 270 keV. Next slide please.

Yes. So this is the energy spectrum, and from Glenn Flux et all, and they have provided three areas, one, two, and basically three areas, three peaks, and they use these three peaks or calculations of residence time. I'll go to that, but I'll say that this is what is the main thing.

Then there are other things. Next slide please.

This engineered scans that shows that in zero, one, two, three and six days following administration of 55 kilobecquerel activated 5 kg, this study confirms that activity is quickly released. This is referenced by Glenn Flux again. Next slide please.

So there are some experiments that we obtained to get the mean absorbed radiation dose, and then five patients with castration-resistant prostate cancer was used. Now whole body dosimetry can be assessed, and then there are some dosimetry from red marrow, from the imaging, and blood sampling, and excretion products. So there's a combination of things are done to get to the absorbed dose. Next slide please.

See, these are the combinations that they are doing. There are sodium ion detector, a gamma ray spectroscopy, sample counter, gamma camera, large samples excretion products and activity quantification. Next slide please.

So these are the experimental data, and then comes a theoretical model. With the experimental values, the theoretical models are used. And these are all in the software used which

has been mentioned by previous speakers that this is new, this is an FDA cleared product.

And this is used mostly for beta and gamma. When they used for alpha, they had to do some special assumptions. Dosing and biodistribution data by Glenn Flux and calculation was done mostly by Sgouros. Next slide please.

Now again, these models discussed, this used mod schema pamphlet 21. It requires accumulated activity, and from there, the residence time. And when residence time is multiplied by the S-value, which is a number from the target to the dose, you get the dose.

So average dose requires that you get residence time which is the cumulative activity or the activity that is being administered, and then used only in the scheme and then a mod 21 pamphlet, and get the S value, is the dose value, average dose parameter. Then you multiply this. And you can use the software, you can use Monte Carlo software. You can use the other simpler phantom to get a value of the dose.

So besides that, then there is a calculation for daughter decays, and Sgouros had assumed that all daughters are decaying at the same

time. So long -- and to simplify. And then there is a particular one, radon, which decays into a respiratory track, and the dose is also measured separately for that. Slide please.

So the absorbed dose calculation, except for GI and heart wall, was obtained using OLINDA. The rest of the thing was specifically done with the daughters and with the same time decay time -- I'm sorry, different decay time, but same place, same time, the decay with the other -- with the parent. And all only the calculation was performed for each daughter.

The result of absorbed dose were weighted to reflect the heat of each daughter in that radium decay. Details regarding GI, red marrow, and heart wall calculation provided by Sgouros. The details are not given here. Next one please. Next slide.

So now here is the final thing that we do. We get organ doses for several organs, and if you look at that, you get -- this is what the calculated dose provided in the leveling. And it is multiplied because six times that activity was administered to the patients. So I multiply this by six and I get the number for total cumulative

dose windows. Next slide please.

So the major radiation is the osteogenic cell and the highest subdural calculated 4.75 gray for single, and when you multiply it by six times administration, it's about 28.5 gray.

The red marrow if you do the same thing, it really goes over the limit, but I did not do that because the red marrow is -- you have to assume that they are new pairing because it is done at different interval. There is enough time between one administration of activity to the next one that this value changes. Okay? So that's why if you simply multiply it by six, you get erroneous result.

Now as also shown on the table one, the 73 kg adult male was receiving this much of radiation, and lung-absorbed doses 4.9 milligray. And if you multiply by -- and with accumulated absorbed dose of 2.4 after six administration, the range of this, 2.8 to 7.2 from the gray is below 17.5 level at which lung toxicity is seen following the whole lung irradiation.

So this is important that the question has come up even into our mind. If it goes, this

goes in the lung, and then what happens, how much dose is given in the lung. Okay, the next slide please.

DR. MARZELLA: Kish, we're coming close to the end of the presentation. Thank you.

DR. CHAKRABARTI: Okay, thank you. So here it is, is the bone fracture -- this is the threshold absorbed dose for one person rate of mortality. And as I said, that these are the calculated average value well within this within the sub q range including for the lungs. Next slide please.

So this is very important, RBE. If you draw a line, you'll see that for x-ray you need a lot more dose than the alpha. And so this is why it is very important to get the RBE value to use. Our previous speakers have discussed that, so I'm going to just simply touch and move on because -- but I want to reemphasize that alpha particle at a lower dose, if you go to the line, it does the same thing and exit at high dose. Okay? Next slide please.

The absorbed dose versus effective dose, another thing, in a therapeutic, particularly for alpha particle when therapeutic,

is more going towards the realm of deterministic effect as opposed to diagnosis which is more of a stochastic effect. So it marks, formation is there, what we do for dosimetry of alpha particle and for therapeutic uses. Next one please.

Okay, that is pretty much my story, but I will just touch a couple of slides, the extravasation. What happens to the extravasation when you use alpha particles? There is a pain, swelling, for any radionuclides this happen. That from sometimes you do not have a symptomatic, some of -- a symptomatic extravasation can be also seen.

And this is very -- next slide please -- this is very noting that happens in all therapeutic. It loses diagnostic therapeutic efficacy, and the reaction, and ulceration, and scan can happen. So these are known for all radionuclides. Now what happens with the introduction of alpha into this? Next slide please.

So as I said, that this is a -- extravasation happens for soft x-rays and surgical intervention can be -- there has to be required dosimetry has to be used. Next slide please.

Only one published literature that we

found extravasation from alpha emitter, which is here. And beyond that, we are keeping an eye on this, and we continue to monitor any information that comes to FDA or post-market adverse effect. But right now this is everything --

(Simultaneous speaking.)

DR. MARZELLA: We need to conclude because we are taking time away from the --

DR. CHAKRABARTI: Next slide please. The conclusion slide. We have discussed radium-233 for sole alpha radio -- approved by the FDA. Alpha emitters rapidly and increasingly finding use in nuclear medicine.

Want of proper imaging technology makes it very difficult to estimate absorbed organ dose. Determination of proper RBE is also an important issue. Extravasation incidents are still few and far between. FDA continues to monitor through its post-market recording system this issue. And thank you for your attention.

DR. MARZELLA: Great. Thank you, Dr. Chakrabarti, for that very informative presentation. If I may, then I would like to begin our panel session, and introduce as a panel member Dr. Anthony Fotenos.

Dr. Fotenos is a nuclear medicine imager at Johns Hopkins. He has been a team leader in the Division of Imaging and Radiation Medicine where he leads a group of scientists and reviewers that are working on radiation medicine issue. He's also contributed importantly to imaging guidance in general.

So with that, I would like to address some questions that have been raised in applications to the FDA and questions that have been emailed to us. And so I would like to ask Dr. Saber first to respond.

And so the first question is an example that has occurred where a sponsor has conducted non-clinical studies to support a diagnostic imaging indication. They now decide to pursue a therapeutic anti-cancer indication, and will be replacing the radionuclide. Dr. Saber, what non-clinical studies are needed in support of the new indication?

DR. SABER: Hi. It is an interesting question. Again, if you have conducted already non-clinical studies in support of the imaging, then we do have a guidance that describes non-clinical studies for a therapeutic

radiopharmaceutical.

Do you need to redo all your non-clinical program? No, you just compare and to see what non-clinical studies have been conducted and what are the studies that are missing. And usually speaking, if you've done a toxicology study of the cold pharmaceutical for the imaging agent, then usually another study with a cold pharmaceutical for the therapeutic phase is not needed.

In terms of at the biodistribution study in the animals, then it depends on the radionuclide that was used for the imaging versus the radionuclide that will be used for the therapeutic phase, and whether there are theranostics or not. If there a theranostics, then the data generated with the imaging could be used.

And if there are not theranostic pairs, you may need to consider a biodistribution study complete, or like a bridging biodistribution study. And the details of it then will depend on the actual product.

DR. MARZELLA: Thank you. Another common question to Dr. Saber, which relates to

first-in-human studies of alpha particle emitters with targeted radiotherapy intent, what is the current thinking to conduct dosimetry studies prior to first-in-human studies?

DR. SABER: Thank you for that question. We do describe the recommendations for biodistribution dosimetry in the animals and the guidance, and you have the link to the guidance.

Briefly speaking, if you do want to take into consideration of the method that you want to use in rodents, it's often a sacrificial method and having a sufficient number of animals per time point. We do not want you to use too many animals. If the half-life is long for instance, the end of the curve could be estimated.

You do want to consider design that you're proposing your clinical protocol. If, for instance, you are proposing to use a protecting agent before administration of the radiopharmaceutical, you do want to consider that same combination in animal studies because that could change the biodistribution of the product.

And again, beyond what is already in the guidance, I don't have a particular recommendation because any recommendation we will

have it's dependent on the product itself.

DR. MARZELLA: Many thanks. And the final question regards the radionuclide impurity, particularly actinium-227 has been a concern, and it's been discussed this morning. Do you have additional perspectives to offer, Dr. Saber?

DR. SABER: I think Ravi very nicely answered that question, I just want to emphasize what he said. And we don't have a magic number for the amount of actinium-227 acceptable levels. What we know at the production, it might be a, you know, a very low amount, but at the time of use in patients, that amount can increase.

And what we do want to know is that it will be eliminated through the biological processes and it's very much dependent on the ligand. You might have a ligand that results in a retention of actinium-227, or not very stable. So it will distribute and goes to the bone, and then remains in the bone. And you might have another one that will result in more efficient elimination.

So the details of it would be really based on the actual percent, and the properties of the ligand, and the radiopharmaceuticals in

general. The lower, the better of course. Somebody said the lower the better, and I agree, the lower, the better because there is no benefit, it's just toxicity.

DR. MARZELLA: Great. Many thanks. The next two questions go to Dr. Plyku. So the first question, Dr. Plyku, is one that's also been touched upon this morning, and also presented in Dr. Saber's presentation. And this is a question regarding the ability to extrapolate either using lutetium-177 or radium-111 for use in the -- for, you know, calculating exposure in the actinium-225 studies.

DR. PLYKU: Yes, that is a good question, especially considering, you know, the challenges that exist to image actinium directly. You know, there is a low administer activity and not enough photon emissions. So indium-111 or lutetium-177 can be a good surrogate in that sense to be used to provide some target distribution for actinium-225.

But it also depends on the targeting molecule because if it is an antibody, it may be easier to do this for a small molecule. Swapping indium for -- or actinium for indium, it may be

easier to do this when it is labeled to an antibody. But if it is a small molecule, then maybe the chemistry is more complicated.

However, I want to mention that if we use indium or lutetium as a surrogate for actinium, then we need to remember that we are projecting doses only for the parent radionuclide, so actinium-225, and not the daughter. So we don't take into account the daughters in this method. And particularly, the concern is for bismuth-213 that may accumulate to the kidneys if it becomes unconjugated.

Also in addition, you know, actinium-225, there is work that has been done to image directly, and to develop methods to do that. It depends on, you know, how feasible those methods can be. And the comparisons between imaging it directly and these other methods will be available then. Louis, I think you're muted.

MS. LOPAS: You're on mute.

DR. MARZELLA: Thank you, Dr. Plyku, for that response. The next question reads please explain how to extrapolate the time-activity curve beyond the last measured time point to infinity.

DR. PLYKU: Yes, thank you for that

question. That shows the details of the calculation. So if we model the time-activity as a rate of function, then we can just interpolate the function to infinity. Or if we have used the hybrid method like trapezoidal and some other exponential decay, for example, then we can look at the last two measured time points, and use a measured biological clearance rate from a biological clearance rate from there.

If that is shorter than the physical decay, then we use that, or we just estimate that the activity is decaying physically beyond the last measured time point. And we can just integrate the function that way to get the time integrate activity. So, you know, these are in general what is done. So --

DR. MARZELLA: Thank you.

DR. PLYKU: So, in addition, Louis, I want to make a point of clarification on my slides, and this was brought up to us by Dr. Stabin present here. And I appreciate his presence and his comment on this, you know, on this workshop.

So he pointed out that the Olinda-EXM software package that is commonly used to perform dosimetry calculations does not use the MIRD

phantoms and the MIRD formalism, but the RADAR phantoms, dosimetry phantoms and the RADAR formalism. So I want to make that point of clarification, and I apologize for combining that in my slide to show the example of software used.

DR. MARZELLA: Appreciate that clarification. Thank you, Dr. Plyku. I would like to turn next to Dr. Chakrabarti and Dr. Fotenos for sort of a broad question that, again, has been sort of debated this morning. And the question broadly is how effective are organ dose estimates with alpha emitters as radionuclides? Dr. Chakrabarti?

DR. CHAKRABARTI: I think it's a great question, and we all know that we do need some determination, some estimate, so to speak, of radiation dose in the organs. For instance, we see that you need certain things to the blood, through the -- it goes through the other part of the body.

Now question is how good is the calculation when we are using alpha without proper in vivo imaging. I think the estimates come out to be fairly acceptable, and with time, I'm pretty sure that the alpha particle doses, organ doses

will improve. Even at this point, what do we have received for one approved radionuclide for alpha-emitters, the numbers are quite acceptable.

DR. FOTENOS: And I would just add I think we could combine this question with one received later which was -- to date with the exception of Bexxar which is no longer on the market, no RPTs have included dosimetry as part of their approvals, are there any incentives to perform these complex studies on the FDA side?

As it stands, it appears that treating these agents as little more than radioactive chemo has worked for the company that's developing them, why would they bother with this cost complexity which could be all cost and risk with little reward potential?

So, you know, that's sort of another version of how effective are organ dose estimates with alpha emitters, just different flavors of the same question I would think. And I think there's sort of a different way -- there's certain categories that it may be helpful to place these concepts in.

So in animals -- the dosimetry in animals which is what the regulatory, you know,

comes out of our code of federal regulations as regulatory requirements, and its primary objective is not primarily quantitative.

Its primary objective is identification and prioritization of critical organs so that -- both to help identify a low tolerated dose for dose escalation in first-in-human translation, and also to focus attention of the development pathway on potential safety signals as dose is escalated. Sort of tying into the concept Dr. Wahl raised that, you know, the patient is also the ultimate dosimeter.

The idea that Bexxar is the only therapy with dosimetry is, at least from FDA's perspective, a false premise because all labeled pharmaceuticals, if you go to the prescribing information, also available on drugs at FDA, you'll see that it's usually -- it's section 2, dosing administration and such, and there will be what we would consider cohort based dosimetry. And that comes from humans.

So the idea there is that the animal estimates are refined, and added to the human prescribing information, again, to help focus attention on -- and prioritization qualitatively

on critical organs. And that's, again, that's per code of federal regulations per requirement.

The question of potential future, I guess -- I think the question about Bexxar came from is that Bexxar is the only marketed product currently not marketed in which dosimetry at the patient level in practice in the post-market setting was used to inform the administered activity for each patient. And that is -- we would consider that, you know, individualized post-marketing -- individualized post-marketing dosing administration instructions.

And it's true that there are trade-offs in terms of feasibility, costs, complexity, but also obviously, potential benefits particularly as the accuracy and reliability of absorbed dose estimates, not just in normal tissue, but in tumor.

If those start to approach what people are used to in the external beam setting, that convergence of accuracy and reliability I think will help broaden sort of the clinical implementation of these therapies just because -- and certainly in the clinical setting, it's an extremely multi -- you know, radiation medicine is extremely multi-disciplinary involving

physicists, nuclear medicine physicians, radiation oncologists, oncologists, et cetera.

So having a common language of gray that means the same thing in different context is something to aspire to, but we may not be there yet. And so --

DR. MARZELLA: Sure. Anthony, if I may --

DR. FOTENOS: -- I think those context are important to help address the question of efficacy --

DR. MARZELLA: We are --

DR. FOTENOS: -- in real life --

DR. MARZELLA: -- unfortunately, running out of time. But I think we can -- we started an important conversation, so I'd like to invite other perspectives. And, you know, I wonder if Dr. Saber, you have comments to provide on this point?

DR. SABER: It was a different -- someone sent me a question. I was wondering if we are done with this particular topic. I can read that question and answer it.

DR. MARZELLA: I see. So the final comment I guess would be related to the question

of, you know, broadly -- and this is not something that I would like to be applicable just to this particular context of use. But it's a broad sort of legal question that FDA has with various products. So the regulations and the laws require that a product be safe and effective. They don't specify, you know, what the risk/benefit is. So that's a, you know, a very difficult calculation that is made.

So in the, you know, the question is if, you know, if the disease is dire and there's very few options and the product is safe and effective, does it need to be optimized? And the answer typically is no.

And so we would reserve, you know, post-marketing research and studies to determine whether, for instance, an optimization to either decrease risks or improve efficacy would be required. So just a general comment. Dr. Saber, please go ahead with the question that you wanted to answer.

DR. SABER: Yes. I'm going to paraphrase it. The question was on human dose selection when patients have previously received another line of radiation therapy such as, let's

say lutetium-177, prior to receiving actinium-225, how do you select a dose?

I want to say that our group and a non-clinical group looks at the non-clinical data to estimate and come up with a first-in-human dose for human dosimetry, and that is in consultation with our biophysicist.

And the first-in-human dose for dosimetry is usually is single dose administration, and it's a low dose. I doubt that that dose will cause any toxicity even if patients had previously received lutetium-177. But I don't want to talk for the clinicians.

So our role is the first-in-human dose. After that, there would be dose escalation and other doses would be looked at, and our clinicians and biophysicists will pay closer attention to the dose escalation. So I'll turn it over to Anthony and Donika to follow up on answering this question.

DR. FOTENOS: Sorry, can you clarify?

DR. SABER: Yes. So --

DR. FOTENOS: And there's some points in that chat box I also want to address, but --

DR. SABER: Yes. So the question is how do you select the dose in humans if these

patients have previously received a radiation therapy such as Lutetium-177? So patients previously received a radiopharmaceutical, let's say Lutathera, and now they're going into a study receiving actinium-225, will you consider toxicities from lutetium-177? How do you select a dose?

DR. FOTENOS: Yeah. So, again, at least to inform the early dose cohorts of an escalation scheme and for the chronic toxicities, the cumulative exposure sort of would be factored into the clinical specification of a safe starting dose. So I hope that addresses the question.

I also, with respect to prior framing discussion about the different sort of categories and ways to think about utility of dosimetry, it was pointed out that MIBG has a patient-specific imaging component. But I -- I apologize for lack of clarity, but the dosing still is weight based. It's sort of more a safety check.

So when it comes to individualized patient administration, Bexxar sort of remains the lone example of that -- sort of that ultimate example of personalized medicine as it were.

DR. MARZELLA: Right. So, you know,

we agree that it's an important area for further investigation, but that would not necessarily be required for initial approval. But we beg the forbearance of the group, we have -- we're going to go three more minutes.

And I'd like to end by asking Kish to clarify, you raised a question of one of the daughters of actinium, radon, and, you know, is that a concern in terms of what the absorbed dose would be in the lungs?

DR. CHAKRABARTI: Again, this is a very good question. This has been discussed inside, and this has been -- also I have seen the published paper where the question is there. But what the sponsor has provided, and indeed, the red one is in the lung and in the respiration system, but their calculation has so far shown that the limit is well within the ICRP 118.

In this context, I'll say one thing, that we should all talk, including this question what Mitch Anscher said that we have not have good information from radionuclides as opposed to external beam, that what happens in a matter of six months, one year, two year follow up.

The follow up is probably very

important, then other things will show up. That, yes, this is probably a one-time snapshot of during the trial that they provided us. And we look at it, it looks good. Most likely we hope that this is the way it will remain.

But as Mitch said, that the follow up is necessary to get to information of the accumulated dose in other part of the body whether the patient gets prior radiation, or the person gets another radiation somewhere for some reason.

DR. MARZELLA: Yeah, I agree that, you know, the question of long-term safety is an important question. And that may be something that multiple stakeholders would have to take on, not only commercial manufacturers, but also potentially, you know, public health and other agencies.

So at this point, I think that it's time to close the panel and I would like to thank the participants for the wonderful presentations. And the audience's participation. With that, I think we will go the break. And we will reconvene at 2:10. Does that sound reasonable?

MS. DIMMICK: Yes, that's correct. Thank you, Dr. Marzella, we'll resume at 2:10.

DR. MARZELLA: Thank you very much, all.

(Whereupon, the above-entitled matter went off the record at 2:00 p.m., and went back on the record at 2:10 p.m.)

MS. HAMMOND: Good afternoon, welcome back everyone. This is Session IV, User and Industry Perspectives. I am Michelle Hammond. I will be your moderator for this session. I am a Health Physicist in the Material Safety and Tribal Liaison Branch of the Office of Nuclear Material Safety and Safeguards at the NRC.

First up we will have Dr. Victor Paulus. He is currently the Senior Vice President of Regulatory Affairs at Fusion Pharmaceuticals. He has over 30 years' experience in the pharmaceutical industry including 20 years specializing in regulatory affairs.

Dr. Paulus' presentation is titled "Targeted Alpha Therapy Use of Actinium-225 Regulatory Interactions, Now and Tomorrow." Dr. Paulus the floor is yours.

DR. PAULUS: Thank you Michelle. Good afternoon, my name is Victor. I have been working in regulatory affairs for bit over 20 years. At some

point I may have learned a few things and maybe even a little about regulatory.

I'm an employee of Fusion Pharmaceuticals. The views expressed in this presentation are my own. If you disagree, it's okay, lots of people do.

Radioactive drugs are regulated by FDA to the same extent that FDA regulates other drugs with the exception of certain research uses of radioactive drugs. All radio pharmaceuticals are considered to be new drugs and subject to the applicable provisions of the FD&C Act.

Is this still valid? Is this question even relevant to this talk? The question is rhetorical. Of course this is a valid statement, but a recent court case may cause us in regulatory to alter some processes in the future. I will voice my personal opinion on this near the end of the presentation.

On July 28, RIND fusion was cleared by the FDA. But this was not one IND, there are two INDs. One for each part of the theranostic pair. The information presented in coming slides was used by us at fusion to hold the clearance, to help ensure clearance in a single review cycle.

This slide comes from decades' worth of FDA presentations, industry surveys and my own earlier

mistakes with vaccine INDs. These issues are common across all therapeutic areas and radio pharma is no different.

Frequently observed IND CMC deficiencies are incomplete information regarding the quality of the material used to manufacture the product. The manufacturing process development, for example, no process development runs, safety, quality and stability testing, cross-referenced information. It's actually quite easy to mess up the cross references. I've done it quite frequently. Manufacturing facilities. Descriptions that are inadequate. QA/QC issues and shipping problems.

A common problem, poorly organized submissions and that one is usually gathered with experience, it can be quite a challenge. A lack of alignment on the CMC development. Timeline in association with the clinical time line. No comparability plans when planning is sorely needed. The pharm/tox deficiencies, free clinical testing program is not comprehensive enough. Differences between the pre-clinical and clinical products. Inadequate pre-clinical study design, study conduct issues and safety concerns based on the toxicity profile.

Knowing and understanding the, sorry, knowing and understanding the expectations of regulators will reduce the number of deficiencies. Regulators expect completeness. Unfortunately, they don't buy the argument that a miracle happened. That you have a perfect product or that just trust approach to drug development. None of that works very well, yet people try. I've met them.

This first sub-bullet might be something all in the regulatory space really do want to focus on. Particularly the important impurities part. You have heard this morning and it's obvious the FDA loves to talk about impurities and so must we. We need to understand the critical quality attributes and the chemical, physical, biological and micro biological attributes. They can be defined, measured and monitored, should be.

To ensure final product outputs remain within the acceptable quality limits, we need to establish a standard for risk and control in clinical studies and robust analytics enable manufacturing changes both during development and post-approval. These are in my humble and personal opinion, current issues relevant and specific to radiopharmaceuticals.

The regulatory considerations. One

theranostic pair, two INDs that have a 70 percent overlap with simultaneous reviews conducted in parallel and two separate divisions in this case, my specific case, DOP and DIRM, there are multiple drug substance sections as shown very nicely during Dr. Kasliwal's presentation earlier this morning. These regulatory considerations require extra planning and coordination within the company, the development team and obviously the regulatory team.

CMC considerations. We all know our drug products due to their nature decay over time, making retrospective analysis of the drug product impossible. The only CMC guidance that exists is a PET guidance. They are exceptions for radio pharmaceuticals in the USP.

In non-clinical assessments there are certain cell-based nonclinical safety studies that may not be addressable or relevant as the therapeutic isotope may impact the test system. The justification of approach, including the use of cold equivalents, must be developed and provided. This is extremely important, but then everything we do should be justified and written somewhere because at some point, now or in the future, you will need to explain your product and your process and why the process is as it

is.

Specific quality expectations for radio pharmaceuticals. Batch data results must be provided for radionuclidic purity and submitted to the IND. You must demonstrate the manufacturing processes are capable of purging the actinium-225 decay products. The fate of radio-active decay products during shelf life of an actinium-225 containing product should also be included in the IND.

The really huge expectation, the question that a mere regulatory person cannot possibly answer, is are generator and accelerator produced of antinium-225 products of equivalent quality? Provide the data you have. If you don't think you have enough, neither will the agency.

Certificates of analysis for generator and accelerator-derived materials must also be provided. Some specific quality expectations also a continuation, details regarding the method used to determine radionuclidic impurities should be included in the IND. Details on the methods used to quantitate other alpha and beta emitting impurities that may be present in your antinium-225 containing product should also be detailed in the IND. A decay team graphic will help.

Regulatory agencies globally need to be prepared for new approaches in nuclear medicine and must be flexible in their regulatory approach. The FDA has said for decades that products are evaluated on a case-by-case basis. While this does apply to all products, I think it might apply to our products even more pointedly. Particularly with theranostic pairings.

Different nuclides can be used for diagnostic and therapeutic applications. Different investigational products require separate INDS even when there is only one clinical program. This is something that I personally need to accept as fact and work with.

Regulatory agencies need to work with sponsors to streamline theranostic development. The theranostic approach allows for targeted patient selection while increasing the likelihood of a strong therapeutic effect. The imaging agent of the theranostic pair a companion diagnostic, a diagnostic imaging agent or something else when co-developed.

This is not semantics, this last part is something I would really like to discuss with other regulatory professionals and with the FDA. And I'd also like that to be a question at some point before

this meeting ends.

As developers of radio pharmaceuticals we must be able to explain the very complex and simple weights or at least in small bites. We must also adapt to supply chain challenges. Import challenges and my personal favorite, dealing with customs officials.

Then we come to the known impurities. The co-production of actinium-227 is a known or specified impurity. We all know that the supply of generator-produced actinium is at capacity and that additional generator supplies won't be available in near term to support all of the planned clinical studies. Accelerator-produced actinium must be used until additional technologies become available. Yet this new material contains the long-lived impurity. Process qualification information must be generated and provided to regulators. The radionuclidic impurity limit just be produced as a specification and justified. Again, justification for the use of material containing this impurity must be provided in the IND.

Other points of concern are NRC and RAM licensing and waste disposal. And those are meant to be specific to the actinium-227.

The heading for this slide is Tomorrow,

but tomorrow really is in fact today. A demonstration of comparability, interchangeability of generator and accelerator-produced actinium-225 should be expected and should be attempted. Technological improvements, will they come and when? I've heard said this is just a simple purification issue. Yes, I've heard a lot of people laugh when that gets said.

A waste disposal with clinical sites and also once approved is a consideration as mentioned previously. The global acceptability of actinium-227 is a question that I have and hope to find an answer to soon. We have -- I understand the FDA's position, but I have yet to explore the rest of the world or EU.

Multiple INDs for a single theranostic pair. Two seems like the standard number but that too is product and concept dependent. Managing the expectations of one or more than one review team has the potential to be a challenge with communicating similar or identical information to more than one division. Coordination of information requests across review divisions will undoubtedly be a drain on regulatory staff and the entire project team. Actually and practice, it is draining.

If I could talk for another hour I could tell some painful stories of the public perception of

radio pharmaceutical manufacture in our neighborhoods. Product approvals help perception but not much. Active industry outreach may be better. People know Chernobyl, but they don't know the Xofigo or Lutathera.

Establishment of clinical medical disciplines that focus solely on radio pharmaceutical therapies, like expanded nuclear medicine departments and becoming independent revenue generators, would be great for the industry as a whole.

Partnering with regulators to develop combination therapies which capitalize on patient dosimetry, imaging and therapy. This is something that I love conceptually, but in practice a lot of coordination and energy is required.

It's a logical advancement of actiunium-225 production is absolutely needed. Increased interactions between suppliers, FDA, NRC, and radio pharmaceutical companies will help.

Going way back to the beginning of my and my rhetorical question, there is no question that the FDA will continue to regulate imaging agents, but some of us, me specifically, have a limited skill set and my skill set has never included CERH. So if the changes precipitated by this court case require me to learn device regulations, I guess that's a new opportunity

for me. Theranostic pairings are complicated and they will never be simple.

My duty as person who communicates with regulators regularly is to number one, stay on their good side. To try as best as possible to partner with the regulators. Know the expectations and try to fulfill them. Meet with regulators, take full advantage of every meeting available.

Know the formal meeting guidance, address every concern by the regulator before you submit an application. Do not submit an application before it's ready. Beware the desire for speed. This one often is particularly difficult especially with four quarter submissions. I tried to tell my team if you can avoid a December submission, by all means do it.

I don't like presenting slides at FDA meetings. The discussion should be focused on the briefing document and FDA's preliminary comments. It worked well for me for years. Until I met with a Division of Imaging. During a meeting I was told we really like pictures, so here is a picture.

There once was a man who hated doctors. When he finally did see a doctor it was too late. He was a veterinarian, a scientist, teacher, a logical thinker, but as he said prostate cancer is a

slow-growing thing, something else will kill me long before it does. He was wrong.

Tap in your products, your technologies. Be an advocate and educate. Thank you and thanks for my colleges at Fusion for always providing the details. And if you look closely, you will see that in that change plan a miracle occurs. So thank you for your time. I apologize for talking very fast, but that is sometimes what I do. Thank you.

MS. HAMMOND: Thank you Dr. Paulus. You actually had about four minutes left on that. But hopefully we can utilize that at the end of the session during the Q&A to address some of the questions. So thank you.

Next up we will have Dr. Mark Berger. He is currently the Chief Medical Officer at Actinium Pharmaceuticals Incorporated. Dr. Berger has 25 years of experience in oncology drug development in the pharmaceutical and biotech industries. With agents ranging from small molecules to antibody radio-conjugants. Dr. Berger's presentation is titled "Industry Experience and the Development and Clinical Testing of Antinium-225-Based Radio-Conjugates." Dr. Berger, the floor is yours.

DR. BERGER: Thank you Michelle. Let's

see if I can show my slides, I believe I can. Tell me how I am doing now, is that --

MS. HAMMOND: Yes, you're good if you want to put it in the, yes, there you go. Thank you.

DR. BERGER: There we go. Thank you very much. Good afternoon, I'm Dr. Mark Berger, Chief Medical Officer at Actinium Pharmaceuticals. My presentation will be on the clinical development of actinium-225-based radio-conjugates. There are a number of characteristics, some of which have been discussed today already of actinium-225-based ARCs, or antibody radio-conjugates. Making them particularly amenable through clinical development by industry.

First alpha particles generated by actinium-225 have a high end, they lead a double strand breaks and they cause cell death. In addition, because the path of alpha particles is short, about the length of 4 of 5 cells or so, you can hit what you aim at and not much else. Which is a safety event.

In comparison, the path link of beta particles is much longer, approximately 100 cell lengths. Shorter broader range of cells are targeted with therapies that emit beta particles.

Importantly the ten-day half-life leaves

adequate time for manufacturing and distribution. And alpha particles are easily blocked such as by a piece of paper, by a patient's skin, with simplifying the administration and minimizing restrictions of locations after receiving these drugs.

We'll use the term Actimab-A to refer to the anti-CD33 antibody lintuzumab labeled with actinium-225. We'll use the development of Actimab-A as an example of the clinical development of actinium-225 based ARCs since Actimab-A was the first actinium-225 labeled agent in clinical trials. It has the largest clinical experience.

Using the Actimab-A term will help distinguish actinuim-225 level lintuzumab from earn earlier version labeled as bismuth-213, which we will also talk about.

We've termed the AWE platform, Antibody Warhead Enabling Technology, using Actimab-A is a powerful way to molecularly target radiation to within cells. This is a flexible technology which can accommodate many different isotopes and many different targets.

Critical to the industry development of any drug, including ours, is having a robust intellectual property portfolio so that a wide range

of possible development pathways accompany it. Without which drugs can't be developed.

Anti-CD33, which an excellent target for the treatment of acute myeloid leukemia. The question on the malignant cells of 90 percent of AML patients also expressed in myeloid cells which are infection fighting white blood cells and its expressed myeloid and platelet cell precursors leading to the CD33 class effect of myelosuppression that these drugs are given. CD33 is a validated target as Mylotarg and anti-CD33 antibody drug conjugate is FDA approved for the treatment of AML.

One major difference in Mylotarg as antibody drug conjugate Mylotarg requires internalization into the cell to be activated whereas Actimab-A and other ARCs don't need to be internalized to be effective. In the case of CD33 though on the antibody binding the CD33 antibody could be brought into the cell and is internalized in this particular case.

Drug development is a step-wide process. We will illustrate this with a clinical trials that have been performed with the anti-CD33 antibody lintuzumab. Since occasional responses received early studies with a naked antibody lintuzumab, the first question evaluated by clinical trials was whether

lintuzumab would add to the activity of other AML treatments. Two phase 3 clinical trials again showed no survival advantage when lintuzumab was added to a low dose cytarabine treatment for older patients or to accommodation chemotherapy regimen called MEC in younger patients.

Development then switched to using lintuzumab as a targeting agent for AML cells. Lintuzumab was labeled with the alpha bismuth-213, which has only a 46 minute half-life. Although these trials were difficult to carry out, they provided proof of concept as most patients had decreases in AML blast cells in the bone marrow as shown here.

Accommodation with a standard dose cytarabine treatment, lintuzumab labeled with bismuth-213 had consistent decreased in bone marrow AML blasts but few results that reached the level of responses. That limited efficacy on the short half-life of bismuth-213 leads it not being an attractive agent for initial development.

However, those trials lead to the idea of labeling lintuzumab with actinium-225. Since actinium-225 provides 4 alpha particles instead of the 1 from bismuth-213, and since the actinium 225 half-life of ten days is much longer than the 45 minute

half-life of bismuth-213.

Single agent, single dose trial with Actimab-A in patients with relapsed, refractory myeloid leukemia documented bone marrow blast increases in a majority of patients. Dose limiting toxicity was myelosuppression and this was a, seemed to be a good start and some promising results.

This was followed by a Phase 1 trial providing Actimab-A with low dose AMC and it uses of a fractionated dose of Actimab-A and one on day one, and the same dose again on day 8. Although the toxicity level was not reached the phase 2 dose of two uCi/kg/faction was chosen to limit prolonged myelosuppression.

Phase 1 trial combining Actimab with low dose Ara-C had an overall response of 28 percent. Responses were dose-related with none of the lowest dose of 0.5 uCi/kg/fraction and 4 out of the 5 responses at the two highest dose levels.

This lead to a phase 2 trial. This is performed in older patients with previously untreated acute myeloid leukemia. Using a fractionated schedule of Actimab-A at the 2 uCi/kg/fraction dose identified in the phase 1 trial. Myelosuppression was not used in this trial.

This study had a high overall response with 69 percent, which was excellent but also had grade 4 myelosuppression for more than 6 weeks in approximately 40 percent of patients. This was considered too high a rate of prolonged myelosuppression and the dose was lowered by 25% to 1.5 micro/kg/fraction. At this lower dose the overall response rate fell to 22 percent but the rate of prolonged myelosuppression was still significant.

I summarized what was learned from a single agent after the trials. It made several advantages over labeling lintuzumab-bisuth-213 and a half-life of ten days, adequate times for manufacture and distribution, as well as certainly more potent than lintuzumab and labeled with bismuth-213 is demonstrated by the increased number of patients with responses and by the dose load. Importantly there were no significant non-hematopoietic adverse events. So the targeting in the agent was excellent.

VOD over-deliver was not seen unlike the antibody drug conjugate Mylotarg which is associated with VOD. Actimab-A was determined to be a potent anti-leukemic drug and the side effects of myelosuppression was clearly dose-related.

These two data and given the further development

of Actimab-A was concluded that there were two ways you could use this drug. One was a high dose and the other is a low dose approach.

First it could be used as a single agent, not in high dose in situation where myelosuppression wouldn't matter. Such as just prior to a bone marrow transplant.

Second, it could be used in lower does in combination with other anti-leukemic drugs it increased the myelosuppression side effects and we'll give two examples of this approach as well.

So high dose approach you draw up plans to study myelodysplastic syndrome. CD33 is expressed in the myelodysplastic syndrome cells in the vast majority of myelodysplastic syndrome patients. And they all need curative therapy for myelodysplastic syndrome is a bone marrow transplant. Actimab-A in high doses used prior to bone marrow transplant will be used to destroy myelodysplastic syndrome cells and myelosuppression would be limited by the drafting of the bone marrow transplants.

Using the low dose approach, the team is conducting a phase 1 study combining an Actimab-A with the salvage chemotherapy regimen called CLAG-M. It is used in younger patients with relapsed refractive

acute myeloid leukemia, it adds one dose of targeted radiation in Actimab-A to the CLAG-M chemotherapy regimen.

The ongoing CLAG-M Actimab-A trial showed a dose-related increase in response rates. This 0.75 uCi/kg dose had 100 percent response rate at CR and which is called CRIs. This compare is quite favorably with the 54 percent CR and CRI rate in the previous series of patients treated with CLAG-M alone at Medical College of Wisconsin which is the site where the study is being done.

And very importantly, 7 out of 10 of these CRs have been MRD-negative, that is measurable residual disease negative, of CRs which indicated they are very deep remissions. The phase 1 trial is continuing and has escalated to the next dose.

A second phase 1 study with a low dose approach actinium is combined Actimab-A with venetoclax, which a commonly used drug in older patients with AML. There is strong preclinical data behind this combination. Venetoclax is an inhibitor of the MCL-1 family of pro survival of proteins but doesn't' inhibit a member of the family MCL-1. High levels of MCL-1 are common cause of venetoclax resistance. In venetoclax resistance AML cell lines the additional of Actimab-A

a to the venetoclax treatment will restore sensitivity to the xenograft. The combination of Actimab-A and venetoclax increased survival of xenograft models as well and was mediated by decreases in MCL-1.

Holding on those three clinical data, each one combining the venetoclax and Actimab-A is ongoing. First dose cohort 0.5 uCi/kg are those that had no responses in the single agent Actimab---A trial had one partial response and one CRI in three patients. Additional doses are being evaluated.

The Actimab, the actinium program is also being utilized in collaboration with Astellas against solid tumor drugs. Targeted radiation has a significant potential advantage in solid tumors over external beam radiation. In that target radiation can treat both the primary tumor and the metastases, both known and unknown. The external beam radiation by contrast is limited to the area in which the radiation is being targeted.

In summary, actinium-225 has a number of characteristics that make it a desirable therapy for development by industry. Ample using Actimab-A industry development was facilitated by previous studies using the naked antibody as well by proof of concept studies for alpha particle therapy using

bismuth-213.

Actimab-A was an early actinium-225 labeled therapy and as a result has, at this point, the largest clinical experiments. Of course Actimab-A is involved in a number of studies, but now involved to focus in the combination with other ML therapies.

Actinium Pharmaceuticals is now expanding the AWE platform in the solid tumor space in our collaboration with Astellas and is (audio interference) to add other targeting agents to its portfolio.

Thank you.

MS. HAMMOND: Thank you Dr. Berger. Now we will have Dr. Neeta Pandit-Taskar. She is a Nuclear Medicine Faculty at Memorial Sloan Kettering Cancer Center with extensive experience in diagnostic and therapeutic nuclear medicine. She is particularly interested in molecular imaging and development of novel techniques in diagnosis and treatment of cancer, with special focus on novel targets including radioimmunotargeted imaging and therapy as well as alpha and beta radio isotopes

in theranostics.

Dr. Pandit-Taskar's presentation is titled "Clinical Utilization of Actinium-225 Alpha for

Target Therapies, Potential and Challenges." Dr. Pandit-Taskar, the floor is yours.

DR. PANDIT-TASKER: Thank you. My topic is utilization of actinium-225 for targeted alpha nucleic activity, potential and challenges. So I'll be mainly focusing in the clinical aspect and a lot of the, sorry I'm trying to see how I can, okay. So mainly focusing on the clinical studies and where the field is moving and especially for saying on whereas come to the clinical studies and publications over the last year, especially in the last few years how things have moved.

So this is an overview of my talk here. So just doing a quick compartment search, one can see that the publications on literature related to the targeted alpha therapies has increased quite a bit, almost twofold over the last decade and especially the momentum has gained over the last 5 years and especially since we are talking about actinum-225 you can see that over the last 5 years there has been significant multifold increase in the literature that is related to actinium-225 and there are other alpha therapies or alpha isotopes can see that relatively the actinium-225 related work that has been published is several folds higher.

So this has been alpha, this has been discussed in the prior talks also but as pertinent to the clinical studies essentially the fact that the alpha higher NET and lower range in the tissue the majority of the clinical studies have focused on applying the alpha meters and actinium-225 in clinical setting where prior treatments like standard of care or even mutation or beta immunotherapies have produced no responses if the disease is refractory and also in certain scenarios which are discussed essentially the part that you could have better cell kill and limit toxicity especially when widespread disease is present.

So there are a number of other alphas and as discussed in prior talks actinium-225 we have good creation and that is, of course, the daughter decay that is of concern, especially transition from location to other tissues and in this case, kidneys, urine, liver or bone, may be other targets where the doctors have seen but many of the clinical studies have shown that these toxicities can be fairly limited.

So the current clinical scope includes four clinical studies that have been published that includes mainly the ligands and small molecules and as well as some of the clinical trials that are ongoing

with antibody targets. The majority of the work that is so far published comes from outside of U.S., mainly from Europe, Australia and Asia that has looked at actinium-225 labeled PSMA targeting prostate cancer as well as actinium DOTATATE or the PRRT in uterine endocrine tumors.

So the antibody targets are under phase 1 or higher studies including those targeting prostate cancer, multiple solid tumors or hematologic malignancies.

So as mentioned, the alpha therapies are of interest because there are, they maybe resistance or lack of response in patients who have received prior treatments. So focusing on the drug ligand therapy, the PSA or the PRRT, we know that a number of patients that do not have responses are following treatment with lutetium-177 targeted ligan or PRD there may be lack of response or progression at the later stages so in order to provoke responses in these patients use of alpha has been investigated.

So the other strategies that include not only just the patients who have progression or lack of response but the beta therapy, but also combination therapies or tandem therapies utilization in chemotherapy therapy.

There is ten patients and patients with poor prognosis so I'll just go through some of the clinical studies that have come through and some of the upcoming studies include strategies such as utilization of old alpha and beta parameters, combination of small molecules and antibodies with combination with chemo and immunotherapy and possible radiation therapy.

So following the approval of the lutetium DOTATATE following the medical trial, there is extensive use of lutetium DOTATATE uterine endocrine tumors. We know that the majority of patients who have stable disease, and of course, there is eventual progression in a sub-group of patients who have shown responses to lutetium DOTATATE. So initially this group from the Heidelberg investigated bismuth DOTATOC and given good results they have further evaluated patients using the actinium-225 DOTATOC. And in this example and the study as published earlier this year, they have provided a 5-year follow-up.

As you can see that patients who were progressing with the standard case received actinium DOTATOC in variable dose starting off 50 megabecquerel and then the 20 megabecquerel maintenance dose and the patient had partial response and stabilization of

disease for almost 6 years following which there was subsequent progression of disease so you could have slowed responses, or long-term responses with actinium DOTATOC.

They looked at the dosimetry and those dependent on hematologic toxicity was noted at single doses but could be avoided for, hematologic toxicity could be avoided with the cumulative doses were within 60 to 80 to megabecquerel. One is obviously concern about the nephrotoxicity of the PRRD and they found that the average GFR decrease was 8.4 ml per year but the annual decrease was 8.4 ml and the incidence was 9.9 percent, which was similar to what has been seen with the beta therapies.

In another study, this is from Asia, the actinium DOTATATE was given in doses of 100 kilo Becquerel in two cycles with interim assessment and if there was disease progression, then further dosing was stopped. However, if there were responses, additional cycles of actinium DOTATATE were given and in 32 patients responses were evaluated using this criteria and also by chemical responses and levels. And as you can see that 24 out of 32 patients had partial remission and the others had civilization of disease.

Again, we see that there is radiation in the amount of dosing that treatment doses that have been or activities that have been used for dosing. What is notable that this patient population that they valued included quite a few patients who had higher tumor proliferation and that's and also there were many patients who had high tumor burden involving skeletal disease as well as liver disease.

So basically it points to that fact that patients were not just refractory, but who have larger tumor burden may be able to obtain response by using the actinium-225 DOTATATE.

A long-term follow-up in patients, this abstract was presented in SNMMI this year and Dr. Wahl also referred to this study. This is again from Asia, what is important to note here is is again, the variable doses that have been given and up to 9 cycles were administered in patients. Of the total 80 patients 32 patients did not receive prior PRRT with lutetium DOTATATE. So basically again there is a bit of a shift in the strategy where actinium DOTATATE can be applied or use in treatment of further up of before the beta therapy.

And then you can see that the 24-month progression of survival and also survival are high in

these patients and of note is that only 2 patients experienced anemia and two patients experienced two thrombocytopenia and there are no hepatic toxicities.

Regarding the application in prostate cancer, the VISION trial is, the results are related to the approval to the FDA so we do expect a lot of treatments with the actinium therapy happening especially in the U.S. however, we note that it may be subgroup of patients who do not have responses, and based on the European experience this could be almost 30-40 percent of the patients.

So we are hired a group focused on utilizing the actiunon-225 PSA in these patients with two strategies. One is those who did not respond to the lutetium PSMA and then others who were treated prior to lutetium PSMA treatment.

So an example here you can see that there is extensive disease. This patient actually had peritoneal disease, was treated with two cycles of lutetium-177, however, it had progressional disease and was subsequently treated with two doses of actinium PSA with significant response and further consolidation with other treatment dose, led to near normalization of the PSA levels.

In this patient the micro-metastatic

disease and as far as alpha is concerned, in the peritoneal may be able to produce higher responses as compared to the beta radiation.

Another patient example where this patient actually was not treated with lutetium-177 previously, again that the idea that the extensive disease in the marrow because of the low LET of alpha maybe more suitable because it produced less hematologic toxicity. This patient was treated with 3 doses of actinium-225 and you can see that there is extensive response in this patient. Further treatment of actinium dose will decrease the PSA levels to near normal.

Subsequently, a dose-finding study was conducted where the dose was escalated from 50 kilobecquerel to 200 kilobecquerel. The dosimetry was projected from the lutetium-177 PSMA dosing and the doses essentially included entire, at higher levels in this patient for example, treated with 100 and 200 kilobecquerel per kg extensive disease and chose normalization and here you can see large lesion in the liver shows significant decrease in size.

What is to be noted is that the while the salivary gland exposure radiation was slightly higher than the lutetium PSMA doses, the kidney and marrow

doses were similar.

The meta-analysis just summarized the results from ten studies, many of these have been published this year or last year. So again, showing increase in the interest over the last two years and use of actiunn-225 PSMA, what is noted in this 256 patients and ten studies is again, there is variation in the doses that have been given and then the cycles that have been given. Most studies did use 100 kilobecquerel kg dose but the doses were spread over 1 to 8 cycles given at intervals of 8 to 16 weeks.

Significant PSA responses have been noted. Most of the studies have noted more than 50 percent, some close to 90 percent. Many of the patients showing increased progression free survival and overall survival and another strategy that has been applied is the stratification, stratification of the patients has also been discussed before.

The Fact that lutetium has a beta emissions whereas the actinium-225 has alpha emissions, whether the patients that have extensive disease in the bone should be actually treated with the alpha emission. So this group actually followed ischemia for stratification and treatment selection in these patients where those with more soft tissue disease and

less bone marrow disease were treated with lutetium-177 as a dose, those others who had extensive disease being treated with the actinium doses.

So again, the dose that has been used was 100 kilobecquerel per kg given every 2 months and 31 patients were treated. And as you can see in this example, excellent response was seen in the bone disease, 62 percent of patients had more than 50 percent PSA decline and the median duration of tumor control was 9 months.

Another strategy in this study comes basically, a used actinium-PSMA-617 treatment in patients with chemotherapy naïve. So again, shifting the paradigm to earlier implementation in the clinical presentation in patients. And out of the 17 patients you can see 11 had complete resolution of disease.

They used actually variable doses again and the dose de-escalation ischemia was used starting from 8 megabecquerel doses and the de-escalation was essentially based upon the response and tolerance defined by the toxicities. So again, radiation, in how you administer in terms of how much activity and what dosing you give based on the disease extent in these patients.

In these two examples, you can see

extensive bone disease patient was treated before 3 cycles with significant response and here the dose de-escalation as you can see significant response in this patient.

Another strategy that has been applied is combination of actinium-225, lutetiium-177 PSMA ligan and, in this example, you can see that again, extensive disease in the liver and bone marrow and the combination treatment given up front caused decrease in the burden of the disease in this patient.

These patients were, all these patients were naive as far as the lutetium PSMA dosing was concerned. But you can see, again, many of these patients had extensive disease and had been heavily pre-treated. And those who showed responses actually had better survival as compared to those who did not.

And just to mention that again this year, there has been some literature, the actinium-PSMA-I&T, the responses and treatment paradigms have been pretty much similar. Again, those who had prior lutetium therapy being treated with again actinium-225 PSMA ensuring responses.

So beyond the clinical studies and data that is in using the ligan therapy much of the actinium-225 usage in radio immunotherapy has been

through the ongoing trials.

Over the last year a number of new trials have been initiated. These include application as to solid tumors and hematologic malignancies.

A quick surge of the clinical trial start side you can see that a number of trials have been ongoing or are being initiated. Of these, the surge performed using the key word actinium-225 showed this list which actually included two studies with the ligans, but the majority of the others are using the radio immuno-targeted therapies.

An example is the phase 1 trial of actinium-225 label J591, which an antibody that targets GSMA. Earlier experience with lutetium J591 is published by this group is being performed at Cornell New York and they have phase 1 studies ongoing that is looking at those escalation.

Again, here you can see that the escalation phases to various levels and 42 patients are going to be studied in this. The concept is being extended to other trials and combination therapies for example, another trial that is proposed utilizes a combination of actinium-225, J591 with lutetium-177.

Again, basically both these drugs will bind and then your combining the readout with the alpha,

looking at the combined effect of long as sharps LEG vs the high, high vs. the lower LEG agents.

Another target is the, against prostate, is the HK2 that is, there is a trial that is going on that utilizes labeled antibody humanized 11 -- H11B6 his actually is a target it is trypsin-like antigen that is used by the columnar cross cells and is AR driven.

Pre-clinical study done at our institution showed good targeting and then responses to tumor shrinkage in pre-clinical models.

And this is a phase 1 study that is ongoing that is using dose escalation sponsored by Janssen.

We had an earlier talk about Fusion Pharma, so they have antibody which is actinium labeled FPI1431 that targets IGF-1R. This a highly attractive target that is presented in multiple solid tumors and that is a phase 1 study that is ongoing that incorporates dosimetry estimation using indium-111 emission, modified 3+3 design using dose escalation at previous doses as designated here, started ten kilobecquerel per kg extending to 120 kilobecquerel per kg and doses will be defined by normal or dosimetry in these patients.

Another attractive --

MS. HAMMOND: I'm sorry, Ms. Pandit-Taskar, you have just a few more minutes. Thank you.

DR. PANDIT-TASKAR: Yes. Another attractive target is the actinium lintuzumab. This target is 32 which is expressed virtually in all patients with AML and it's expressed regardless of the site identity mutations. And dose escalations 30 and phase 2 doses actually showed excellent responses of 69 patients and blast change in majority of the patients, 125 patients have been studied so far. And given these excellent and encouraging results, further trials and combination therapies are being planned as was overviewed by the prior speaker.

And just to mention that a number of pre-clinical studies are ongoing that are looking at novel targets. So we can expect moving forward that there may be more coming through. There are number of challenges which I will not discuss in detail, but these have already been addressed in prior talks. These are related to the fact that dosimetry is important and how much can be done given the limitation of managing actinium itself so surrogates are needed. For example, indium-111 is being used as a surrogate in two trials that I mentioned previously. And imaging

has been performed by some of the prior investigators. There is radiation in the treatment doses that are given and currently most are using empiric doses in the clinical studies that have been published from Europe.

This is again highly debatable, one I believe would want dosimetry but again, the practical aspects of demanding dosimetric-based treatment ischemia has its own challenges.

The advantage of actinium-225 are that alpha is essentially that it's the ease of use, radiation exposure doses are low. The half-life allows for transporting. The major limitation currently is the supply which Cathy Cutler has already discussed in her talk.

But what we need to, either in clinical setting for treating patients or for actually doing clinical trials, is more consistent and uninterrupted supply with flexibility of base and availability of the agents to be given to the patients. And decrease in lead time for ordering.

So to conclude, I think there is a huge potential for using actinium-225 both for use of small molecules or antibodies as we are seeing that they are increasing clinical applications and the variety of

our spectrum of the clinical setting in which it is being used is broadening and they are practical ease of use, we must overcome the supply issue and other issues in actually administering these does. With that I will end this talk. Thank you.

MS. HAMMOND: Thank you so much Dr. Pandit-Taskar for that extremely interesting presentation. So last, but certainly not least, we have Ms. Megan Shober. Ms. Shober is an Advanced Nuclear Safety Specialist with the Wisconsin Department of Health Services. She has over 18 years' experience as a license reviewer and inspector and has been the state representative on NRCs Advisory Committee on the medical use of isotopes since 2018.

Ms. Shober has been actively involved in developing radiation safety controls for actinium-225 and currently oversees 9 licensees using or pursuing actinium-225 for research or medical use. Her presentation is entitled "Radiation Safety Considerations for Novel Radionuclide Therapies." Megan the floor is yours. Thank you.

MS. SHOBER: Okay. Thank you. Let's get the slides sharing here. Okay can someone let me know if they see the slide show?

MS. HAMMOND: Yes, you are good to go.

Thanks Megan.

MS. SHOBER: Okay wonderful. My name is Megan Shober and I've been working the Wisconsin Radioactive State Program for quite a while. To finish off today's presentation, I am going to spend some time focusing on radiation safety and regulatory considerations for actinium therapeutics. This is going to be a pretty different flavor from a lot of the other talks that we have heard today.

Over the past few years we have had a steadily increasing number of licensees approach us with radiation safety questions related to the use of actinium-225. From most of the time that I have been working for the Wisconsin Radioactive Materials Program, the use of alpha and beta emitters has been very rare. Mostly restricted to academic research labs and then trickling into hospitals following the FDA approval of radium-223 dichloride. But since 2015, we have been growing licensee interest in actinium-225.

So the use of actinium-225 are really any alpha emitter presents regulatory challenges. Although alpha emitters have favorable characteristics for limiting external exposure, there is significant dose consequences associated with accidental internal

update by radiation markers.

So in general terms, we want to know that licensees can detect and measure actinium-225 with available equipment and decontaminate surfaces as necessary. I will review some of the available guidance and share some lessons learned about how we have applied this information to licensed users.

We have also heard previous speakers talk about the demand for actinium-225 and we expect production of actinium-225 to increase in the coming years. At this point, all or virtually all of the actinium-225 in the United States is produced by the Department of Energy through the Tri-Lab Project.

However, the next ten years we expect some of that production to be supplemented by triage sector efforts. My office is preparing for actinium-225 production in Wisconsin. My colleagues and I are talking about these issues almost every week. So at the end of this presentation, I will highlight a few of the additional radiation safety challenges associated with actinium-225 production.

So in Wisconsin, we began seeing requests to use actinium on, around 2015. We have a handful of licensees authorized to possess actinium-225 and at least five licensees have received and used it mostly

in research and development applications.

We had one site participate in a clinical trial with a local radio pharmacy supporting that effort. The activity in parenthesis on these slides show what licensees are able to receive, so that's a maximum possession limit, but typical quantities used to date have been more on the order of 100 microcuries.

So how does a licensee receive authorization to use actinium-225? So medical use licensees have a general authorization to use unsealed material requiring a written directive. A written directive is basically a prescription and actinium-225, because it's therapeutic, would require a physician who is approved on a radioactive materials license as an authorized user to prescribe a dosage to a patient.

The use of actinium-225 radio pharmaceuticals would be in the same regulatory category as iodine 131 or the lutetium-177. In these cases, regulators may not be aware once they begin using actinium-225 as licenses allow the flexibility to acquire novel radio pharmaceuticals without license amendment.

However, broad scope licensees, which are typically large academic hospitals and pharmacy

licensees, may need to amend their license to allow possession of actinium-225. This is because typical broad scope and pharmacy licenses authorize possession of radioactive materials with atomic numbers 3 through 83 and actinium is outside that range at atomic number 89.

I also want to note that in radioactive materials licenses, typically do not identify impurities or daughter products on the licensed document itself.

So as we have heard several times today, impurities can present as many or greater regulatory challenges than the product itself. Of course for actinium-225, the impurity of concern is actinium-227. Radioactive materials licensees who possess significant quantities of unsealed radioactive materials with a half-life exceeding 120 days, must provide financial assurance for decommissioning.

The vast majority of medical use licensees do not possess radioactive material requiring financial assurance. However, financial assurance is required for actinium-227 in quantities exceed 10 microcuries. In the past several months, I have had conversations with two licensees on this very subject. So one licensee significantly lowered its requested

possession limit of actinium-227 and a second licensee is delaying acquisition of material that may contain actinium-227, while they work out their financial assurance considerations. So the potential for licensees accumulating actinium-227 is a big concern for us.

So as a regulator what do we do? Do we limit licensees to actinium-225 from only certain production methods? So do we limit them to only generated sources of actinium-225 or do we require financial assurance for all licensees that are authorized for actinium-225? I don't have answer for you, but we don't want to end up in a situation where a licensee is accumulating more than 10 microcuries of actinium-227.

So, back in 2015 when we were first approached about actinium-225, we came up with a list of radiation safety concerns as shown here. Ultimately all of our regulatory infrastructure is set up to limit the potential for radiation doses to individuals or releases to the environment.

So how do we do that? One way that relative risk of radio isotopes is captured in regulatory space is by the term annual limit on intake. So this is an amount of radioactive material, which

if taken into the body leads to certain dose thresholds and those values are listed in 10 CFR 20 Appendix B. So the annual limit on intake is also used in other ways. For example, to determine reporting thresholds for spills.

So as you will notice in this table, the annual limit on take for actinium-225 is very low. And the limit for actinium-227 is 3 orders of magnitude less than that.

So how do I incorporate concerns about relative risk as practical specific license requirements that address the issues on the left?

So as in many areas first I review available nuclear regulatory commission guidance. I survey the best of what Google has to offer. I talk with the applicant. What equipment do you have? What are you willing to commit to? If we come to a mutual agreeable decision on risk management.

So the Nuclear Regulatory Commission publishes licensing guidance documents in its NUREG 1556 series. And these documents contain a variety of model radiation safety procedures which licensees can commit to follow. The three documents that are relevant there are NUREG 1556, Volume 13, which is for radio pharmacies. NUREG 1156, Volume 7 which is for

research and development. And NUREG 1556, Volume 9 which is for medical users.

I was specifically interested in contamination action levels. So if someone is surveying for contamination, at what level do they need to take remedial action? The radio-pharmacy and R&D NUREG share the same table. But the table has no action level for actinium-225 and it has an action level of 20 disintegrations per minute for actinium-227.

The medical NUREG contains values for both actinium-225 and actinium-227, but as you see, they are different from the values in the radio-pharmacy and R&D documents. So we use that guidance as our starting point and then ultimately have to say is this what we want to propose to our licensees?

So I also read material from several of the university radiation safety programs across the country and most were variations on the themes presented here. So engineering controls -- how to detect contamination. What instruments to use?

I also spoke with our applicant. They identified some challenges with detecting actinium-225. The sensitivity that we are asking for using the standard equipment that they had in their facility.

And so ultimately as a regulator, we have to decide how to license this and so what we have been coming up with, what we have come up with, is a series of decisions here.

So to address concerns about contamination, we've been requiring our licensees to perform day of use wipe surveys and the purpose of that is to limit spread of continuation if any was found. In terms of chemical separation, the medical and the pharmacy licensees are limited in what they can do with actinium-225 and they are restricted to unit dose distribution.

We did not require bio assays. We did require engineering controls. We used an action level of 200 disintegrations per minute for medical and pharmacy users. Those sites that would have well counters and we required action levels of 20 bpm for users that would have liquid scintillation counters.

We have concerns about skin over exposure and those also concerns on the medical side for extravagation. That's a whole separate topic that I don't have answers for today but we are closely following the NRC efforts on that.

For training, we are requiring isotope-specific training for our users. It's

important to raise awareness about alpha radiation safety. We have run into said situations on inspection where radiation workers were not familiar with isotope-specific decontamination procedures and that's caused some issues.

And then regarding waste disposal. We had authorized decay and storage several years ago when Oak Ridge was the only supplier of actinium-225. Now we have two licensees who are receiving actinium-225 for the purpose of studying the actinium-227 impurities so decay and storage is not an acceptable disposal method for waste which includes actinium-227 and detection of actinium-227 within this waste can be a big challenge if the daughter products have been chemically separated from the parent material.

Okay. So just to kind of close up here, I did want to spend a few minutes highlighting some of the challenges that we will face licensing commercial production of actiumum-225. So as I mentioned before, right now, virtually all that production and processing experiences are with the national labs, yet commercial suppliers more than likely are going to end up under state jurisdiction. So we are motived to license actinium-225 producers in a way that reduces impurities. Both to lower the

radiation safety impacts on site and to reduce the downstream consequences for end users.

I as a regulator need to have deep understanding of the underlying physics and chemistry involved and measures that we may consider include restriction on beam energy to limit coproduction of isotopic thresholds for target purity, etc. We are learning that to the extent possible the market prefers no carrier added isotopes.

So this is already being seen with lutetium-177 and I would expect as some more push to no carrier added actinium-225 once there is enough actinium-225 to balance demand.

So to that end, we need to re-acquaint ourselves with radium and remember its legacy. In the 20th century, industries jumped on the radioactive material band wagon with radium-226. And then migrated to other safer isotopes or non-radioactive chemicals. It's been a long time since we've licensed significant unsealed sources of radium-226, and if you remember from Cathy Cutler's presentation this morning, the avenues that they are looking at for producing actinium-225 without actinium-227, all start with radium-226.

So how a licensee builds, store, use and

recycle radium-226 targets. As we all know, radium-226 has a long half-life and is the case for gaseous daughter whose half-life is long enough to migrate.

So what happens to that radon gas? At this point, I don't know enough about the potential waste streams, but we are keeping an eye on these issues as technology progresses.

Any commercial production of actiumum-225 will require a decommissioning funding plan, the plan for the disposal of activated component and long-lived waste. So appropriately modeling activation and other radiological impact is essential to determining the amount of money needed for safe, effective and timely site decommissioning.

And finally, it is possible that commercial producers of actinium-225 and other alpha emitters could exceed 10 CFR 30 Appendix B thresholds for requiring consideration of an emergency plan. The emergency plan limit for actinium-225 is 2 curies. Operations exceeding these thresholds must demonstrate that radiological impact off-site will not exceed certain dose thresholds or they must provide formal emergency planning. And this is a very complex regulatory effort.

So when it comes to specific design and handling requirements for actinium-225 production facilities, at this point there are lot of things we don't know. So we're working hard to build up our knowledge of accelerator physics separation, chemistry and affluent monitoring. We're doing everything that we can to be ready to license production of these materials.

So to the extent the people in the audience have experience with actinium-225 production facilities, for either proton or electron accelerator production, we will need to learn from you. So please contact me, I would love to talk with you.

And again, just a reminder, these things are a lot of things that we just aren't sure about so we are managing what we have now or looking to the future and I thank you for your time today.

MS. HAMMOND: Thank you so much Megan for that very interesting -- yes, you are still sharing. Thank you so much for that very interesting presentation, I really appreciate that. So we are going to go ahead and move into our Q&A session.

Thank you to those who submitted questions previously, we'll begin with those and then we'll move to any questions that may be in the chat. I've been

kind of monitoring that and I'm not sure if we will get to all of those questions, but we definitely are going to try, and even if we don't get to those questions, we will be sure to follow up with individuals on those particular questions.

So this first question I believe will be for Dr. Berger. How does the Actimab-A clinical development experience define some of the requirements for industry development of antibody radio-conjugates?

DR. BERGER: Thank you Michelle. That's exactly what we wanted to show in the presentation and we really started off noting that IP is critical. Intellectual property is absolutely critical element and the ability to have intellectual property around to target a particular treatment that's been, that's being evaluated is one really important aspect.

There is one aspect actually that I didn't talk about which are pre-clinical models. Which is certainly highly desirable in the case of CG33 lutetium antibody does not recognize CG33 in animals at all. So that wasn't part of the conversation there, but I wanted to mention it because it could be applicable to many other target situations.

And clearly the potential for having some initial therapy to get proof of concept is very

important and that's what really was done with the bismuth studies with bismuth labeled anti-CD33 antibody which were done in academic setting. And that of course lead to the potential to use have industry development and actinium-225 labeled lintuzumab CD33 antibody and that's of course, what's ongoing.

And there one of the important aspects is really the potential to use that drug in combination with other approved therapies. Because in general many of these therapies are going to get approved by showing that we can do better than the present care. So we hope that the example we have given have provided some guidelines for some of the important aspects of initial development.

MS. HAMMOND: Thank you Dr. Berger. We are going to go ahead and move into the next question, it's also for you as well. Please compare the clinical characteristics of alpha emitters, actinium-225, bismuth-213, astatine 111 for use in antibody radio-conjugates.

DR. BERGER: Again, Michelle, thank you that's a very good question because there are a number of different alpha particles, alpha emitting nucleotide in development and potentially is like more over time, and there are certainly others that are being

looked at. But I think the important characteristics of or with industry development, half-life is critical.

We actually have worked very hard to make sure that we use radio nucleotide. In this case actinium-225, it has a ten-day half-life that gives us actually plenty of time to be able to conjugate the nucleotide to the antibody to purify and to distribute it around the country and potentially around the world.

But, for instance, these methods as I mention one of the real difficult, the difficulties of that earlier academic development was that the half-life was 46 minutes and really Dr. Josick who was at Sloan Kettering at the time, deserves a lot of credit for doing those difficult studies that were done very quickly after the material was made.

Astatine 111 is another interesting molecule it has some certainly potential but its half-life is seven hours. And I think for industry development, that is a severely limiting factor.

The other factor that I mention is really the number of alpha particles. It essentially determines the potency of the molecules. So both astatine 111 and bismuth-213 emit one alpha particle and actinium-225 really is very attractive because it emits 4 alpha particles, you get much more bang for

your buck so to speak, and it's clearly much more potent.

So I think those are two really very important aspects of radio-nucleotides that help determine what really can be developed by industry.

MS. HAMMOND: Thank you Dr. Berger. Appreciate that. So the next question, this will be for Megan. In your opinion is there regulatory guidance that should be updated to facilitate radioactive material licensing of actinium-225. I know you mentioned some of them during your presentation, but maybe you want to weigh in on that.

MS. SHOBER: Sure, it is a challenge for us to, especially in those places where there aren't defined action levels for alpha emitters, so it would always be more helpful to have consistent guidance with those specific levels.

In general terms though I think that just from a big picture from the licensing standpoint, I think we have perhaps more work to do on the financial assurance and waste disposal end so those will involve some conversations with the different regulatory stakeholders to come to some kind of consensus on how to roll out some kind of consistent regulatory path for those issues.

MS. HAMMOND: Thank you Megan. And I would definitely agree with you on that, there definitely can be some additional efforts with respect to revising the guidance to include some of the challenges that were discussed and that various presenters have identified during this workshop in particular. Thank you so much.

The next question, this will go to Lisa. Could NRC comment on the expected training for handling of alpha emitters, a clinical operations perspective at sites? I know Megan did touch on that a little bit about how Wisconsin was handling that, but Lisa perhaps you could provide some insight?

MS. DIMMICK: Sure. So as long as actinium-225 the drug product is in clinical trials, NRC would consider that it can be regulated under its medical use regulations specifically meeting the requirements that it's a parental administration of a radioactive drug that contains a radionuclide that is primarily used for its electron emission, beta radiation characteristics, alpha radiation characteristics, or proton energy of less than 150 kb for which a written directive is required and Megan had mentioned that. She identified like iodine 131, lutetium 177 and others.

Actinium is a therapeutic drug requiring a written directive. So physicians who are using this drug need to meet the training and experience requirement in part 35 for authorized users of that modality.

So while we are gaining operational experience with actinium, and certainly Wisconsin is obtaining lots of experience in having a number of regulated sites, we'll continue to review how actinium is used and whether or not additional radiation safety considerations, such as additional training for facilities and also how surveys are being done.

If additional guidance or is needed, and then we would make a determination how, if additional regulatory controls are needed to be implemented.

I did want to add that the NRC's Advisory Committee on the medical uses of isotopes of meeting next -- on October 4th. And the Committee will be discussing a report on specific or specialized practice and policy requirements needed for the safe use and handling of emerging radio pharmaceuticals and theranostics. So it is a very similar-related topic, meeting specifically on the training component. And also in the ACMUI meeting there will be related presentations on production challenges for

therapeutics, for therapeutic radio pharmaceuticals and also the future of personalized dosimetry.

So I guess the point being that we are talking about this a lot in NRC and we're, so there is a lot of dialog so we are trying to obtain information, obtain operational experience so that we can better prepare those specific licensees who want to use actinium for things they need to consider when add it to their radiation safety program.

MS. HAMMOND: Thanks Lisa.

MS. DIMMICK: Michelle, I just to add one more thing, just to piggy-back on something that Megan had said. We talked a little bit about decommissioning financial assurance. Please be aware that NRC is initiating a proposed rule on Appendix B to Part 30 which does, it has the values that require decommissioning and financial assurance values so that's something to keep a close eye on to see how these alpha emitters fit in that table and the updated values that might be included for financial assurance and decommissioning funding plans.

MS. HAMMOND: Thanks for adding that Lisa. I appreciate that, I was going to try to get to that one as well. I appreciate it. So the next question is based on long-lived radionuclide impurities in an

actinium-225 drug product such as actinium 227. Is there a trigger for an environmental risk assessment? So I am going to go ahead and take that one, or take a stab at that one at least.

So it appears that intention for 51.22 for categorical exclusions under C14 that would basically say that they would be categorically excluded from having to have an environmental risk assessment. Of course if there were additional guidance documents that would be developed, that would be something that would be looked at and addressed, but just at first looking at the regulation, it appears that that would, that these types of licensees would fit into the categorical exclusion category under 51.22.

So this next question is actually for, I just wanted to circle back to Dr. Paulus to discuss some regulatory issues. I mean I wanted to give Drs. Fotenos and Marzella an opportunity to respond regarding some challenges with respect to the FDA. Did we lose Dr. Paulus?

DR. PAULUS: No, I'm here. I'm not sure what the question was Michelle.

MS. HAMMOND: Okay, I apologize. I think there was a presentation earlier where there was some discussion about some of the challenges or maybe that

was -- I apologize, let me take a look and see if I can go back to the chat.

DR. PAULUS: I do see a question about regulatory guidance and the requirement when you change a chelator in the course of chemical study. But I don't, I am certain there is no specific guidance to address that directly. But if you're changing a material, that material needs to be characterized. You need to have the toxicological data that goes along with it. So essentially you need to have the same data that you had for your original chelator.

DR. MARZELLA: Victor, this is Louis, perhaps I could pinpoint the questions that I thought might be work some comment.

MS. HAMMOND: Yes. Thank you.

DR. MARZELLA: And the first one relates to the companion diagnostic issues.

DR. PAULSON: Thank you.

DR. MARZELLA: Perhaps I can ask Dr. Fotenos to comment to that. We think it is a very important question that we are trying to work on. We're trying to incentivize manufacturers who are doing therapeutic development to also, you know, to the extent that they can leverage for therapeutics anyway, you know, with the pre-clinical and the clinical.

Potentially there could be potential for, you know, getting an indication for the diagnostic as well. So let me stop there and ask Anthony, Dr. Fotenos if you are still on to comment on that.

DR. FOTENOS: Sure just to, but I've -- because your talk raised some questions about the complexity of dealing with multiple review divisions, it's important for us to emphasize that FDA tends to be organized, particularly CDER, is organized by end points so imaging products and diagnostic products in general have different sort of end points than therapeutics and so that sort of explains some of the organizational foundation, but when that, so the idea of a new pathway to get the two products on the market leverages essentially. To large extent one phase 3 trial is actually to add additional options in the net might reduce the regulatory burden compared to developing each product sort of independently and stand-alone and based on, you know, multiple phase 3 trials.

So and it's also important just to point out how much, despite our sort of organizational logic based on end points, that there is extensive internal communication and collaboration to try to ease those cross references. We are very familiar and make

mistakes from time to time ourselves. I just wanted to just sort of put that framing on that issue you raised. Thank you.

DR. PAULUS: Thank you. For someone who has not developed, who has never developed a companion diagnostic, as soon as I hear the phrase I think device. And it's, I guess it just the connotation of companion diagnostic that introduces that confusion.

DR. FOTENOS: No, and we acknowledge that the companion diagnostic device guidance and precedent does, you know, is specific to the different regulations concerning devices and drugs, and so while this concept of leveraging a common source of phase 3 data is shared, we don't, you know, we are leery about using that exact phrase, companion diagnostic, you know, theranostic is the popular term, parallel imaging radio pharmaceuticals and other potential nomenclature, but it's, we are certainly inspired by that guidance and pathway but it doesn't apply identically because the, and in this case, both products are drugs and so this is, you know, the intention of trying to create through a pathway is to, I mean we acknowledge that the pathway is not well trod.

And secondly that the idea is that it adds additional flexibility for those seeking to leverage

their shares of data. That is the fundamental rest on.

DR. PAULUS: Thank you.

MS. HAMMOND: Are you on mute Dr. Marzella?

DR. MARZELLA: Thank you Michelle. So I also wanted to comment on the other issue that is raised is of great interest. That is the Genus decision which Victor you also mentioned and so the, you know, just to give some background, there was a U.S. Court of Appeals decision about classification of barium sulfate products. And that decision sort of called into question the ability of the FDA to exercise regulatory discretion to regulate the products that could be classified as either devices or drugs.

So the implications of this decision are that the FDA is actively doing intensive work and deliberating on mechanisms of actions to try to understand how to properly classify, you know, a number of products and in particularly contrast agents and imaging drugs are you know affected.

And if for those of you that are interested in looking more into this topic, I would point you to the August 9, 2021 Federal Register Notice. If you just Google Genus FR Notice, it will come up. And it

will have a lot of information for you to look at in terms of what the FDA strategy is and there is a common session, and also a session, an invitation to ask questions, provide comments, and unfortunately the deadline for that is up in 16, days it's October 8, but for those of you interested in providing feedback and comments, that is a potential avenue.

So I just wanted to direct you to that source to either, you know, sort of understand how the FDA you know views the farming of the legal decision and how the FDA plans to move forward.

MS. HAMMOND: Thank you.

DR. MARZELLA: I appreciate the opportunity to comment. Thank you very much.

MS. HAMMOND: Thank you very much for that insight, really appreciate that. So we are going to move to just, this is for Dr. Pandit-Taskar. To just kind of give us an idea of the current scope in the U.S. and the potential growth as well as some clinical trial and translation challenges and barriers that you may have wanted to touch on a bit. Dr. Pandit-Taskar are you there?

DR. PANDIT-TASKAR: Yes. Hi. So as I mentioned in my talk also there are definitely, there is a lot of interest and as I pointed out there is both

in terms of the ligans, radio label ligans or small molecules as the immunotargeted agents. There is definitely data out there that the ligans justify using sub-group of populations and in terms of creating, you know, targets there are extremely attractive targets that we are already looking at. I pointed out two or three clinical trials that are ongoing and in battle to the ligan therapy antibody itself and based on the distribution of the antibodies which have less accumulation in the salivary glands, hopefully they will be less toxicity but again, the data is yet to be, you know, advanced trials, but these you know alpha therapy offers an attractive alternate to the beta immuno-therapies.

And other targets I mentioned the HK2 again, in prostate, and prostate cancer results, the importance and beyond the VISION as study which would allow us to use lutetium-177 PSMA that maybe be sub-group of patients who may not respond. So other targets are required, you know, required. We are always looking for novel targets, and the other ones is for example, the HK2 in prostate cancer. Again that trial is ongoing and we are excited that hopefully we will see good results with that.

And Mark has already given us an overview

of the leukemia study and the use of Actimab-A and I think there is a huge potential there. We see that patients who do not respond to the standard induction therapies and combination therapies will also offer speedier results. So I think there is a huge potential overall not only just for alpha in terms of not just, all the alphas were critical we have more experience with the actinium-225 so moving forward we are expecting that the demand is going to be higher and that brings us to some of the logistical issues, and as I mentioned in my talk, I think one of the major things is the application.

When getting clinical trials, if there is dosimetry involved, that basically can be challenging. The trials are generally based upon the use of the surrogate imaging so indium-111 in most of the cases, that actually makes the treatments chemo and the logistics of patient's visits and convincing the patient to participate is a bit of a practical issue.

So a balance of how many time points and how you do the imaging and the application come back X number of times can be important and especially in terms of accrual.

Some of the other alpha treatment isotopes where multiple time points are included in imaging,

we have seen logistical difficulty in actually accruing patients.

So that's one aspect of it but dosimetry is most important but we also have issues in terms of the methodology and the whole discussion of, you know, what's the optimal way in assessing how much dosing is to be given in terms of the activity administered.

So those images definitely critical, yet, I guess when it comes to practical issues, some kind of balance is needed.

Secondly, as I mentioned in the trial that we are already conducting, we had issues where doses could not be available so while the patient were scheduled to come and get the treatments, these had to be canceled. So that combined with the fact that patients may ultimately go on to other treatments. If these options are not available, we lost patients and accrual. So we have a lot of practical issues when it comes to supply and being able to administer doses to these patients.

So I think as Cathy had mentioned that there are different labs that are making the isotope but again, the idea would be great if we could have supply that is similar to other label agents that we get, but the more flexibility we have, the easier it

will be to translate, conduct clinical trials and eventually being able to do these therapies on a routine basis on patients.

So moving forward we definitely, as the utilization will increase, which we think potentially will, I think we really need to have this supply mechanism be streamlined and opened up a bit more.

MS. HAMMOND: Thank you. Thank you for that. So I am going to try to get to maybe one to two questions that are in the chat before we begin to close. This question is for Megan. If decay in storage of actinium-225 is not an option for disposal of the actinium-227 component, how should sites verify that actinium-227 is not present prior to disposal of waste associated with the accelerator produced actinium-225?

MS. DIMMICK: Megan I think you are on mute.

MS. SHOBER: Thanks. So I think we have to assume that if the actinium-225 is produced from protons spallation it's going to have the actinium-227 in it. So it really is driven by the production method and so I don't know how aware the end users are of how the material was produced. And that's what we really need to work out when it comes to waste disposal.

Again it's that the threshold for

financial assurances is so low that it's just, not just what licensees are used to. They didn't think it affects them, and it will quickly affect them if somebody is not paying attention.

MS. HAMMOND: Thank you Megan. Very great point about the waste. That's definitely something, that challenge that we are going to be looking at moving forward with any potential guidance that will be coming out with respect to these types of technologies.

MS. SHOBER: I just had one other comment too along that lines. When actinium 225, when we first started seeing it in 2015, there really was an absence of guidance on the federal level and I just wanted to point out that over the last 5 or 6 years the Nuclear Regulatory Commission has made very positive strides to get that guidance out there. So I want to acknowledge that effort and we are really in a much better place than we were 5 or 6 years ago.

So now we can all definitely build in that, but we are already -- we are heading in the right direction with that.

MS. HAMMOND: Definitely appreciate that Megan. I agree, I think we are definitely headed in the right direction in taking a more collaborative

approach to some of the challenges that we are all facing from the production to the clinical part, to the regulatory, to being -- and the users in the field, the inspectors, and the license reviewers. So I really appreciate that.

So with that this concludes Session IV and I would like to thank all the presenters and the audience for your participation. I will now pass this over to Ms. Lisa Dimmick for closing remarks. Thank you.

MS. DIMMICK: Okay. Well thank you everyone for attending today's workshop on targeted alpha therapies, or targeted alpha emitters with the focus on actinium-225. This is the third joint workshop of the FDA and NRC.

Today's speakers spoke to you about standards development, product quality, supply and demand of novel radio pharmaceuticals, clinical considerations for development of these novel radio pharmaceuticals and then finally with perspectives from industry, clinical users and the regulator.

The workshop organizers really appreciate the panel discussions and while we weren't able to answer all of the chat questions, the FDA and NRC do have the chat questions and we will use them to help

inform, you know, our path forward with, you know, regulating actinium-225.

I know the NRC will definitely use the chat questions and, you know, understand, you know, the issues and concerns especially with regard to some of the waste that was presented today or questioned today.

Let's see. So the FDA and NRC do look forward to having continuing ongoing dialogues on a number of topics in novel technologies and with that we are adjourned for today. And we look forward to a future FDA/NRC workshop. Thank you and thank you for your support.

(Whereupon, the above matter went off the record at 3:59 p.m.)