Official Transcript of Proceedings

NUCLEAR REGULATORY COMMISSION

Title: Enhancing Development of Novel Technologies: Radiopharmaceuticals and Radiological Devices FDA-NRC Workshop

Docket Number: (n/a)

Location: teleconference

Date: Wednesday, October 14, 2020

Work Order No.: NRC-1127 Pages 1-327

UNITED STATES OF AMERICA

FOOD AND DRUG ADMINISTRATION

and

NUCLEAR REGULATORY COMMISSION

+ + + + +

WORKSHOP

ENHANCING DEVELOPMENT OF NOVEL TECHNOLOGIES:

RADIOPHARMACEUTICALS AND RADIOLOGICAL DEVICES

+ + + + +

WEDNESDAY,

OCTOBER 14, 2020

+ + + + +

The Workshop convened via Video Teleconference, at 8:00 a.m. EDT.

PRESENT:

LIBERO LOUIS MARZELLA, FDA

KEVIN WILLIAMS, NRC

VINCENT HOLAHAN, RRS

JOHN AMARTEY, FDA

MITCHEL ANSCHER, FDA

DENIS BERGERON, NIST

JAMES BERTRAM, FDA

DENISE CASEY, FDA

KISH CHAKRABARTI, FDA

DANAE CHRISTODOULOU, FDA

LISA DIMMICK, NRC

HUGH EVANS, Eckert & Ziegler Radiopharmaceutical

ANTHONY FONTENOS, FDA

JAMES HARVEY, NorthStar Medical Technologies

MARC GARLAND, DOE

BILL GOECKELER, Bayer Healthcare

TOMAS HERRERA, NRC

DONNA-BETH HOWE, NRC

TIMOTHY HSIAO, ASTRO

HOSSEIN JADVAR, University of Southern California

CHRISTY JOHN, FDA

ANA KIESS, Johns Hopkins University

RALPH LIETO, ACR

SARAH LOPAS, NRC

FRANK LUTTERODT, FDA

JOSH MAILMAN, NorCal CarciNET Community

MAURIZIO MARIANI, Advanced Accelerator Applications

JULIE SULLIVAN, FDA

JOSEPH RAJENDRAN, FDA

KATIE TAPP, NRC

SUE-JANE WANG, FDA

CONTENTS

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

8:03 a.m.

DR. MARZELLA: Good morning, everyone. Can you all hear me?

MS. LOPAS: We can.

DR. MARZELLA: Great. Dear colleagues, then, good morning and welcome to today's program. My name is Louis Marzella and I direct the Division of Imaging and Radiation Medicine in the Center for Drugs Evaluation and Research.

On behalf of the Food and Drug Administration and the Nuclear Regulatory Commission, it is my distinct pleasure to welcome our distinguished speakers and attendees to our second FDA NRC workshop on radiopharmaceuticals and radiological devices.

This workshop is prompted by the considerable ongoing innovation in the field and our aim is to enhance the efficiency of development of novel technologies and products. We have planned an agenda that will provide you with a broad overview of FDA and NRC regulatory processes. And we will be focusing on recent experience and novel products. Our aim, again, is to clarify expectations for marketing

and licensure of new products and to consider your questions and comments.

I want to acknowledge the participation of many stakeholders with whom we work with daily to advance product development. These include the representatives from the Department of Energy, the National Institute of Standards and Technology, the American Society for Radiation Oncology, the American College of Radiology, and of course the Pharmaceutical and Device Manufacturers with whom we interact on a daily basis.

We also want to acknowledge the many academic and commercial clinic investigators that are joining this call. And of course, we always want to hear from patient advocacy groups.

Today's program is divided into five sessions starting with product jurisdiction and regulatory processes. It will be followed by product quality considerations and then by the discussion of characterization of safety and efficacy of products. We will then also consider specific device related aspects and experiences. We have included time, plenty of time, for panel discussions and we look forward to hearing the perspective and experiences of manufacturers, of clinical investigators, and of

patients.

We have a full agenda for today and we are excited to have you participate with us in this planning --- in today's agenda.

With that, I would like to introduce my colleague from the NRC, Kevin Williams. Kevin?

DR. WILLIAMS: Good morning and thank you, Dr. Marzella.

As stated, my name is Kevin Williams. Welcome to everyone to this FDA NRC collaborative workshop. I am the director of the Division of Materials Safety Security State and Tribal Programs in the Office of Nuclear Materials Safety and Safeguards at the United States Nuclear Regulatory Commission.

Last October, the FDA and NRC held a symposium to exchange information on each agency's regulatory process for approval and clearance and licensing of medical devices and drug products that contain radioactive materials. The symposium objectives were to leverage knowledge of regulated products and do determine opportunities for parallel regulatory reviews. As a result of that symposium, the FDA and NRC decided to hold a public workshop to seek input from the regulated industry, users, and

other stakeholders.

I would like to thank the FDA and the NRC staff and the workshop steering committee who have worked to plan so diligently and to coordinate today's effort. I would also like to thank all the presenters for their support. Substantive experiences represented by panelists and attendees at today's collaborative workshop, including regulatory authorities, scientists, positions, and other healthcare professionals, and patients with various areas of expertise, focus on advancing novel radiopharmaceutical and radiological device technologies. This workshop provides a forum for the exchange of information and perspectives on the regulatory and compliance of radiation safety of novel technologies amongst all stakeholders, from patients, physicians, pharmacists, nurses, researchers, materials transportation, facilities, 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.

In closing, 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. I will now turn the meeting over to Dr. Vince Holahan for his remarks.

DR. HOLAHAN: Thank you, Kevin.

Good morning. I'm Dr. Vincent Holahan. I'm a senior level advisor in the office of Nuclear Materials Safety and Safeguards at the U.S. Nuclear Regulatory Commission.

On behalf of Dr. Susan Bailey, the President of the Radiation Research Society, I'd like to welcome you to this joint FDA NRC workshop. The Radiation Research Society was founded in 1952 by a group of dedicated scientists and physician scientists who understood that radiation was a tool that could be used for the advancement of mankind.

The Radiation Research Society's objectives are threefold. First, to advance radiation research in all disciplines of science and medicine. The fields and disciplines of the society include biology, chemistry, physics, medicine, and epidemiology. Second, the society strives to foster

collaboration with a community of researchers interested in the study of the properties and effects of radiation. This is fostered by conducting annual meetings to include a virtual annual meeting that will be held next week, and the creation of the Radiation Research Foundation whose mission is to support the research and educational efforts of all qualifying early career personnel engaged in radiation research. Finally, the dissemination of knowledge in radiation research to the scientific community and to the public.

Shortly after its discovery in 1895 by Wilhelm Roentgen, ionizing radiation has been used as a tool in the diagnosis and treatment of injury and disease. Radiation biology research has led to fundamental scientific insights regarding the deposition of ionizing radiation and its biological impact. There is very robust and reliable evidence that DNA damage responses, including induced mutation and chromosomal damage, effect the frequency of cancers after exposure at all doses and dose rates. The responses relate to direct damage to DNA in the form of double strand breaks and complex lesions and to indirect damage attributable to the generation of reactive oxygen species. DNA repair activities can

serve to reduce yields of mutations and rearrangements but they are not 100 percent effective.

A major goal of radiobiology is to achieve selective radio-sensitization of cancer cells by modulating molecular response to radiation injury. Clonogenic survival is the gold standard for assaying radiation sensitivity in vitro as well as for testing the efficacy of agents that modify radiation survival. Discoveries such as DNA repair, mutagenesis, connections between mutagenesis and carcinogenesis, genomic instability, cell cycle checkpoints, and others are now recognized as integral to the DNA damage response and have contributed to our understanding of the risks and benefits of radiation exposure. Innovation and progress in radiation oncology depend on discovery and insights realized through research in radiation biology.

With the advent of the COVID-19 pandemic, a variety of experimental treatments are being evaluated to improve the clinical outcome of COVID-19 patients. Recently, the National Cancer Institute, the National Council on Radiation Protection Measurements, and the National Institute of Allergy

and Infectious Diseases convened a virtual workshop to discuss available data concerning the potential risks and benefits of low-dose, whole-lung radiation therapy. The impetus for low-dose, whole-lung radiation therapy comes from case studies of patients treated with thoracic radiation for pneumonia between 1905 and 1943, suggesting improvement without toxic side effects. Workshop participants discuss three main areas: clinical trials and trial design, pre-clinical studies, and radiobiological and immunological mechanisms for low-dose radiation therapy.

While no clear consensus emerged among the workshop participants on the efficacy of the use of radiation in non-cancer settings, it is evident that there is an immediate need for further information among radiation oncology, biology, and protection communities. It is clear that more pre-clinical data are needed, that little data exists regarding the path of physiological effects of treating a lump with low-dose radiation therapy in the midst of the vasculopathic viral pneumonia.

With this in mind, I'd like to return the program to Ms. Lisa Dimmick and she'll introduce our first session.

Lisa?

MS. DIMMICK: Thank you, Vince. So our first session is the overview of regulatory process for marketing and licensing of radiopharmaceutical products. There are two segments in this session. The first is product jurisdiction devices, drugs, and combination products with speakers from the FDA and the NRC. The first speaker is James Bertram who is currently an assistant director with the regulation policy and guidance staff which supports the office of product evaluation and quality and CDRH.

Dr. Bertram? The floor is yours.

DR. BERTRAM: Thank you, Lisa. Can everyone hear me?

MS. DIMMICK: Yes.

DR. BERTRAM: Okay. Give me one second, sorry. I'm getting feedback from my phone. Can you still hear me or is there an echo?

MS. DIMMICK: The audio is good.

DR. BERTRAM: Thank you for the introduction. So, my name is James Bertram, and I am an assistant director in regulation policy and guidance staff and Center for Devices and Radiological Health in FDA. And as part of that role, I have the privilege and the ability to serve as a

product jurisdiction officer in --- and represent CDRH across the centers. So being one of the first talks in the morning, really, looking to provide a high-level overview as well as provide you --- kind of get the blood flowing. So many of the following presentations will go into significantly more detail and provide a lot more clarification on what we do.

So with that, next slide please. The purpose of my presentation, thank you, is to provide some definitions and then look at how these definitions --- provide clarity as to how your product may be regulated as a drug, device, or possibly a combination product. And the ultimately these will all have developmental implications. And again, just some high-level implications and others will speak to more specifically.

Next slide, please.

So the last thing you probably wanted to do or hear about this morning is what I am or what I do. And to be honest, when I get involved, most people are like, why are you here? So with that, though, and I was putting together these slides I realized that, actually, the summary and overview of what I do can actually provide sort of a nice summary of how the agency works in looking at jurisdiction and

classification of your product.

As a jurisdiction officer --- first of all, I have counterparts that are jurisdiction officers in CDER and CBER as well and we are, for our respective centers, we are focal points on combination product questions and issues. We serve as a liaison with the office of combination products, and we provide recommendations on behalf of our centers for classification and assignment of combination products as well as single entity products. Single entity products being drug, devices, or biologics. And then, again, we represent the Center on policy issues regarding combination products. And then, ultimately, we also work with OCP on guidance documents, regulations that affect our respective centers and how they affect the other centers. And also, we are a resource for external stakeholders and once you get clarification regarding where your product resides, we also get involved in help with providing clarity on where --- pathways for your product.

Next slide, please.

The agency basically functions and categorizes your products based on definitions that are either a statute or in the regulations. So,

specifically, for drugs, device, and combination products, these are defined in the Food, Drug, and Cosmetic Act. And biologics which we really won't speak too much here are defined in the Public health Service Act.

So, next slide.

The definition for drugs, in section 201(g) FD&C Act is sort of the foundation and devices kind of stems from that, and I'll get to that on the next slide. Notably, a drug is an article that is intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or animals. And, see, it also clarifies that it is intended to affect the structure or function of the body of man.

Next slide, please.

I'm not going to reiterate everything regarding the device definition, but you see a lot of similarities in the context of sub-bullets one and two. But the highlighted text really focuses on what's of interest for a device in sort of the exclusionary aspects of how something may be drug, but if it meets this exclusionary criterion, it would be then regulated as a device by the agency. And notably --- I'll read this underlined text of which

is an article that is intended, or sorry, instrument, apparatus, et cetera, as defined higher in the definition. But it's one of these which does not achieve its primary intended purpose through chemical action within or on the body and is not dependent on being metabolized for the achievement of its intended purposes.

I only have ten minutes with you this morning, so I could probably give a day long presentation and have a provocative discussion on the third bullet and the underlined text. In fact, the agency has guidance that looks to help clarify this underlined text for stakeholders and help further elucidate what is a device versus a drug as there is a lot of, sort of, interest in play in this area.

Next slide, please.

Not to, again, leave out biologics, not really as much of a focus of our presentations today, but as I indicated PHS Act defines biologic really based on its identity. Again, I won't go through all this, but this biologic meets the definition on what it is.

So defining the three fundamental pillars of products that are --- from our purposes of regulating in the agency, you get to, what is a

combination product?

A combination product is comprised of two or more of any of the previously identified entities. So that could be a drug and device, a drug and biologic, or the combination of all three. So purposes of this Venn diagram, it's the overlapping shaded areas. These are only where combination products will reside.

Next slide, please.

Types of combination products are defined in the regulation. You could have some that are physically or chemically combined as a single entity, co-packaged in a kit --- a convenience kit, or sold separately, but labeled exclusively for use with each other. Some examples of these include, so single entity is drug-eluting stent, cardiovascular drug-eluting stent. For the kit you could have a first-aid kid that has bandages and, say, an anti-biotic ointment. And then photodynamic therapy where the drug and the device are sold separately but labeled exclusively for use with each other. These are all considered to be types of combination products.

What would not be a combination product? Two drugs packaged together. Two devices packaged together. As well as --- Sorry, next slide. So, again,

already touching on the drug-drug, biologic-biologic for example are not combination products. And food, for example, having aspirin with your beer. If that was packaged together, that would not be a combination product. Nor would, say, dandruff shampoo, that if it wasn't for dandruff, it may otherwise be a cosmetic as a shampoo, but because it is also intended to treat dandruff that would be regulated as a drug. That necessarily would not be a cosmetic, per se. Sorry, it would not be a combination product.

Next slide, please.

Product assignment. As a general rule of thumb, drugs go to CDER, Center for Drugs. Devices go to Center for Devices. And biologic products will to CBER but they also, obviously can go to CDER. And there is some further exemptions within. Some devices are regulated in CBER as well. Again, won't go into all the nuances for purposes of our conversation.

But what about a combination product?

Next slide, please.

As I alluded to earlier, the Office of Combination Products sometimes will be involved with the regulation review of a combination product and help elucidating where it goes. So the Office of

Combination Product, as depicted here, resides within the Office of the Commissioner, and they have the authority to assign jurisdiction of combination products or single entity products to the respective centers. This is really only pulled in or utilized when it's unclear. Most products go to effective centers without any uncertainly and with little involvement of OCT.

OCT also serves as a focal point for internal and external stakeholders for combo product related issues. And they have general, broad oversight responsibilities in covering the regulatory lifecycle of combination products.

As a general matter in looking to assign a combination product --- next slide, please --- the agency looks to establish what the primary mode of action is. The primary mode of action may be that of a drug, a device, or a biologic product and primary mode of action, or PMOA, is the single mode of action of a combination product that provides the most important therapeutic. This is further defined in the regulation.

A couple examples of products that are assigned to their effective centers on primary mode of action, say, is a drug eluting stent. That's

assigned to CDRH on primary mode of action. And a drug eluting disk, however, would be assigned to CDER on primary mode of action as the disk is really --- the device is just to sustain the delivery of the drug.

Next slide, please.

However, if primary mode of action is not clear, the agency then, for the regulation, looks to first sort of allocate the product based on consistency. Is there a similar product that is regulated the respective centers? If that's not clear, then they'll go to look at what center has the most expertise to address the most significant safety and effectiveness questions associate with the product. This is referred to as the assignment algorithm.

An example of a product that is assigned, that may be assigned, on algorithm is a contact lens that has --- is there for refractive correction as well as a including, say it's coated in a glaucoma drug for treatment of glaucoma. Two independent modes of action, neither subordinate, neither primary. So it would be assigned based on which center has a similar product or the most expertise to address the most significant safety and effectiveness questions.

In this case, I believe, the product was assigned to CDER.

Next slide, please.

I'm not going to go into detail on these remaining slides. One, because I'm running out of time, but also there's subsequent talks that go into much more detail. As I mentioned in the assignment algorithm, and often times OCT isn't even involved, there's a lot of precedence regarding respective products in the respective centers. Here's just a number of considerations from a device perspective. There are regulations for diagnostic devices ss well as therapeutic devices. And then those really apply to Class II and Class I products. But we also have Class III, so PMA products or HDE, maintain device exemption products that may be regulated in CDRH as well.

And here are just a few examples. Next slide, please.

And as I'm sure many of you are aware with having your own product regulated in the Center for Drugs, there's clear definitions for drug products for a radioactive drug that is included in the regulations.

And we'll also be taking into

consideration from OCP and the Center jurisdiction officers if it's unclear where a product resides. So, next slide, please.

Again, just another citation of what a radioactive drug, and in this particular case, how it takes into consideration, whether it be a radioactive biologic based on what the product is. Next slide, please.

So, how do I get classification/ jurisdiction assignment? So again, if it's not readily clear, you can go to the Office of Combination Products. They can be contacted at the provided email.

They also can help provide clarity on say review and sort of regulatory considerations as well. And this is all achieved through the submission of a Request for Designation.

And this is the mechanism by which OCP opines on the jurisdiction and classification of products in front of them. But -- and it may not again, as I alluded to earlier, it may not just be combination products, but it could also be single entity products.

For a pre-RFD or a pre-Request for Designation, the outcome is the same. But it's not

a formal determination per se.

But the Center still utilizes that input. This is clarified and articulated in a final guidance. And just for note, this is the most common option which companies will utilize to get clarity.

And then the more historical, well-established mechanism is the formal RFD. And there are a number of more restrictions that are associated with that.

For example, page length. But there's also guidance on that. So, next slide, please.

So, developmental implications, your product, either as a combination product, single entity would go through a lead center.

And it also may have -- impact obviously the application type. For example, if you're in CDER, it could be an NDA or an ANDA versus CDER HFGMA (phonetic) or 510(k) possibly, or even a de novo.

But one thing that's either way, you have a lead center. There will be collaboration across the centers.

And if and when a product is classified as a combination product, it will not change. And it carries on that designation throughout the -- throughout the review process.

But, it will be regulated as -- in the pathways or as products customarily in those centers. And then again, you -- and being a combination product, or a designation, you must comply with the applicable regulations of the constituent parts of your product.

So, if you have a device and drug, then you will have obligations to abide by the drug and device regulations. So, next slide, please.

So, just kind of recommendations. Work with FDA early in the development process to make sure jurisdiction and classification are clear.

Be familiar with all applicable guidance documents. And to the extent possible, leverage available and existing data for, if you have a combination product, the constituent parts.

However, being a combination product, you will have to consider synergies. And the agency may likely ask you questions on that.

So, just again, look at your product individually with the constituents' parts, but also as a whole. And then again, can't stress enough, recommend early interactions when developing your product.

With that, I am done. And I'll turn it

back to Lisa. Thank you.

MS. DIMMICK: Okay. Thank you -- thank you, James. And we look forward to questions during the panel session.

Next up we have Donna-Beth Howe. Dr. Howe is a biophysicist on the medical radiation safety team at the U.S. Nuclear Regulatory Commission.

DR. HOWE: Thank you. I'm going to be, in the next slide, I'm going to be giving you an overview of how NRC regulates.

First of all, we have the Nuclear Regulatory Commission. And the Commission is made up of five individuals who -- who govern the NRC as a collegial body.

And we have a Chairman that has additional functions in case of an emergency. But our five Commissioners each have a single vote.

We have a headquarters here in Rockville, Maryland. And we have four regions in, just outside of Philadelphia, outside of Chicago, outside of Dallas, and in Atlanta.

And our regions will have our inspectors and our licensing staff. We do a little bit of licensing in headquarters for exempt distribution

products.

But the majority of our inspection and licensing is done out in the regions. And for medical purposes we also have a very important group called the Advisory Committee on the Medical Uses of Isotopes, the ACMUI.

Now, one can't really talk about the NRC without also talking about the Agreement States. From early on, certain states entered into agreements with NRC in which NRC relinquished its authority to regulate radioactive material, certain radioactive materials in that state.

And so when I'm talking about what we do today, as I go through my talk, I'm actually going to be talking about the NRC and the Agreement States. Because right now, there are a lot more Agreement States than there are states that are regulated purely by NRC.

And NRC also works with other federal agencies. And one of the primary federal agencies that we work with, in the medical area, is the Food and Drug Administration.

And we work with all the centers there. Primarily with the Drug Center and the Device Center, but we also get involved with Biologics.

And how do we regulate? Well, we have regulations. We're in the 10 -- Chapter 10 of the Code of Federal Regulations. And that tells us what we can do and how we regulate the public.

We also produce guidance documents. Some of them are quite hefty. Some of them are very small. In which we provide guidance to our licensees, our inspectors, and our license reviewers.

And we issue licenses. For medical purposes we issue licenses to facilities. We do not license individual doctors. We do not license individual medical physicists.

We do not license individual pharmacists, unless they own -- own a facility, and that facility is in business as their name.

We perform inspections. We have people out in the regions that go out on a routine basis and inspect all of our licensees.

And that's one of our -- our strongest points at NRC, is that we will visit you. We do not announce our inspections, because we believe that on any given day, you should be operating in accordance with the regulations in your license.

And if you're not operating in accordance with the regulations in your license, then the

inspectors will write up violations. And we have an Office of Enforcement, which will look at the severity of your violations and make a determination on what the consequences are from not complying with NRC regulations in your license.

For medical use, we actually have a special document that gives us a very general outline of how we regulate medical uses. And that is our policy statement.

And it is really only four lines. And essentially it says that we will continue to regulate the medical use of materials in order to protect the safety of workers and the public.

And we will not intrude into the medical judgements affecting patients, unless necessary to provide for the radiation safety of workers and the public.

And then when justified, we will also regulate the patients, to protect them and to ensure that they are given what they are -- what the physician wants them to have.

And then we will use global standards when we're adopting new regulations. Next slide.

So, what do we regulate for materials? I think it's important to tell you that we regulate

from cradle to grave.

So we regulate from the first production or isolation of the material, until it is disposed as waste.

And for medical use, we regulate byproduct material. Byproduct material is defined in the Atomic Energy Act, and also in our Code of Federal Regulations.

It used to be byproduct material was only reactor-produced. And it could be produced in a reactor either by -- isolation of fission products, or neutron activation.

But, with the Energy Policy Act of 2005, we now also regulate accelerator-produced radioactive materials. We do not regulate the accelerator. We regulate the materials that the accelerator produces.

So, we would also regulate the activation products in the walls of the room. But we don't regulate the accelerator.

We also regulate other materials. And they are source material. So, that's material used, if you're in a medical facility, you may be familiar with depleted uranium, which is used for shielding and counterweights. But the use of that shielding is not medically produced.

We also regulate special nuclear material, which is generally plutonium and uranium. And we do have plutonium-powered pacemakers, although most of those are disappearing as the patients that they were implanted in have died off over the years. Next slide, please.

So, how do we regulate medical use and all of the radioactive drugs and the radioactive devices and the sealed sources that go with them?

Well, Part 30 in our Code of Federal Regulations is our basic regulation of byproduct material. It tells us when we can issue licenses, and how to permit transfers of radioactive material between different licensees.

Part 35 is the specific part that tells us how we regulate the medical use of byproduct material. And as I indicated before, we regulate that in private practices. We regulate it in clinics, hospitals, and government medical facilities.

And what is the medical use? And I'm -- I'll be coming back to this later. It is the intentional, internal, and external administration of byproduct material or the radiation from byproduct material to patients or human research subjects under

the supervision of an authorized user.

And for us, an authorized user in medical use is always a physician. In some special cases it could be a podiatrist or a dentist.

And the key element that I want you to think about here, is that in medical use, we regulate not only the regular clinical use of byproduct material, but we also regulate the investigational uses.

And because we define medical use as for patients and for human research subjects. So, all of our licensees are automatically authorized to use these materials either for routine patient use, or in human research studies.

So, what about the pharmaceuticals? The drugs? We regulate those under Part 32. And we regulate not only the commercial nuclear pharmacies, which generally convert the drugs into unit doses, in some cases they make their own.

But, we also regulate the big manufacturers. So, we regulate the Mallinckrodt, the Lantheus, under Part 32.

And we regulate those distributors that may be middlemen that receive materials from one of our other Part 32 licensees, and then distributes it

onto the medical use licensee.

So, Part 32 focuses primarily on the manufacture, distribution, or preparation of radioactive drugs for medical use. And in 32.74, we work primarily on the manufacture and distribution of medical devices.

We also regulate under Part 50. And I bring this in because right now Part 50 licensees are very important to medical use.

We -- the small reactors and the non-power reactors may be producing neutron sources to activate certain isotopes like molybdenum to make molybdenum-99.

They also may activate other products, such as the natural glass seeds for the TheraSpheres, to activate them into the yttrium.

And also, we have certain, certain entities now that are looking to Part 50 to make moly from fission products. And traditionally Part 50 has been the big reactors.

But in SHINE's case, we are now regulating an entity that is somewhat like a reactor in that it has uranium. Unlike a reactor, the uranium will not go critical.

And unlike a reactor, it doesn't have

control rods. But, like a reactor, it has an accelerator that puts the neutrons into the uranium to cause the uranium to fission.

So, we have some interesting Part 50 licenses that are also helping us produce radioactive materials we regulate. Next slide.

MS. DIMMICK: Dr. Howe, you need to start to wrap up, please. Thank you.

DR. HOWE: Okay. Then we have a -- radiochemicals and radiopharmaceuticals. That's always a big question.

If the radioactive material cannot be used directly, and injected into the patient, then we consider it a radiochemical and we regulate it under Part 30.

If it is a radiopharmaceutical, then it is used under Part 35, as is most of the things, like the technetium-99, and the rubidium from the rubidium generator, and the gallium.

But they are not the germanium that forms the germanium-gallium generator. So, some of our generators produce radiochemicals, and some of them produce radiopharmaceuticals. The next slide, please.

These are just to give you some

interesting pictures. Everybody knows about these. These are the diagnostic pharmaceuticals and how they're being used.

There's the gallium and then there's the technetium. Next slide.

The I-131 capsules from radiopharmacies. And then also some of the new technologies, Xofigo, which is the radium-223. Next slide.

We also regulate sealed sources as the permanent brachytherapy prostate implants. And the very tiny brachytherapy sources for the yttrium-90 microspheres. Next slide.

And we regulate the very big devices like the stereotactic radiosurgery devices. And then the very high energy and high radiation dose devices, such as the high dose remote afterloaders. Next slide.

I've already described what medical use is. I've already kind of introduced you to things that may be used in medicine, but we don't consider them medical use.

We don't consider the shielding around devices to be medical use. We don't consider the plutonium in the pacemakers to be medical use.

We don't consider the production of

medical isotopes to be medical use. Or the manufacture and distribution of radiopharmaceuticals, or the manufacture and distribution of sealed sources and devices.

Or administration of radioactive materials to animals for use in research studies. And we don't consider blood irradiation in medical use.

We regulate all of these things, but we don't consider them medical use. Next slide.

These are various licensees we have. I talked earlier about, we license the hospitals and the clinics. That's our limited specific.

If it's a really big hospital, it's a Medical Type A Broad Scope. And we have certain government entities like the Veterans -- Departments of Veterans Affairs, Navy and Air Force, which we allow them to issue their own licenses and inspect, do their own inspections.

But they are NRC licensees. They are not Agreement States or equivalent to Agreement States. So, next slide.

And these are some of our additional resources that you might be interested in. Thank you, Lisa.

MS. DIMMICK: Okay. Thank you, Dr. Howe. The next segment in this session is Clinical Development of Radiopharmaceutical Products, Regulatory Considerations for FDA Approval and NRC Licensing.

The first speaker is Frank Lutterodt. Frank is a Senior Regulatory Project Manager at the Office of Regulatory Operations and the Office of Specialty Medicine at CDER.

Frank?

DR. LUTTERODT: Good morning everyone. Today I'm going to talk about a clinical development of radiopharmaceutical products, focusing on regulatory consideration for FDA approval. May we advance to the next slide, please?

I am currently -- can you go back one more slide? With the outline? Okay. So, we'll go over the schematic on the overview of the drug development process.

The use of radioactive drugs in basic research, pre-clinic office, clinic office, meetings, and NDA submission and review.

And I also want to point out that the overarching regulations governing other therapeutic development also applies to radiopharmaceuticals and

PET drugs with only a few caveats. Next slide, please.

We'll go over the schematic on the overview of drug development process. The use of radioactive drugs in research and all the other aspects of FDA processes.

And perhaps this scheme -- or as you see here, the schematic is the overview. And perhaps this is an oversimplification of the process. Next slide, please.

I'm going to start here with regulating radioactive drugs in basic research. FDA regulates the radioactive drugs in basic research through their Radioactive Drug Research Committee, or RDRC, under 21 CFR 361.

The RDRC program began when FDA published in the Federal Register, classifying all radioactive drugs as either new drugs requiring an investigation new drug application, commonly referred to as INDs, for investigational use.

Or, generally recognized as safe and effective when administered under the conditions specified in the RDRC regulation.

Under the RDRC, research is considered basic science, and is done for the purpose of

advancing the knowledge intended to obtain basic information regarding the metabolism, human physiology, pathophysiology, or biochemistry.

The intent is not for immediate therapeutic or diagnostic or similar papers. And nor intent to determine the safety and efficacy for clinical use.

And I wish to point out that FDA's oversight is on the RDRC Committee. And the IRB has oversight of other clinical studies. Next slide, please.

The drug development process starts with pre-clinical research involving synthesis and purification where target affinity and selectivity studies are done. Animal studies, under which there is PK proof of concept toxicity and translation, dose translation to humans.

I also want to point out that generally all drugs, biologics, including radioactive drugs, go through similar development process. Next slide, please.

The new drug development process has Phase 1 approach. The Phase 1 approach involves an IND, which either can start with an exploratory IND, or a traditional IND.

I also want to point out that INDs are regulated under 21 CFR 312. And INDs are used to establish the safety or effectiveness of a drug to support the approval of a new use.

And although that is the case, Phase 1 studies is -- the focus on Phase 1 studies is on the safety of the new drug. Next slide, please.

I'm going to move on with some definition about exploratory IND. An exploratory IND is a clinical trial that is conducted in early Phase 1.

It involves very limited human exposure, and has no therapeutic or diagnostic intent. The main purpose for this approach is to find promising drug candidates that, to enable the sponsor to proceed efficiently with their most promising drugs.

It's also -- it's still important to emphasis that throughout all these clinical phases, there are many options for continued dialog with the FDA, and that direction of Phase 1 exploratory IND is expected to be limited, and usually seven days.

And it's always advised that once the -- the studies are complete, the sponsor will withdraw their IND and submit an approval IND. Next slide, please.

A traditional Phase 1 clinical trial

usually involves healthy volunteers to determine the drug's most frequent and serious adverse events. And often how the drug is metabolized and is treated in the body. It involves a small number of participants, usually in the range of 20 to 80 subjects.

During Phase 1, sufficient information about a drug's PK effect should be obtained to permit the design of a well-controlled scientific valid Phase 2 study. Next slide.

During Phase 2 clinical trial, if more information is gathered about the drug safety and effectiveness in the condition or disease being studied. There are larger groups of subjects enrolled in these kinds of studies and subjects receive the drug -- receiving the drug maybe compared with others receiving placebo. Safety and short-term adverse reactions continue to be evaluated during this phase.

And this usually involves more than several hundred subjects. Next slide, please.

A Phase 3 clinical trial is intended to gather additional information about effectiveness and safety that is needed to evaluate the overall benefits, risks, and relationship of the drug.

And to provide an adequate basis for the labeling. And at this stage, the numbers of subjects could range from several hundred to several thousand.

And if safety and efficacy are adequately confirmed, clinical studies testing may end at this step and a new drug application may be submitted. Next slide, please.

And as I'll be saying the FDA encouraging -- encourages the sponsors and applicants throughout all these phases of drug development to communicate.

And the -- we have the guidance of formal meetings. And the agency encourages all the sponsors to seek guidance throughout this process.

I'd like to refer you to the meeting guidance link on this slide. And this guidance discusses the principles of good meeting management practices, and describes the standardized procedures for requesting, preparing, scheduling, conducting such meetings.

And there are four types of meetings. There's the Type A, Type B, Type B end of phase meetings, and a Type C. Next slide, please.

As you can see in this table, these are the meeting types and the expected goal dates for fulfillment of these meetings.

A Type A meeting is generally needed to help an otherwise stalled product development program to proceed. A Type A meeting should occur within 30 days of the FDA's receipt of the meeting request.

And background package is due at the time of the meeting requesting this case. These examples are dispute resolution, clinical hold, special protocol assessment meetings will be considered as Type A meetings.

Type B and Type B end of phase meetings are held at certain stages during development. Examples of Type B meetings are, for example, the pre-IND meetings, and pre-NDA meetings, or pre-BLA meetings in certain, in the case of biologics.

Type C meetings are those that do not qualify as either Type A or B meetings, to gain guidance for development of a review product. Next slide, please.

So, and following all the pre-clinical trials, pre-clinical data, and a submission of an NDA, pre-clinical data and data from the -- from all the clinical trials assists FDA in making a risk benefit assessment.

And a favorable risk -- benefit risk assessment culminates in the review of, and approval

of the drug labeling. Next slide, please.

And since I just mentioned labeling, I just briefly want to go through some terminology. What do we mean by labeling?

In general, a label is usually there immediately on the drug container or the carton containing the drug.

And labeling is the written printed graphic material that accompanies the product. And this involves basically everything else. Next slide, please.

As you can see over here, the carton and container labeling, PI, prescribing information, med guides and manuals, are all considered the labeling. And I wish to point out that the PI is written to the prescriber and not the patient.

It should contain the summary of the essential scientific information needed for the safe and effective use of drugs and biologic products.

So, the entire drug development process contributes to data to support the NDA and the labeling. Next slide, please.

And continuing on a few of -- a few discussions of other labeling. FDA implemented the physician labeling rule in 2006.

These revisions are expected to make it easier for healthcare practitioners to access, read, access, read, use the information in the prescription drug labeling.

These revisions enhance the safe and effective use of prescription drug products, and reduces the number of adverse reactions resulting from the medication errors due to misunderstood or incorrectly applied drug information.

The highlights have concise summary of very important information. And the full prescribed -- prescribing information is organized according to the clinical relevance.

And in the next slides, I'm going to talk about the pregnancy and lactation labeling rule. This label format change was made to reflect integrated assessments. Next slide, please.

Integrated assessment to -- relevant to the pregnancy, lactation and infertility based on the available and information of that -- available information or data.

A summary and a review of the available relevant information that supports the labeling content. Next slide, please.

Here is a typical table of contents,

which mirrors how the information is organized and approved prescribing information. And notice how the clinical sections, such as in the cases and usage, are followed by a dosage and administration, are all ordered first.

And then the chemistry and the clinical pharmacology are ordered later in the labeling. Next slide, please.

So, once a product is approved, when FDA issues a letter, the labeling is attached. The labeling and the labels are attached with the approval letter.

And after approval, there is -- there's not -- the approval is not a complete, a completion of the activity of the drug.

The applicant may file supplements. It can continue with further safety studies and IND. FDA continues with site inspections, active surveillance, and the applicant submits periodic safety reports. Next slide, please.

I want to use this slide to highlight examples of classes of radiological drugs regulated at CDER.

We've got positron emission tomography agents, scintigraphic agents, magnetic resonance

imaging media, ultrasound contrast media, iodinated contrast media, non-iodinated contrast media to mention a few. Next slide, please.

So, to wrap up this presentation, the discovery and the development of new drugs follow a well-defined regulatory path. Which I believe is -- today's presentation is an oversimplification of what basically goes on.

But, from the conception to marketing of application of a drug, FDA engages with sponsors to optimize drug development.

And for radiopharmaceuticals and contrast agents, NDA and labeling regulations, we should refer to 21 CFR 314, and 21 CFR 201.

Thank you.

MS. DIMMICK: Thank you, Frank. Next up, we have Katie Tapp. Dr. Tapp is a medical physicist on the Medical Radiation Safety Team at the U.S. NRC.

Dr. Tapp?

DR. TAPP: Thank you, Lisa. Today I'm going to talk about medical use licensing for the Nuclear Regulatory Commission. I'm going to go over the slides fast but there will be some examples on the slides that you can look at.

Next slide, please. Through the licensing process the U.S. Nuclear Regulatory Commission authorizes an applicant to possess, use, process, export and import nuclear materials and waste and handle certain aspects of their transportation.

As Dr. Howe mentioned earlier, the NRC regulates a lot of different types of uses of nuclear material but the focus in 10 CFR 35 contains requirements and provisions for the issuance and licenses authorizing the medical use of nuclear material.

Next slide, please. NUREG-1556, Volume 9, Revision 3 contains the guidance that licensees and applicants can use for preparing applications for the medical use of nuclear materials. To apply for a license, applicants should complete and file an NRC form 313 to the appropriate NRC region or agreement state.

Next slide, please. A medical licensee needs at least 1 individual authorized to use nuclear material for medical purposes. This individual is known as an Authorized User. An Authorized User is defined in 10 CFR 35 as a physician, dentist, or podiatrist who meets training and experience

requirements listed in 10 CFR 35 for specific medical use, and is listed on the NRC or Agreement State license or permit authorized to use nuclear material for medical use. An NRC Form 313a can be submitted with license applications to document individuals who meet the training and experience requirements listed in 10 CFR 35.

Next slide, please. 10 CFR 35 has several subparts. The first three subparts A-C provide the general information, administrative requirements, and technical requirements for all types of medical uses.

Subparts D-H have specific requirements for specific uses and they provide the specific requirements such as training and experience requirements, and health and safety procedures for these specific uses. I'll cover each of these subparts further in the presentation.

Subpart K (35.1000) is known as other medical uses of nuclear material. This is a subpart that allows for uses that are not captured in other subparts.

Next slide, please. The first specific subpart is Subpart D, 35.100. This subpart provides the regulations for update, dilution, and excretion

studies of unsealed byproduct material for which no written directive is required. This is for administration of small (usually microcuries) quantities of byproduct material, generally by intravenous injection or oral administration.

Next slide, please. The second subpart is Subpart D, 35.200. This provides the requirements for imaging and localization studies using unsealed by product material for which no written directive is required. This is for administration of usually millicurie quantities of by product material to create images. One example would be an intravenous administration of 20 to 25 millicuries of technetium-99m HDP for uptake in bones.

Next slide, please. 35.200 also provides specific requirements for generator breakthroughs. There are two types of generators listed in 35.200. The first is the moly/technetium generator, and the second is Strontium/rubidium generators. The breakthrough limits for other types of generators are evaluated on a case-by-case basis and the limits are listed in guidance in 35.1000 at this time.

Next slide, please. The next subpart is Subpart E, 35.300. this is for therapeutic use of

use of unsealed byproduct material for which a written directive is required, normally for therapies. There are three categories.

The first is oral administration of Sodium Iodide-131 requiring a written directive in quantities less than 33 millicuries. This does contain one example which is more of a diagnostic which is 2-5 millicuries of whole-body scan for thyroid carcinoma patients. Also, as an example would be 7-30 millicuries for treatment of hyperthyroidism.

The second category would be oral administration of sodium iodide 131 in quantities greater than 33 millicuries. The final category would be parental administration of any radioactive drug used for primarily its electron emission, beta radiation, alpha radiation, or photon energy less than 150 keV.

Next slide, please. Subpart F, or 35.400, provides the requirements for manual brachytherapy, including temporary and permanent sealed source implants. An example would be a temporary intracavitary Cs-137 implants for gynecological cancers.

Next slide, please. Subpart G, 35.500,

contains requirements for sealed sources for diagnosis. One important note is Iodide-125 seeds used for tumor localization and excision is not considered under 35.500, but is instead licensed under 10 CFR 25.1000 because 35.500 did not cover all the conditions for this type of modality.

Next slide, please. Subpart H, 35.600, contains the requirements for Photon Emitting Remote Afterloader Units, Teletherapy Units, and Gamma Stereotactic Radiosurgery Units. This subpart contains specific calibration and spot check requirements for these units. Recent GSR units have been updated that the specific requirements in 35.600 could no longer be met.

An example of this would be the calibration of relative helmet factors. As recent GSR units no longer have helmet factors, they need to be licensed under 35.1000. Examples that are included in 35.600 are the Gamma Knife Model C, High-Dose Rate Remote Afterloaders, Low-Dose Rate Remote Afterloaders.

Next slide, please. Subpart K, or CFR 35.1000, is a subpart that captures other medical uses of nuclear material. This is the subpart, as I mentioned earlier, that captures uses that do not fit

under the earlier subparts. If a licensee wishes to use a modality or medical use that does not fit into the other subparts, they may do so under this regulation. They would do that by applying and submitting the information as required by licensing under 10 CFR 35.12(b) through (d); and

The applicant or licensee would have to receive written approval from the Commission in a license or license amendment to use this material in accordance with the regulations and specific conditions the Commission considers necessary for the medical use of the material.

Next slide, please. The NRC develops licensing guidance to list the regulations and specific conditions for radiation protection that the Commission has evaluated and considers acceptable to use specific medical uses. The NRC works closely with the FDA, manufacturers, early users, and Agreement States to develop these guidance documents.

License guidance is not necessary to issue a license for a 35.1000 medical use but it helps to make sure the licensing process is efficient between the NRC and licensees. It is very beneficial for manufacturers to contact the NRC early to start working on this guidance to help make sure efficient

licensing of the 35.1000 modality.

Next slide, please. In the interest of time, I'm just going to leave this slide up which provides current examples of 35.1000 modalities. This is where we have licensing guidance currently already available for licensees to use to request approval or authorization to use these medical devices and drugs.

Next slide, please. This concludes my presentation and hopefully I caught up some time. Please ask questions if I went through something too fast. Thank you.

MS. DIMMICK: Thank you, Dr. Tapp.

Just a reminder for everyone. If you have questions for any of the presentations, please submit your questions to the Chat.

This concludes Session I and we'll pose questions to the Session I speakers at the panel discussion after Session II.

Now we're ready to begin Session II. Session II will discuss Novel Radiopharmaceuticals, standards development, product quality considerations, and supply and demand.

Our first speaker is Marc Garland. Dr. Garland is a program manager for the Isotope Program

operations and the deputy director of the DOE's Isotope Program.

Dr. Garland, welcome.

DR. GARLAND: Thank you, Lisa.

MS. DIMMICK: And your audio is good.

DR. GARLAND: So I'm Marc Garland. I'm with the Department of Energy Isotope Program. What I would like to do in this presentation is give you a very brief overview of who we are, what we do, our development, our production and distribution of isotopes, our development of model radioisotopes.

Then I'll focus on one isotope in particular, actinium-225 because it brings up a number of issues that are relevant to this workshop in assisting in the advancement of model radiopharmaceuticals and radiological devices.

Next slide. The Department of Energy Isotope Program produces and distributes radioactive and stable isotopes that are in short supply, those that are not readily available from private industry. That includes, as you heard from the NRC, byproducts, any surplus material, and then the related isotope services such as custom manufacturing of the chemical forms of different isotopes.

We also maintain the infrastructure

that's required to produce these isotopes to be able to supply priority isotope products and services. Then a significant component of our program is to conduct R&D to develop new and improved production techniques to be able to make novel isotopes available to the community.

Down at the bottom you see another thing that we really put a lot of emphasis on is to reduce the U.S. dependency on foreign supplies if isotopes. The history is what's happened with Moly-99 is a good example of why the U.S. should not be entirely reliant on foreign supplies of isotopes.

Next slide, please. So our program does have sole authority for the producing and distribution of isotopes on behalf of the Department of Energy unless other legislation dictates otherwise so the other legislation that would dictate otherwise, you see the examples down at the bottom in red.

Moly-99. The responsibility to develop domestic production of Moly-99 legislatively was given at the National Nuclear Security Administration, part of the Department of Energy, because of the historic use of highly enriched uranium for the production of Moly-99, and then NSA

has the direction to eliminate the use of highly enriched uranium.

Also, plutonium-238 is given to the Office of Nuclear Energy who works with NASA to provide the power sources for space missions. Then special nuclear material for weapons is also in NNSA.

Next slide, please. This is an overview of the Department of Energy's efforts. I really won't go through this exhaustively in the interest of time, but to point out that we have major accelerator facilities at the Los Alamos Major Proton Accelerator facility at the Los Alamos National Laboratory in New Mexico.

The Brookhaven National Laboratory out on Long Island. For many years the primary products of those accelerator facilities for strontium-82 and germanium-68, the production of which the Department of Energy initiated. We fostered the development of products by providing those isotopes for decades.

Now that the market has matured to the point where it has attracted private sector investment in developing production, that has transitioned into the private sector which ideally the Isotope Program looks at that as a success story. We're here to develop novel isotopes and ultimately

when they are commercially viable have a private sector take over.

We also have an electronic accelerator at Argonne National Laboratory which we have stood up production of Copper-67. We're bringing in accelerator/cyclotron facilities at universities mainly for the production of boutique isotopes that are more economically produced at the university than a national lab the first of which was the University of Washington producing Astatine-211. We also have high-flux reactors at Idaho National Laboratory that produces high specific activity Cobalt-60 for gamma radiosurgery.

At Oak Ridge National Laboratory, the high-flux isotope reactor you can see produces a number of isotopes for medical applications. Also, the University of Missouri is part of our program to produce research quantities of lutetium-177 for drug development, and selenium-75 as a biological tracer.

Next slide, please. So the Department of Energy Isotope Program is based in the DOE offices in Germantown, Maryland. We manage all those facilities that you saw on the previous slide. We also have the National Isotope Development Center which handles all our business affairs. That's

staffed by contractors at the Oak Ridge National Laboratory. They handle all contracts with our customers. You can see that they have expertise and transportation, quality assurance, communications.

They deal with cross-cutting technical issues. They do marketing and our market assessments. They are the primary point of contact for customers such as yourselves. Customers also maintain technical discussions with the sites, the ones who know the technical details of the isotope production.

WWW.isotopes.gov is our website. You see the front page there. I would encourage you to the green button up at the top to use to get on our mailing list. You'll get notices of isotope availability such as when we make batches of Copper-67. There are other novel isotopes, all kinds of other relevant information about isotopes.

Down in red I would like to point out that a lot of people at the agencies and drug developers that are participating here had been dealing with our manager for quality assurance and regulatory affairs Ariel Brown. Ariel left the program but I'm glad to announce that Jennifer Cross joined the program last week. All of you will have

an opportunity to meet Jennifer as she takes over responsibilities for the things that we're going to be talking about today.

Next slide, please. One of the focuses of our program has been the development of alpha emitters for therapy. For many years we've been producing actinium-225 and bismuth-213. As I said, I'll get into more details of that about where we're headed on those two isotopes.

As I mentioned, we've also started producing Astatine-211 at the University of Washington. We're bringing in other university facilities to make astatine. We produce Lead-212, Bismuth-212 generators for targeted therapy development. We supply thorium-227 and radium-223 from actinium-227 cows that we have again for targeted therapy development.

I'll point out, while I don't show it here, we also provide the actinium-227 commercially for Bayer's drugs. Finally, on this slide you'll see we're developing production of uranium-230, thorium-226 generator for targeted therapy using thorium-226.

Next slide, please. So this is a summary of actinium-225 which I'll go through quickly. It's been very high priority for development of alpha

radioimmunotherapy for a long time. Since 2009 when we stood up they are a component of our program. We've been a world leader in the development of production of actinium-225.

ORNL has been extracting actinium-225 from thorium-229 since the mid-90s. We can produce up to 1,200 millicuries per year. Because of the logistics of the frequency of milking the thorium-229 we typically will produce about 1,000 millicuries per year which is the entire U.S. supply and well over half the world-wide supply of actinium-225. As you'll see in the next slide, that supply just can't support clinical trials and approved drugs.

We've been going forward with developing additional production capacity for actinium-225 most prominently through the development of high-energy proton accelerator production of actinium-225 which we started in 2017.

Over on the right you'll see that stage 1 of that project is complete. That was where we were developing 50 millicurie batches of actinium-225. We're now in stage 2 with a goal of developing 10 to 100 millicurie batches. We're already at 150 millicuries per batch.

The goal of the final stage, stage 3, is

to increase production up to one-curie batches. The program is also investigating other production routes for actinium-225 and its parent thorium-229 that you see listed in that bullet.

It's important to point out the product is available now. The cow product is fully subscribed but the accelerator product is not. As you can see, we are even scaling up production, much greater production from the accelerator route in the thorium-229 cow route.

Next slide, please. This I'll just go through quickly. The current world-wide supply of actinium-225 is possibly up to 1700 millicuries per year. As you can see over on the right, approved drugs and robust research into new drugs will require hundreds of curies per year. The thorium-229 derived material is just not sufficient.

Next slide, please. This is a summary of the production routes. I said there were various production routes that we're looking into. This is a summary of those. As shown in the large text in bold, I'm going to focus on the high-energy proton production of actinium-225 because it brings up the issues that I'd like to talk about that are relevant to this workshop.

Next slide, please. So this slide shows the production of actinium-225 as a function of proton energy showing that the higher energies you get much better production. And also showing that -- I'll show on the next slide where we do the targeted radiation at Los Alamos and Brookhaven and then target processing at Oak Ridge National Laboratory. The accelerators we're using at Los Alamos and Brookhaven ultimately could get to 2,000 millicurie batches.

Next slide, please. So, again, targets are radiated at accelerator facilities. In the middle at Los Alamos is the Isotope Production Facility under the MeV Proton Facility. On the right Brookhaven Linac Isotope Producer (BLIP) which has protons of energy up to 200 MeV. Los Alamos and Brookhaven don't currently have facilities to be able to process those alpha-emitters so the targets are sent to Oak Ridge National Laboratory which, as you can see, has 25 years of experience in the chemistry of these alpha-emitters.

Next slide, please. So one of the issues that comes up with the accelerator production of actinium-225 is not only do you get actinium-225 by bombarding thorium-232 with protons, you also get

actinium-227 which is a much longer-lived isotope by 22 years.

As you can see off on the right, by activity it's very small. At the end of bombardment typically less than .2 percent. As the third bullet shows, it created a set of challenges like customer perceptions and facility licensing issues, patient waste. As I say in the red text, these challenges are not unique. There are other isotopes, other drugs that have addressed these issues for the drug products.

Next slide, please. We have done a lot of work in labeling dosimetry, toxicology, biodistribution studies to give an indication of what the performance of the accelerator actinium-225 product is relative to thorium-229. One thing that labeling research has found at Brookhaven National Laboratory is that the labeling efficiencies of the two products are comparable.

The performance of the accelerator product on bismuth-213 generator is the same as the performance of the cow-derived material on a generator. The impact of the small bioactivity content of actinium-227 on dosimetry is shown to be small. As I'll get into in just a minute, that has

to be demonstrated on a drug-to-drug basis.

So some challenges with respect to the logistical issues with the actinium-227 co-product on facility licensing. Specifically, NRC requirements for decommissioning funding plans. Also, the discussion is ongoing with the NRC to possibly get an exemption to those requirements. There's precedent for that, for the germanium-68 generators. Also possibly patient waste, although that doesn't look like it's going to be an issue for approved drugs.

Next slide, please. So where we are with our actinium-225 products. We submitted a DMF last December for the accelerator product. For the cow product we're going to file a DMF for that by the end of this year. We've had ongoing interactions with FDA on both products and we're committed to make these products available to our customers and to the medical community in helping them address issues associated with the use of these products.

Next slide, please. So here's a summary of the issues. The NRC licensing has financial assurance requirements for isotopes with half-lives over 120 days. I show a list of some things that are medically important or -- isotope medical

applications that could fall under those rules.

NRC Petition for Rulemaking came up in response to germanium-68 is seeking to update the appendix that has a list of the nuclides which unfortunately at this point doesn't include those isotopes over on the right leading to very conservative limits for the use of those isotopes.

I mentioned patient waste and disposal needs to be addressed. Impurities need discussion. We need to talk about how the FDA and the NRC would look at long-lived impurities such as the actinium-227 and the accelerator-produced actinium-225, or even the lutetium-177m in the carried-added production of lutetium-177 which we may hear something about in Maurizio's presentation a little bit later.

cGMP is an issue that has been touched upon by some of the previous presenters of when do we need to go to GMP production. Do we get a DMF. When do we need a DMF. Do we establish a DMF and go to cGMP production which is very expensive, or later on possibly build QA requirements into drug developers IND.

Those are all discussions that we're having with the FDA and the NRC. As I mentioned,

ultimately those will be addressed on a drug-by-drug basis and we are more than happy to participate in the discussions that drug developers need to have with the FDA and the NRC.

Next slide, please. So in summary, routinely producing actinium-225, it's available. We've been distributing quite a bit of it. We're working with companies and hospitals in preparation for clinical trials and submitting DMFs and dealing with issues associated with the actinium-227. We're also working with the FDA and the NRC to resolve any issues that there might be in accelerator actinium-225 and any other novel radioisotopes inequities.

Thank you for your attention and thanks to the NRC and FDA for the opportunity to present.

MS. DIMMICK: Thank you, Dr. Garland. Reminder, if you have questions for Dr. Garland, please submit them into the chat and we'll bring them up during the Q&A session, the panel discussion.

Next up is Denis Bergeron. Dr. Bergeron is a research chemist in the Radiation Physics Division at the National Institute of Standards and Technology.

Dr. Bergeron.

DR. BERGERON: Good morning, everybody.

MS. DIMMICK: And your audio is fine.

DR. BERGERON: My name is Denis Bergeron. I'm with the National Institute of Standards and Technology. I work on the Nuclear Medicine Project which is in the Radiation Physics Division. I'll be talking about development of physical standards for novel radionuclides, especially focusing on some recent experiences with alpha emitters.

Next slide, please. So I think the reason I was invited here today is because of the NIST role in the radium-223 story. Everyone here probably knows radium-223 dichloride as a first-in-class alpha-therapeutic. Where NIST comes into the story it goes back to 2005 when Algeta, the company shepherding radium chloride through clinical trials at the time, approached NIST at the direction of FDA to develop measurement standards.

The reason for that is that we want standard NIST-traceable activity that allows for accurate and precise dosimetry and the establishment of dose-response relationships. We want a standard so that the activity measurements, the dosages, measured in clinical sites, and pre-clinical sites, are the same everywhere all the time. NIST traceability would do that.

NIST did, in fact, develop calibration capability and we reported on settings for radionuclide calibrators, dose calibrators. I'll mention that Bayer now participates in the NIST Measurement Assurance Program so that new shipments of Xofigo product go out to clinical sites include a NIST-traceable calibration source so that every dosage is measured traceably back to NIST.

Next slide, please. So why come to NIST? The NIST mission is to promote U.S. innovation and industrial competitiveness by advancing measurement science, standards, and technology in ways that enhance economic security and improve our quality of life. I would say that activity standards for alpha-emitting radionuclides for medical applications fall squarely within this mission.

Next slide, please. And the mission itself, as far as NIST goes, comes all the way back to the U.S. Constitution where the federal role is established in Article 1, Section 8 giving Congress the power to "fix the standard of weights and measurement." This makes sense when we remember that our Founding Fathers were enlightenment thinkers who certainly understood the importance of standards for measurements to further commerce, trade, and indeed

scientific innovation.

Next slide, please. So NIST is responsible for maintaining the SI and when it comes to activity, NIST defines the becquerel which is the derived SI unit for activity. The becquerel means decays or disintegrations per second of a specific radionuclide. I'll note that 37 megabecquerels are equal to one millicurie and that's the last time I'll say Millicurie, even to this nuc med audience. I also won't say becquerel that much.

At NIST we establish physical standards which are the basis for downstream activity calibrations. Our standardizations are based on measurements with primary methods. When I say primary, I mean something that is internally consistent. It's self-calibrating.

We are not measuring activity using an instrument that's been calibrated with activity. That's a downstream calibration. For the primary standard we have to do something that is totally internally consistent. I'll give the flavor of that can look like as we go on.

Next slide, please. So the way that we establish calibrations and NIST traceability all starts with the source that comes in maybe from a

facility, one of the ones that Marc was mentioning, or maybe from radiopharmacy. We establish links using precision dilutions, gravimetric links between different dilutions where we're adding with the weighing uncertainty less than 0.05 percent uncertainty on those links.

We are able to take a solution, dilute it to a level that's appropriate to measure on clinical dose calibrators, dilute it further to an activity concentration that is appropriate for primary methods which form the base of the pyramid so the dilutions bring us down one side and the measurements take us back up. We have very high precision links across all levels.

Next slide, please. So the primary method that I like to talk about is one that's extremely well suited for alpha-emitting radionuclides and that's the Triple-to-Double Coincidence Ratio, or TDCR, counting method of liquid scintillation spectrometry. The liquid scintillation part means that we're putting a sample into an organic cocktail so that we have perfect geometric counting efficiency for our sample.

At NIST we have special three photomultiplier tube system that we built. With our

home-built electronics we can measure scintillation events where we have coincidence in any pair of the photomultiplier tubes, or in all three. We'll call these double coincidences and triple coincidences. If we count them up over a specific period of time and we can get a ratio. That's this triple and double coincidence ratio. The ratio of the count rates is equivalent to the ratio of the triple and double event efficiencies.

Now we can play a trick by varying the efficiency either using techniques of chemical quenching in those liquid simulation cocktails, or doing the simplest thing where we apply what we call gray filters which is really just linking various shades of gray on transparency paper, wrapping it around the LS vial. It's akin to putting sunglasses on our samples. but we can measure at several different efficiency points that way.

By varying that efficiency, we are varying the triple-to-double coincidence ratio. If we plot that out and manage an extrapolation to where the TDCR is equal to one, the only time that the triples efficiency and the doubles efficiency could be the same is if we're counting with perfect efficiency which means that our count rate in those

channels is equivalent to the decay rate coming from our sample which means that we've now realized the becquerel, decay per second, without calibrating to another becquerel.

This is an internally consistent self-calibrating method. Of course, I'll offer this caveat. In practice, things were a little bit more complicated, but we have really good models. Coming into the next page, I'll show you a little bit about what I mean as far as a little bit more complicated.

With radium-224, which is another alpha-emitter under development as a radiopharmaceutical, without TDCR method in the range that we're doing our experiments, we get about 5.65 counts per radium-224 decay.

I'm being asked to speak a little louder. I'll try to hold the mic up.

So the 5.65 comes in because we have a bit of a complicated decay chain which I'll show. But we can calculate the efficiencies that we expect for each decay type in the chain which lets us build a nice model here for our TDCR experiment.

Next slide, please. The decay chain for radium-224 includes four alpha decays and a couple of betas. Those betas don't have perfect counting

efficiency. We have some intricacies with short-live progeny. In the end we're able to build a good model for our method.

I would also note that the complex decay chain the way that the half-lives conspire, it means that it takes about six days to reach equilibrium. We can see that in the plots on the right here where we have a period of ingrowth for the progeny.

On the bottom if we normalize the progeny activities to the radium-224 activity at any given time, we see it takes about six days after chemical separation to reach equilibrium and that would be where we want to make our measurements at NIST when everything has settled down a little bit.

Next slide, please. So coming back to those dilutions that I mentioned earlier, I'm showing just one example from a recent radium-224 standardization to show how complex these experiments can get. The main thing to take away from this slide would be that we have the incoming solution at the top, we have a series of serial dilutions again performed gravimetricly with very tight uncertainties that get us to the sources at the bottom that we can use our primary methods on.

You can see a couple of TDCR labeled

sources on that bottom level going all the way back up to the ampoules with about 25 megabecquerels in each suitable for counting on ionization chambers and dose calibrators.

Next slide, please. In the radium-224 case I've shown here the development of our activity standard where we have several methods including the TDCR which is a primary method. Live-timed anti-coincidence counting which is another one of our primary methods. And efficiency tracing and a couple of gamma-sensitive 4-pi techniques where we have good Monte Carlo models that let us get to precision activity.

In this instance we see we have good agreement across several different methods. I've reflected here in the different colors a few experiments of different measurement campaigns. We get consistent results. In the end, we developed a national standard for radium-224 activity with a combined standard uncertainty less than half a percent. That standard we can then disseminate by ionization chamber or dose calibrator factors and nuclear decay data. All of this work is described in a couple of papers, recent papers by Napoli et al.

Speaking of the nuclear decay data, the

radium-224 presents an interesting case where some of our measurements, specifically high-purity germanium gamma spectrometry measurements, were showing a consistent bias nearly 4 percent on the activity that we were measuring. This indicates that the gamma ray emission probability that we're using probably requires revision. This is something that we investigate.

In fact, in this case we've recently submitted a paper in collaboration with our colleagues at the National Physical Laboratory which is our sister lab in the UK that realizes that revision of the emission probability for this gamma ray and consider some other nuclear decay data issues at the same time.

Next slide, please. So when someone comes to us to develop a new radioactivity standard, what does that look like? We deliver to the customer a NIST-calibrated reference source at the end that allows local calibrations. We provide guidance on clinical calibrations which would typically include benchmark calibrator settings, as well as some investigation and estimation for geometry and composition-dependence.

That's chemical composition of a drug

product, for example. We usually publish our results in the open literature and that includes a review and often an update of the nuclear decay data as in the case I mentioned on the previous slide, emission probabilities.

Next slide, please. The question that we're often asked are, okay, how long does it take to realize a new standard and how much does it cost? Of course, there's a million caveats and it's very difficult given that every becquerel for each nuclide depends on the decay scheme and a lot of other factors. There's nothing that winds up being typical, but there's my weak attempt at quantifying typical with caveats.

How long? If a standard exists, and we have calibration services at NIST, we can provide calibrations within a week or two. If you're coming to us with a new drug product, that's probably something where we don't have a primary activity standard so we would have to engage in campaigns to develop that. In two recent cases we had standardization campaigns spanning six months to 10 months. I qualify that with that's once work starts. Our lead times can be long. Our queue is often deep as it is right now.

Then the how much. When a customer comes to us, NIST is required to recover costs. That's a difficult thing but in a few recent standardizations, customers have paid between $60,000 to $150,000 for the delivery of a primary activity standard with the framework for subsequent dissemination which means that calibrations of activity down the line are now traceable back to NIST. They are physically meaningful measurements of activity.

Next slide, please. With that, I'd like to just thank the NIST Nuclear Medicine Project Team, especially Dr. Brian Zimmerman, our lead and group leader. And Mr. Jeff Cessna who works with me on primary standards and runs our Calibration Services Program. Drs. Fitzgerald, Pibida, Laureano-Perez, and Colle help us out a lot with our measurements. I'm looking forward to the panel discussion. Thank you.

MS. DIMMICK: Okay. Thank you. We look forward to it as well.

So next up is Danae Christodoulou. Dr. Christodoulou is a branch chief with the Office of New Drug Products at the FDA.

Danae, when you're ready.

DR. CHRISTODOULOU: Can you hear me?

MS. DIMMICK: Yes. Your audio is fine.

DR. CHRISTODOULOU: Great. Good morning, everyone. I'm Danae Christodoulou and I am the Branch Chief in the Office of New Drug Products that supports diagnostic pharmaceuticals.

Next slide, please. FDA is committed to ensuring availability of safe, effective and high-quality medical isotopes and imaging drugs. This comes from our mission statement.

Next slide, please. In terms of pharmaceutical quality, a quality product of any kind consistently is supposed to meet the expectations of the user.

If we can skip a couple of slides beyond this slide, please. Medicines are no different and patients expect to have safe and effective medicine with every dose they take. This is all about drug product quality.

Let's skip to the slide with the outline, please. In my talk today, I will be talking about some critical quality attributes of radiopharmaceuticals and how in our evaluations of new drug applications we establish this critical quality attributes.

The most important aspect is to establish

the identity of the radiopharmaceutical bridging various formulations that have been used in the clinic with the commercial formulation, and also regulate the production of radionuclides. Finally, to establish with CMC data and support the FDA label of the drug.

In addition, during our evaluation of radiopharmaceuticals, we rely in these inspection assessment of manufacturing facilities and the GMP production of radiopharmaceuticals.

Next slide, please. The drug substance is the entire chemical entity that contains the radionuclide and pharmacophore. The challenges for us chemists is that the drug substance is prepared in situ, not isolated and then directly formulated to the drug product. This is different than any other therapeutic pharmaceuticals.

In addition, the commercial process and the product has to be representative of what was used in the clinic so that we can establish the identity, purity, potency and reproducibility of the drug. As patients receive doses in different health centers, they have to be receiving the same drug, the same identity drug and the same quality drug.

Next slide, please. How do we establish

identity for a radiopharmaceutical? A critical aspect is to establish a cold reference standard. This is particularly important with metal complexes as radiopharmaceuticals. For example, in the case of gallium-68 Dotatate the natural gallium Dotatate complex has been established and characterized.

Usually from FDA perspective we like to see at least two orthogonal methods of characterization of the cold reference standard. One of them has to be HPLC and the other can be NMR spectra and mass spectra.

Next slide, please. The radiotracers today have evolved to very sophisticated molecules and, therefore, a rigorous physicochemical characterization reference standard is appropriate. Sometimes with respect to the metal complexes we observe the stereoisomers. This can be resolved by suitable HPLC assays. A reference standard can be helpful in establishing a mixture of isomers that can be qualified as a drug substance, and determination of the isomeric ratio.

We encourage physicochemical characterization in establishment of reference standards. Usually this can be isolated from a high purity GMP batch. The referred standards have to be

authentic and stable.

Next slide, please. After production of the drug substance, the drug product is formulated. When we receive new drug applications, one of our challenges is to establish that the commercial formulation is really representative of what was used in the clinic. Ideally, we would have the same commercial formulation and the same formulation used in the clinic, but this is not practical when we have multi-center trials that involve also different stages of development.

When we evaluate the new drug application, we have to take into consideration a side-by-side comparison of all the ingredients in formulation. Not only the drug substance consideration, but also sequence in active ingredients and those should not affect the pH of the formulation.

Next slide, please. This is an example of some clinical drug product to commercial drug product. In this case in the clinical drug product no stabilizers were used, just a buffer or water. Critical quality attributes are radio concentration, mass, volume, specific activity, and so on.

Next slide, please. Production of

radionuclides also is regulated by the FDA. These are components of the radiopharmaceuticals. My colleague John Amartey will further discuss production of radionuclides. Usually technology used is a cyclotron nuclear reactor or a generator.

Our expectation is that the production of radionuclides will be either included in the NDA application, or in a cross-reference Type II Drug Master File. That's a very common route because a lot of the technologies have proprietary and then a different company may be producing radionuclides than the NDA applicant.

Usually we would like to see some nuclear chemistry characteristics of the parent and daughter radionuclides, radiation emissions half-lives. Then the composition of the parent and daughter radionuclides and their specifications.

Next slide, please. So here I would like to acknowledge the contributions of the Isotope Program. Marc Garland just presented us with the different research and also production of medical isotopes. Actually, in the supply chain sometimes the isotope program becomes a very important contributor because when we have shortages they may be able to produce a certain radioisotope until the

market stabilizes.

Next slide, please. Finally, the diagnostic and therapeutic radiopharmaceuticals will have the FDA label prescribing information that Dr. Lutterodt talked about earlier today. The CMC data actually has to support several aspects of this label. In the dosage administration, especially in processes where we have a cheat that is to be constituted with the radionuclide, then we need to have details of the radiolabeling procedure that frequently we will see in the prescribing information. In the CMC section of the application, we need to have supporting information and details of this radiolabeling procedure that has been validated.

In addition, in the description section we will see the chemical characteristics of the radiopharmaceutical and in the how supplied section we will see information as to how the drug product is presented and what is the shelf life of this radiopharmaceutical.

We also evaluate the product container labels and the shield labels.

Next slide, please. I'm going to skip to the next slide, please. As I said earlier, in the NDA application we would like to have supporting

information for any radiolabeling reaction that will be forming the radiopharmaceutical. All of these details are part of our CMC assessment. So we also like to see the executed batch records in the application. Typically, we ask for three validation runs. All of this information will support the label.

Next slide, please. So additional labeling materials are user manuals, especially for very complex systems such as computer-driven generators as the radiogenic system or cardiogenic. This new technology study includes complex instructions for the end user.

The safe use and delivery of the accurate dose should be accurate and they should be consistent. They are very important for the cleaning-up practice. Very often human factors studies account for end user ability to perform the system manipulations according to labeling so the FDA may require human factors studies for such complex technologies that we currently encounter.

So the user manuals actually undergo interdisciplinary review of the FDA. Other than the chemistry section and the instructions we will have clinical review of these user manuals and everything

has to be understood by the end user for the safe use of the product. Also sometimes complex systems require recertification or they require maintenance instructions that the company may be responsible for.

Next slide, please. So NETSPOT and LUTATHERA is a theranostic pair that we approved the last few years and it was an example of two radiopharmaceuticals that FDA and NRC collaborated.

Next slide, please. This is the structure of gallium-68 dotatate which is a metal complex. This metal complex appended the formicle that targets the somatic receptors.

Next slide, please. These are some of the characteristics of the gallium-68. One of the previous speakers mentioned gallium-68 is a radionuclide, not a radiopharmaceutical itself. In the case of gallium dotatate this had to be qualified by validation runs and reconstitution with the radionuclide with an expert kit. Other generators also had to undergo the same validations.

I would like to mention here that in INDs we permit generators that may not be GMP in early stages. However, for an NDA submission the expectation is that the generator is produced under GMP and we have inspection assessments for those.

Next slide, please. This is an excerpt from the NETSPOT package insert, the FDA label. What FDA and the NRC agreed upon was the breakthrough limit of .001 percent, a very stringent limit for the long-lived germanium. That was based on process capability and safety of this limit.

Next slide, please. Lutetium is prepared in a nuclear reactor and there are two different methods for production of lutetium. The NRC licensed lutetium-77 according to existing guidance so they did not have to issue a special license for lutetium-77.

Next slide, please. This concludes my talk. The FDA is committed to timely reviews of safe, effective and high quality medical isotopes and radiopharmaceuticals, encourages innovation and engages with stakeholders and sister agencies to make available new technologies to patients. We leverage data in IND studies for NDA submission.

With respect to sufficient CMC information the identity of the radiopharmaceutical has to be established but also critical CMC information such as chemical characterization of new pharmacophores, radionuclides and other components on the radiopharmaceutical. CMC information supports

product labeling. Thank you.

Next slide, please. I look forward to questions in the panel. Thank you again.

MS. DIMMICK: Okay. Thank you, Danae. I just wanted to announce that we are a little bit behind in our schedule, so I think we're going to work through the break and not have a break at 10:20 to 10:35.

So we're going to continue on with the presentations in Session II, and then close it out with the Panel discussion and not include a break. So if you need to take a break, you know, please, this is a virtual conference, so you're able to step away.

Okay, so our next speaker is John Amartey. Dr. Amartey is a CMC reviewer at the Office of New Drug Products and the Office of Pharmaceutical Quality at CDER. Dr. Amartey?

DR. AMARTEY: Hi. Can you hear me?

MS. DIMMICK: I can hear you.

DR. AMARTEY: Okay. Good. So I'll be talking about some special quality considerations for the gallium and technetium generators. Next slide, please.

Okay, as an introduction, the utility of

the moly-99 tech-99m generator is well-established in nuclear medicine practice. And it's used in greater than 80 percent of diagnostic procedures by SPECT imaging globally.

Although the germanium/gallium generator was described over half a century ago, it has become prominent in recent years because of molecular imaging by PET and the concept of theranostics, where the diagnostic and the therapeutic agent have developed side by side.

Germanium-68/gallium-68 generator has been qualified through FDA approvals of gallium-68 diagnostics since 2016. Next slide, please.

So as I said, simple outline for my speech. I'll be talking about components of these generators, eluate and radionuclide quality and reactivity, stability and sterility issues, and a conclusion. Next slide, please.

So in general, these generators are made of a column of material, which would be a glass or plastic, piece of glass or plastic, and then an absorbent, a solid matrix with high selectivity for the parent radionuclide. And these are now housed in a lead-shielded container.

Additionally we come across this

terminology, eluant and eluate. Now, the eluant, in this case, will be a solution that is used to wash out the radioactivity of the daughter from the generator column.

Now, what comes out of the generator column? It's a solution containing the radioactivity. And that's the eluate.

And this can be used alternatively as a self -- I mean, actually as a radiopharmaceutical. For example, the technetium-99 generator, the solution that comes out is the pertechnetate, which in itself has an indication. Next slide, please.

So in these two generators, for -- germanium-68 is the parent radionuclide for the generator-derived gallium-68, which is the daughter. The parent has a half-life quite long, 270 days. The gallium-68 has a half-life of only 68 minutes.

The moly-99 is the parent radionuclide for the generator-derived technetium-99, which is now the daughter. The parent has a half-life of 66 hours. The daughter has a six-hour half-life. Next slide, please.

Now, normally I think we had -- Dr. Danae mentioned this slide was come on through our presentation. The technologies for producing these

pure radionuclides are either from a cyclotron, or high-energy accelerator, or a reactor. Our target material is irradiated to produce the parent radionuclide for the generator.

And, again, this was mentioned in the previous presentation, that in an NDA application, the cross-referenced Type II DMF can be cited for complete CMC information to be provided in the application.

This DMF to contain the nuclear reaction describing the formation of the daughter or the parent radionuclide would start from the parent. The decay modes for these radionuclides should be also mentioned.

And the chemical form and composition of the parent and the daughter, with specifications, has to be included in this application. This is not exhaustive, but other information is also required in the application. Next slide.

So for the production of germanium-68, a parent radionuclide for the manufacture of germanium-68/gallium-68 generators is by proton irradiation of a target material in a cyclotron.

Basically, pure gallium metal can be used as the starting material for producing the parent

radionuclide. Purity of this target material should be controlled. It has to be of high quality to avoid production of unwanted radionuclidic impurities.

Or it can be an alloy, such as the gallium and nickel alloy. The composition of this alloy should be specified and controlled in the application.

So in effect, high-quality target materials are required. There are a limited number of suppliers of this parent radionuclide, as was mentioned by the previous presenter. Next slide, please.

So in the case of the gallium generator, the absorbent material has to be stable, and should not undergo degradation in the high radiation field of the generator. In this case, titanium dioxide has been the absorbent of choice.

Now, high-quality target materials, as I mentioned in the previous slide, have to be used to produce the parent radionuclide. A solution for loading the generator is the gallium tetrachloride solution. And it has to be processed under GMPs.

The elution efficiency of the generator should be high enough and reproducible, so that enough radioactivity can be washed out of the

generator to make the application and the subsequent production of the product reliable.

The eluent quality and reactivity should be very high, in the sense that they are setting trace metals present in the eluent would interfere with the reaction involving the gallium and the chelator that is used in most of these places.

The control for the potential breakthrough materials, in this case, for the gallium generator, it is the parent germanium-68 which, from time to time, may leach out. And also, titanium, in this case, has not been a problem, from what we have seen so far.

But the geranium breakthrough has to be controlled. And like Danae said, it's been established that 0.001 percent of the germanium breakthrough is attainable. So that's the limit that has been set.

Sterility assurance over the shelf-life of the generator. The parent has a half-life of 270 days, and therefore the shelf life of this generator is a year, or that time frame. Next slide, please.

Okay, for the moly generator, which -- moly-technetium generator has been around for a long time, and, again, the material source of the moly has

to be of high quality to avoid contaminants. The absorbent material for this generator is alumina.

The elution efficiency, again, should be high and reproducible, so that enough activity is attained for intended application. The eluate quality and reactivity should be assured.

In the technetium generator, this eluate that comes out has been pertechnated, which can be used to label kits for radiopharmaceutical production. The reaction may involve certain agents, which has to be reserved, in the sense that, in this case, you don't have to have an oxidant in the eluate.

To control potential breakthrough material -- alumina or the moly, again, can leach out from the generator column, and this has to be controlled. Sterility over the shelf-life, again, should be assured. Next slide, please.

So for some regulatory considerations, the relevant radionuclidic impurities should be justified for safety and control. And in these two cases, I mentioned the germanium breakthrough and then the alumina and the moly breakthrough.

The equivalency of the generator produced, and then gallium produced, from newer technologies, have to be established, in the sense

that the solution should be able to successfully and consistently label approved kits with acceptable specifications for the drug product.

There's no USP monograph for the gallium chloride solution for radiolabeling, unless there's a European monograph which sets acceptable specifications of the gallium chloride solution.

New gallium-68 sources to an approved product are added through prior approval supplement. And we have seen a few of those in the approved product area. Next slide, please.

Okay, again, I had mentioned this earlier, but I want to emphasize that for NDA submissions, the generator has to be processed under cGMP, and the generator has to be qualified with the proposed approved kits.

Again, Type II DMF or a complete CMC information may be provided in the NDA application. However, non-cGMP generators may be used for IND studies.

In this case, the applicant or the sponsor may provide a DMF or a certificate of analysis of the generator from the vendor. And that is adequate for IND application. Next slide, please.

So for a conclusion, this generator has

to be robust, in the sense that the stability and selectivity of the solid support has to be very high to retain the parent radionuclide and easily release the daughter from the column.

The elution efficiency should be high enough, and consistent, to produce enough activity for the energy use. The sterility and reactivity of the eluent, the ability of the eluent to label approved radiopharmaceutical kits, and with high efficiency, is required.

And, again, the microbial issues have to be very taken into consideration. Trace metal levels and radionuclidic impurities have to be controlled and regulated.

So recent FDA approvals and clinical practice highlighted critical quality and safety attributes for these generators. And the FDA continues to engage with stakeholders and sister agencies to ensure that novel technologies become available to patients. Next slide. So that's the end of my presentation. Thank you.

MS. DIMMICK: Okay. Thank you, Dr. Amartey. And just a reminder, if there are any questions that you want to ask any of the panelists, please submit them to the chat and select all

panelists.

In our last segment of this session, we'll talk about product quality considerations, recent experiences with radiopharmaceuticals, approval and licensing.

And the first speaker is Hugh Evans. Hugh Evans is Director and Company Secretary at Eckert & Ziegler Radiopharma, Inc. Welcome, Hugh.

MR. EVANS: Good morning, everybody. I I'm Hugh Evans. I'm the Company Officer of Eckert & Ziegler Radiopharma. This is a subsidiary company of the Berlin, Germany-headquartered company Eckert & Ziegler AG.

I am the company representative responsible for liaison with the FDA and the NRC for approvals and licensing of our products. And we have products approved in both Europe and the USA.

And in my short review today, I will often contrast and compare certain regional differences experienced when pursuing the approval and licensing of our GalliaPharm germanium-68/gallium-68 generator. Next slide, please.

From our preliminary meeting with the FDA, we had a -- we confirmed that the gallium-68 chloride eluate would be considered a drug substance,

requiring the submission of a Type II DMF. However, subsequent early questions from reviewers were focused on PET drug product.

However, fortunately, with help from the CMC staff, we quickly realigned the questions back to the relevance of the product as a drug substance. As expected, germanium-68 breakthrough was an area of significant interest, as mentioned by John Amartey.

And it is relevant to indicate here how we in fact benefited from experience in registering the GalliaPharm generator with the European Medicines Agency. The EMA considered the gallium-68 chloride eluate from the generator as a drug product, while still restricting the use to in vitro radiolabeling.

And we were able to benefit from the established germanium-68 breakthrough parameters that were published in the European pharmacopeia, as also referenced by John Amartey.

As a drug substance, no such monograph is available in the U.S. However, the European standard was accepted by the FDA. The inherent difference regarding the regional classifications of drug substance and drug product does engender some issues.

Within the EU, it's possible to have the GalliaPharm approved for radiolabeling carrier

molecules that are specifically developed and authorized for radiolabeling with gallium-68.

The FDA requires that each NDA application is specifically approved for use with the GalliaPharm, so there is no generic approval of generators for drug production by radiolabeling. Next slide, please.

In the reviewing process, there was a great focus on the feedstock germanium-68 production and associated targetry. At one stage, we were even asked for geographical source information on the ores used to produce the metal targets.

The maintenance of lifetime sterility of the generator eluate was necessarily of major importance during the review, and our initial approval was limited to a maximum number of elutions or a one-year shelf life.

A later amendment for an increased maximum number of elutions was achieved via the submission of further data. Interestingly, the EMA imposed no such limitations on the number of elutions during the approved shelf life.

Even with the tight specification of feedstock germanium-68, and resultant gallium-68 eluate, it has been necessary to submit amendments to

the GalliaPharm DMF for each new germanium-68 feedstock supplier.

And the NDA owner is required to conduct three radiolabeling validation trials on the GalliaPharm loaded with the new supplier's feedstock germanium-68.

Potential new NDA holders find it somewhat frustrating that, despite the highly specified feedstock analysis of the germanium-68 and the eluate specifications, both chemical and radiochemical, equivalent to that which is already approved, that they still have to repeat the radiolabeling exercise to prove equivalency.

Feedstock germanium-68 of cGMP production and quality standard to meet existing regulations is indeed a rare commodity. Manufacturing and approving adequate feedstock suppliers have resulted in occasion of feedstock shortages while the approval of alternative suppliers is pursued. Next slide, please.

I now wish to review a few of our interesting occurrences with the NRC experience when approving the GalliaPharm generator. The NRC experiences, in the acquisition of licenses of users of germanium-68/gallium-68 generators, was by no

means plain sailing.

The archaic and unreasonable requirements inherited from the anon days of cyclotron-produced germanium-68 were hampered by the costs and administrative burden of requiring decommissioning funding plans that were focused on the cyclotron production, rather than on the generator users.

Liaison via the Advisory Committee on the Medical Use of Isotopes and the Organization of Agreement States enabled amendments and exemption grants that significantly reduced the burden on potential licensees who wished to begin PET diagnostic imaging using germanium-68/gallium-68 generators.

Direct liaison between NRC staff and Eckert & Ziegler Radiopharma resulted in a legally-binding contract to be established, whereby generators were returned to Eckert & Ziegler at the end of their working life.

The NRC (telephonic interference) to acquire GalliaPharm, perceived somewhat incongruous, that even after receiving the assurance that generators would be returned to the manufacturer at the end of their working life, that the NRC still

requires licensees to carry additional financial assurance over and above the financial assurance existing for decontamination and decommissioning that radiopharmacies require for the general operation of the radiopharmacies.

Thank you. That concludes my presentation.

MS. DIMMICK: Thank you, Hugh. Next up, we have James Harvey. Dr. Harvey is a Senior Vice President and Chief Science Officer at North Star Medical Radioisotopes. Dr. Harvey?

DR. HARVEY: Thank you, Lisa. Next slide, please. Appreciate the time and the opportunity to be part of this important workshop. And based on what I've learned so far, I suggest these clearly continue on a periodic basis.

What I'm going to speak to you about today is our experience with a new moly-tech generator, and how we went through the approval and licensing process, and how some of the lessons learned that we went through could segue into some other future products. Next slide, please.

RadioGenix produces sodium pertechnetate, and is approved by the FDA under a New Drug Application, so I do need to show you the

indication, and -- next slide, please -- the risk information.

I'm not going to read or go through or discuss them in great detail, due to time limitations, but I will note, at the bottom you can visit the North Star website for full prescribing information and all the details on both indication and risk information. Next slide, please.

So what is RadioGenix? RadioGenix is a new approach to producing technetium-99m from non-uranium-based production of moly-99.

This is a new advancement in the industry that allows us to go and produce moly-99 without the use of uranium, and eliminate the proliferation concerns and waste concerns of using the uranium.

It's a multi-step process that starts with target fabrication. We then perform the irradiation and the preparation of the solution that's used on RadioGenix, in Steps 2 and 3.

These two steps are done with our partners at the University of Missouri Research Reactor facility in Columbia, Missouri. And as you can imagine, since these steps are done at the MURR facility, the drug master file was submitted by the Missouri University reactor folks.

And so the process is covered through not only the approved NDA for the system, but also it referenced the Drug Master File filed by MURR.

Once the material is prepared, we fill a source vessel. You see a picture of a source vessel, we refer to it there. It actually also is a Type A container. We put it in a box that constitutes a Type A shipping package.

That material, that container, is shielded and it is shipped to the customer. You can see that we transition from the steps North Star does, in blue, to the steps that are done at the pharmacy, in green.

The customer mounts the source vessel on the RadioGenix system. You see multiple bays on the system. One of the advantages of the RadioGenix system is that multiple sources can be mounted on the system.

The customer can have multiple strengths, and those sources can be in individual states of ingrowth with the technetium products.

So a customer can elute one elution and get a technetium-99m product vial that they can go and make unit doses with, and they can start a subsequent elution from one of the other bays,

because that source is ready to be used again.

So then what does the customer do with the technetium that's generated? They use it to produce unit doses that go to hospitals and clinics for imaging.

When the shelf-life of the product has expired, they send the source vessel back to North Star, where we can reuse the shielded container, after appropriate cleaning.

We can also remove the molybdenum-98 or the molybdenum-100, which is an enriched material, and we can recover it and recycle it for future target use. Today, what is approved does not include the recycling of the material. That is coming -- will be a subsequent FDA approval.

But today, the system is in use in many nuclear pharmacies throughout the United States, on a regular weekly basis, and we have been producing domestic moly-99, for the first time in close to 30 years, now, for almost two years.

So what is our experience, to get to an approval? Next slide, please. We held our first meeting with the FDA in October of 2010. We outlined the approach North Star was planning to take to produce domestic molybdenum-99 without the use of

uranium.

We did our first NDA submission in January of 2013. Through multiple follow-on meetings with the FDA, we clarified what our understanding about the FDA's concerns were in that initial NDA review. We described how we were going to approach answering those concerns.

Subsequently, we received the initial NDA approval for RadioGenix in February of 2018, and we've now had multiple subsequent prior approval supplements approved that invoke some enhancements and improvements to the RadioGenix system and the improved production of non-uranium moly.

Well, we also have a parallel path with the Nuclear Regulatory Commission and the Organization of Agreement States, through a working group that was formed by those entities.

We began discussions with that group, although largely led by the NRC, as early as 2013, relative to a guidance document and a Safety Evaluation Report, that would be used not only by regulators, but for the users of the system to refer to when they were licensing and/or using our RadioGenix system.

The first guidance document was issued in

February of 2018, and there's been one subsequent update to the guidance document, and there have been several other Safety Evaluation Reports issued as new versions of the system were released.

The important thing I want to draw here is, note the dates of these are the same. The initial NDA approval was February of 2018. The guidance document was February of 2018. They actually happened one day apart.

And this is a case where the FDA and the NRC worked very closely together to successfully bring -- to allow this product to be released to market.

And it was a good example of where the two agencies worked together to get new products on the market and allow the end-user to start taking advantage of the new product.

We have ongoing discussions with both the FDA and the NRC on the guidance document. Other prior approval supplements, we may be submitting. And we value these discussions that we're having. So with that in mind, and that background, let me make two suggestions. Next slide, please.

In general, we would suggest that regulatory bodies consider the environment in which

the new technology will enter, and ensure that, whenever possible, that the regulatory approach does not create an unintended barrier to customer uptake.

With the FDA, we value the continued interaction that we're having, and we suggest that the FDA continue working with anyone trying to bring a new product to market, as they are today.

We will continue to bring enhancements to the RadioGenix system to the market. But we also know that there have been reported new, novel, other approaches to moly-tech generating systems that could come out in the future.

And it's valuable to keep these avenues open for discussion with whomever may be bringing such a product to market. But it also allows us to start thinking about the future of other therapeutic isotopes, such as copper-67, such as actinium and bismuth-213.

And then you start asking questions about things like, well, we know what the intended purpose of some of these therapeutic isotopes is today, but we don't know all of the possible uses that could come out in the future.

So we need the FDA to continue to provide guidance and to clarify and improve the required

submissions so that the timeline from a submission to a product to market, provided it meets all of the safety and efficacy and other requirements, is minimized.

And the important thing is that it helps improve the applications as they come in. Next slide, please.

Similar, with the NRC and where the Agreement States are involved, we had, again, with RadioGenix system, we've had continued enhancements that have required one revision to the guidance document, and it required several Safety Evaluation Reports, and continued understanding of the training requirements that are necessary.

But again, it's not just a system like North Star's. It could be one of these new moly-tech generating systems that have been periodically reported in the literature that could come to market.

Same examples of therapeutic radioisotopes in the future. Copper-67, actinium, bismuth. Again, we know what the uses are today. We can anticipate things like radioactive material licenses have to be amended. We can anticipate sale and distribution licenses may need to be generated.

But what happens if there is a change

that is not understood today, that happens very rapidly in the market? How do we respond quickly to that change, such that the new, approved product can be on the market as expeditiously as possible?

And, again, continue -- I'll say the same thing as I did with the FDA. Continue to provide that guidance and clarity to improve the submissions and the understanding of what the product is intended to do and how it needs to be regulated and/or licensed.

In summary, regulatory agencies need to be prepared for new and novel approaches in nuclear medicine. It's a fast-moving field. And they need to be flexible in the timely interactions and responses.

And again, I think of workshops such as this as very valuable in allowing people to get together and discuss what the future may look like. I believe that was my last slide. Thank you.

MS. DIMMICK: Thank you, Dr. Harvey. And the last speaker in this session is Maurizio Mariani. Dr. Mariani is Global Head of Research at Advanced Accelerator Applications, a NovArtis company. Dr. Mariani, welcome.

DR. MARIANI: Thank you. (Telephonic

interference)experience we are generating (telephonic interference)--

MS. DIMMICK: Mr. Mariani? Dr. Mariani?

DR. MARIANI: Yes?

MS. DIMMICK: Your sound is not great at the moment. So I'm wondering if you could make a change with your sound? Maybe not speaker phone? I mean, if that doesn't help, maybe also turn off your video, but right now it's a little garbled-sounding.

DR. MARIANI: Is this any better?

MS. LOPAS: Yes, I believe that is better.

DR. MARIANI: -- any better?

MS. LOPAS: Do another test.

MS. DIMMICK: Give it one more test, Dr. Mariani.

DR. MARIANI: Can you hear me better?

MS. LOPAS: That does sound a little bit better.

MS. DIMMICK: It's a little bit better. It's not quite clear.

DR. MARIANI: Can you hear me?

MS. DIMMICK: Give it one more try. It does not seem to be as --

DR. MARIANI: Is that any better?

MS. LOPAS: It's sounding better, so let's go ahead and give it a try.

DR. MARIANI: Okay. Sorry for that. So I want to speak about my experience in my developing these two recent products. And next? Next slide? This is a disclaimer. So I'm Head of Research for AAA. Next.

So this is only highlighting that AAA is a recently -- is a younger company, founded in 2002. And the company really was focused from the beginning in nuclear medicine.

And in 2010, acquired the right to manufacture Lu-Dotatate, which is a molecule that had many. And following a strict interaction with both IMOH and FDA, a temporary move up, instructed to R&D improvement of the compounding pharmacology criteria, then also the removal.

Now this led us to start something, which went successfully and led us to registration in the Europe in 2015. Then subsequently in U.S. in --then the company's most recent acquiring by Novartis. Next.

The field of nuclear medicine is going through major changes. And in the last three years, we have seen a dramatic split. In the past, the

diagnostics and all of the diagnostic field.

Now we see more and more products, at least at the pharmacy level, that are focused on therapeutics, when actually, the numerous approaches are really coming from a cancer diagnostic approach, working together, the diagnostic and therapeutic, into the same thing, which is a registration.

So we see, as a spectacle of technology bringing up new, how do I say it? Solutions. New treatments and diagnostic agents will bring new solutions to the patients in the next years. Next.

This is the next. In the middle, you see the molecule that we call DOTATATE. Then so this molecule, there is a physical curved quality that does cellular peptide, and then chelated.

When we initially started development, we were focused only on the lutetium during that phase, so the, as I said, the therapeutic agent. And we will go to divert the assay which meant the same ideas to the process.

And now, so when we were already in Phase III, we found a way to also rectify various kits for this. And in this way we're better able to propose and develop a true theragnostic product, in which one molecule was developed to give two products.

Two products of this nature. One was a real contact solution, based on the tissue. Addition of 6.7 days' half-life allowed us to generate a product of three days' shelf life.

The shelf-life of the gallium is only 68 minutes. Right? So we have to find a solution. The solution was to either keep one for the escape, that could be used locally at the, sorry, notarize the pharmacy. So the concept is simple. One molecule, two products.

The making it was quite difficult. And this was the beginning of, in this process, the production in this, because we really were a new client and we needed to interface with several to understand and anticipate potential issues with this. Next slide.

MS. LOPAS: Dr. Mariani, I'm going to ask you one more time to just check to make sure that your computer, there's no papers anywhere near your computer or anything.

It just sounds like maybe the microphone port is covered or something to that extent. Whatever I asked you to do in the beginning seems to have maybe made it worse. I apologize. So if you could go back to your original setup.

DR. MARIANI: Okay.

MS. LOPAS: And we'll go forward.

DR. MARIANI: I am trying now. Can you --

MS. LOPAS: Oh, that is much better. Yes, thank you.

DR. MARIANI: Okay, sorry. Apologies for this. So I've now put the headset, but apologies, sincere apologies for this.

Now, in this slide, you see a picture of that many of you have already seen. These are the results of the NETTER-1 study. So the NETTER-1 study was quite successful in terms of efficacy. There was a study performed on an often indication, progressive GEP-NET patient.

But what's important to note, in this case, is that the study design was really the results of an interaction with a discussion with the authorities.

Because in a study, such a pilot study, Phase III study, it's key to define not only the efficacy parameter that you are looking for, so the power that you look for, but also the expected safety criteria, as well as the, let's say, the interval and the dose that I have chosen for the study.

So the study design in this case was based on previous experience. And then with Phase I, Phase II studies. And what was important for us was to define a treatment scheme that allowed us to monitor adequately the acute toxicity.

So we chose to have intervals of eight weeks between doses. Note that to monitor, really, the acute toxicity that we might have experienced.

The second parameter we chose was to extrapolate the cumulative dose for potential toxicity based on external beta radiation, to give us somehow a, let's say, threshold for, let's say, anticipating potential issues on the long term.

So all this allowed us to define the power of the study, and eventually demonstrate a good efficacy and safety ratio for the product.

So that was, let's say, important, because in this case, in our experience, the monitoring of toxicity for the acute finding and the cumulative threshold for toxicity, in terms of dose administered, were really the key aspect that we're actually with the authorities which were actually successful at the end of the study. Next, please.

Another important part is that we, at the time, as I said before, we had not yet talked of a

combined diagnostic, theragnostic approach. So we had to make a literature on the available diagnostication at the time. That was an Octreoscan, and was a SPECT agent.

And this SPECT agent was key for us, also, to define inclusion criteria that were key for identifying a select patient. Also to, in addition, to evaluate what was the tumor uptake, also the extent of tumor burden for the particular patient.

In this, it's important, it was important for the diagnostic, in this case, was extremely important, because we enriched the patient population and we were also able, by this inclusion criteria, to make a series of evaluations in terms of patient and tumor characteristics.

So essentially the message here is, it's very important to define this criteria beforehand, in order to make sure that there are no surprises during development. Next slide, please.

Now, this I spoke about, the Octreoscan. As I also said, we had in parallel developed the new generation diagnostic agent that was the gallium-68 DOTATATE. And really this is a new generation of agent, so PET agents, while in the past there was the previously used was the SPECT patient.

And of course there are improvements that this has allowed. One must say that in parallel SPECT technology results are greatly improved.

And, really, our diagnostic, the theragnostic approach, that we had to pursue also for a new product has to keeping count, accounting, also the advancement in technologies, for the image technologies. So SPECT agents will benefit if you go for more, better-performing image solutions. Next slide, please.

Now, what we have learned during this development. There are some major advantages that really come from the theragnostic approach, and also from the nuclear medicine approach in general.

So one of the main advantages, say, is -- sorry -- we can separate these advantages in two parts. The one that, say, features can facilitate the, let's say, the patient selection and the acceleration of the development in the one that are also added value during drug development.

So the theragnostic approach allows to see what you inject, of course, and then you see, it allows you to see if you are reaching the target, improves the selection of the patient, and then increases the chance of success with the therapy.

Another advantage that's very important in terms of pre-clinical development is that the treatment with theranostics really is based on few doses, a small amount of product injected.

So essentially with the authorities, you know, we have been able to discuss, agree, on a very fast, very, let's say, short pre-clinical development, as this peculiarity allows the waiver of a certain number of a long-term, pre-clinical studies.

Now, what is important, also, to the development is that some of these agents also allow dosimetric calculation, and in our hands, the estimation of the true dosimetry allowed us to predict possible effects, and especially those that are expected in the long term.

And so this is very important during development, because it allows you to define potential windows of treatment, and also a treatment scheme that would be the most likely to give you success in development.

We have done that during the development phases, but of course we did not apply dosimetry evolution as patient selection for a commercial use. Next slide, please.

So, again, the lessons learned from us was that the treatment scheme and the dose selection should be adapted to the type of patient we have. The dosimetry can be used, it has to be used properly at the early stages.

But more importantly, now we're ahead, the only thing that we have established during treatment cycles was really more effective and more reliable in terms of monitoring of potential toxic effects. Next slide.

Now, one thing that is also a lesson learned in this development is that there are advantages that we can benefit from in nuclear medicine, but there are also fairly, let's say, aspects that are more complex to manage, as well.

So one of these is classically manufacturing a supply chain. One of the aspects of this is to ensure that, from the production of the precursor, so of the isotope, the precursor in this case, lutetium, to the qualification and the release of the active ingredients of the lutetium 177, to the labelling, to the patient delivery, there is a very complex chain.

And this chain has to be really put in place very early during development, because this is

key in the success, in that when we performed a study in 51 centers, and one of the biggest challenges was indeed ensure consistent quality, availability for the patient, a standard quality for the finished product.

And this is, if it's not considered from the beginning, it can be a huge problem for the development. Next slide, please.

So in conclusion, in nuclear medicine there are peculiar characteristics. It can be turned in big advantages. For example, you see what you treat. But also this allows you -- sorry -- for a more effective patient selection to maximize success. And also the scheme can be defining in terms of safety, to control the toxicity parameters.

But this is, although this side hampered by complex manufactory, supply lutetium chain, that has to be considered from the beginning.

But maybe the most important factor of all is that since the beginning, since the early stage of development, a strong close interaction with the authorities is key.

And they for sure recommend it, because this is still a relatively young, let's say, domain, and there are things that need to be anticipated,

things that are, in terms of quality, in terms of study design, in terms of overall approach, including the diagnostic therapeutics.

And this can only be brought to success if there is a good, let's say, a clear, open discussion with the authorities. In our case, we were lucky to have a both in parallel FDA and MIA supporting the program, and it was then brought to successful conclusion. And I'll stop here. This was my last slide. Still, apology for the problem with the sounds.

MS. DIMMICK: Okay. Thank you, Dr. Mariani. Virtual conferences are tough.

So I've had to make a tough decision. Unfortunately, because we are running over and we still have three more sessions to get through, we won't be able to do the panel discussion, as we probably initially envisioned.

So we have all of the questions that have been submitted into the chat. Our plan had been to answer all questions that we're not able to verbalize the answers in the chat. We would provide responses to those in writing.

So our plan will be to respond to all of the questions that were submitted in the chat for

Sessions I and II and then provide them to attendees.

So that leads me to another question we've had, about the slides. We are hoping to make the slides available. And we just need final approvals from all of the speakers that their slides can be shared publicly.

We are also looking at some additional documentation from the meeting that we will be able to provide. So more to come. We'll distribute the information and where you can find it through the same forums that you had received notice about this meeting.

So again, our plan is to be able to provide the slides that we can to you, as well as respond to all of the questions in the chat for the Session I and II panel.

But to keep on time, so that we can try to have the panel discussions in the other sessions, we're going to move on. So with that said, I'd like to go ahead and turn the meeting over to the Session III moderator, Anthony Fotenos. And I'm looking for my notes.

So Dr. Fotenos works as the Lead Medical Officer in the FDA's Division of Imaging and Radiation Medicine. He will be moderating Session

III, which is Safety and Efficacy Considerations for Radiopharmaceutical Products.

Welcome, Dr. Fotenos. And so once you're able to share your screen -- Anthony, are you able to hear us?

MS. LOPAS: I'm checking to see if he's indeed connected to audio, because I'm not seeing any indication of the headset or phone.

So maybe, Lisa, go ahead and introduce the first presenter, and Anthony can see if he can get connected to audio, and I'll try to help him out with that on the side, here.

MS. DIMMICK: Okay. So the first presenter is Christy John. Dr. John is Acting Team Leader in the Office of Clinical Pharmacology and the Office of Translational Sciences. Welcome, Dr. John. And Kelly will bring up your slides. Yes.

DR. JOHN: Good morning, everyone, can you hear me?

MS. DIMMICK: Yes, your audio's coming through great.

DR. JOHN: Wonderful. Thank you. Can I have the first slide I was seeing earlier?

MS. DIMMICK: Kelly will share that in just a moment.

DR. JOHN: Excellent, thank you. Appreciate it. Thank you, everyone. The main objective of review is to find the right dose for the right patient population, based upon extrinsic and intrinsic factors. The intrinsic factors include hepatic function, risk factors include things such --

MS. DIMMICK: Dr. John, how about --

DR. JOHN: -- intake and smoking, et cetera. The exposure response -- can you hear me?

MS. DIMMICK: I'm going to ask you to stop sharing your video, and that will probably help improve the audio. So try that, and then continue on. Thank you.

DR. JOHN: Okay. The exposure-response relationship for both safety and effectiveness of a drug has the availability of the related to the drug exposure helps to establish the relationship between the exposure and the clinical outcome, which in our case is a good image. Next slide, please.

Thank you. The clinical pharmacology review focuses on several aspects. Not only the dose-finding and the dose escalation and the dose selection for the recommended Phase II dose, but also includes exposure response, population PK, drug-drug

interaction studies, hepatic impairment, renal impairment, et cetera. Next slide, please.

That gives the outline of my talk. I'll be focusing on the clinical pharmacology studies needed for the diagnostic imaging radiopharmaceuticals, and also for the clinical studies, clinical (telephonic interference)for the radiotherapeutics and the current theragnostic pairs as well. And then I'll be concluding my talk. Next slide.

So this slide shows various non-clinical studies that are needed before you can have a first in-human clinical trial.

So proof-of-concept of efficacy in non-clinical models is needed, non-clinical studies such as in models like mice or rats or monkeys would be needed for dosimetry.

Nonclinical PK studies would be required, as well as ADME and in vivo methods established for the PK analysis. So those are the studies that are needed before a first in-human study can be conducted. Next slide, please.

So diagnostic imaging agents are generally, as we know, given only once, and for the most part, generally speaking, the diagnostic imaging

agents are administered in microdose.

And the microdose is defined as the quantity of a drug, the mass quantity, less than 100 microgram, or less than 13 nanomoles for an antibody-level product.

The diagnostic imaging agents really require a high sensitivity and specificity against a standard of proof, or we could also have positive predictive values as a clinical endpoint. Dose should be effective in diagnosing a pathology, and should be safe, and a dose-finding study should be conducted. Next slide, please.

So for these diagnostic agents, which are mostly single-use agents, we do expect single-dose PK studies and that would include the biodistribution of the drug, not only in healthy volunteers but also in disease patients, patients with disease.

The metabolism of the drug, and if there are metabolites that are observed in the studies, what is the fate of these metabolites? Are they active metabolites? What is the route of elimination and excretion of the parent drug, as well as the metabolites?

Certainly, the dosimetry studies, as we heard, they are needed, that identify the target

organs and assess the absorbed radiation dose to various target organs. Then the drug interaction study or concomitant drug studies are needed, as well. Next slide, please.

So dose optimization is a very important part of the development and we encourage the sponsors to find an optimal dose. An optimal dose can be selected by having various doses studied and one can use PD as a surrogate marker.

And as we know, SUV value or tumor-to-background or tumor-to-nontarget ratio could be used as a pharmacodynamic marker. We also encourage to find the optimal imaging window where you could have the best images possible.

So identifying the optimal dose and optimal imaging window, based on the PK and PD of the drug, one can select a dose that would be used for the Phase III pivotal restriction trials. Next slide, please.

This slide essentially shows the example of the gallium-68 labeled PSMA in a tumor uptake in a patient. And here, as you can see, the SUVmax for a pelvic lymph node, shown here as a red arrow, the tumor uptake, the SUVmax increases all the way up to four hours.

And so the question becomes, what is the real optimal imaging window here? And you want to have an imaging window where you don't really miss out on the micrometastases as well. Next slide, please.

I touched upon the dosimetry studies. The goal here is to identify the target organs, assess the absorb radiation doses to various organs, determine effective dose, and also determine the variability and the heterogeneity in dose distribution.

In dosimetry and all, to provide the estimated addition of all doses to children of various age groups. Next slide, please. Next slide. I don't think that -- no, go back, please.

It is important to determine the effect of the concomitant drug. The example that I have chosen here to give is the DaTscan, ioflupane, which is indicated for the striatum dopamine transporter utilization in brain to assist in evaluation of adult patients with Parkinson's syndrome.

If you look at the package insert -- next slide, please -- of this DaTscan, the Section 7 that describes -- the package insert that describes the drug-drug interaction, is actually fairly elaborate.

Ioflupane binds to the dopamine transporters, so the drugs that bind to dopamine transporters with high affinity may interfere with the image following DaTscan administration.

And you can see there are a number of drugs that can affect the quality of the scan. So a sponsor should evaluate the effect of concomitant drugs that work through common mechanistic pathways. Next slide, please.

So for single-dose diagnostic agent, the CYP enzyme inhibitors are inactions. Those studies are not necessary. The transporters that are involved in the studies, metabolic process or the take-up process, those studies are not required.

Multi-dose safety studies are not really needed. QT prolongation studies in general are not needed, because the microdose is used.

However, for patients with organ impairment, the effect of organ impairment on efficacy on the diagnostic agent should be evaluated, because if a drug is excreted by a particular organ, for example, the kidney, and you have kidney impairment, it could affect the diagnostic efficacy of the drug. Next slide, please.

So for the radiotherapeutic agents, non-

clinical dosimetry studies extrapolating humans can be conducted, as a first approximation for radiation absorbed doses of various human organs to select a starting human dose.

We expect a first in-human PK biodistribution dosimetry and bioavailability study of a single dose in a cohort of six to eight patients. And generally this study would be conducted with a diagnostic dose. It could use a theragnostic pair for the diagnosis, as well.

And then, in this study, one administration of doses to various critical -- it is important as we heard from the previous speaker, to have the right patient population selected for the therapeutic dose.

So it is very important to define, what are the criteria for patients that meet the requirement for the therapeutic dose? Then, of course, the dose-finding study is conducted, including the dose escalation.

One can use multiple doses in a target population at different schedules, dose fractionation can be carried out. And I'll just use an example here.

One could use five doses, for example,

and 50 kilobecquerel per kilogram at two week' interval. All responsive can use two doses of 125 kilobecquerel per kilogram that can be given at five weeks interval.

Again, it depends on the radioisotope, it depends on the half-life of the drug, and the biological half-life, physical half-life and the biological half-life of the drug, as well.

So during these studies, the maximum dose -- sorry, the dose limiting toxicities are determined and the maximum tolerated doses determined, as well. Next slide, please.

So assessing safety in the radiotherapeutic arena is very important. The limit of radiation absorbed doses for systemic therapy are not known. Radiation dose limits are adjusted based upon the tolerated absorbed radiation doses in human organs.

For example, the factual from external radiation beam therapy is used, for example, for kidneys of 18 to 23 gray are used as safe, and generally we do not encourage sponsors to exceed radiation dose to the kidneys, because of this.

And another very sensitive organ for radiation sensitivity, or radiotoxicity, is the bone

marrow. Generally one to two gray is considered safe. My colleague, Dr. Casey, will be talking more about the efficacy of these radiotherapeutic agents and what factors are involved.

So the cumulative radiation administered dose should be used to determine the first in-human therapy dose, then dose fractionation is proposed. Next slide, please.

So based on the totality of the data, a final recommended Phase II dose is selected based on PK and PD radiation dosimetry, radiation exposure to particular organs, such as bone marrow and kidney, as discussed, and the safety of -- the efficacy of the drug, a dose for the pivotal restriction trial is used that is found for Phase III studies. Next.

For these radiotherapeutic drugs, we encourage sponsors to perform the in vitro evaluation of drug metabolism by cytochrome P450 enzymes and various drug transporters.

And if the results are positive, we encourage to perform the study, in vitro studies, if necessary, certainly in special population, for example, patients with hepatic impairment and renal impairment.

The studies would be warranted, and

QT/QTc evaluation, as well. The safety and efficacy of the drug could be ordered based upon the drug interaction impacting drug disposition and various organ functions, as well. Next slide, please.

So for example, I touched upon this a little bit. If a drug is eliminated predominantly by renal route or hepatic route, do renal function or liver function affect the therapy efficacy and safety results?

PK is recommended in patients with mild, moderate, and severe renal impairment, or patients with hepatic impairment. FDA guidances are available for design of such PK studies in patients with impaired renal function or impaired hepatic function.

We encourage you to look up those guidances, and if there is involvement -- if there's an effect on the efficacy of these drugs, then a dosage adjustment may be needed in patients with renal or hepatic impairment. Next slide, please.

So in conclusion, clinical pharmacology studies depend, based upon the diagnostic intent or the therapeutic intent of the drug.

Dose optimization is really critical, especially for radiotherapeutics, given the radiation toxicities and the latent radiation toxicities,

especially in kidneys and bone marrow.

Dosages flex depending on special population, or personal dosimetry could be used, as well. And I would like to thank my -- next slide, please -- my colleagues, Dr. Marzella, and thank you for your attention.

DR. FOTENOS: Thank you, Dr. John. And I apologize for our earlier audio issues. The next speaker starts the parent of two talks on the subject of extravasation.

He's Kish Chakrabarti, a health physicist in the Division of Imaging and Radiation Medicine and one of my colleagues here at the FDA.

DR. CHAKRABARTI: Thank you, Anthony. Can you all hear me?

MS. DIMMICK: Yes. We can hear you.

DR. CHAKRABARTI: All right. So I'm going to talk about extravasation events that happens and with the imaging drugs and radiopharmaceuticals. Next slide, please.

Just as the scope of the problem, the drug products should be considered, that all contrast agents and radiopharmaceuticals, henceforth I'm going to call RP, rather than saying radiopharmaceuticals all the time.

Then there are patient factors involved, infusion device factors involved, and drug factors involved. Next slide, please?

Now, what is the working definition of extravasation, is an unintentional leakage of the drug, during administration, from a blood vessel into the surrounding tissues. Next one, please.

Now, there are some signs and symptoms of extravasation. And I have given the list, but also I want to note that some extravasation process may not have any symptomatic presence of any of this, and that can only be seen during imaging process. Next slide, please.

What are the clinical consequences? There could be the loss of diagnostic or therapeutic efficacy, and some delayed reactions, which are ulceration and fibrosis. Next one, please.

Patient factors. Patient factors can be volume of affected tissue, age, physical condition, and prior exposures. Next one, please.

Infusion device factors, we'll have type of vascular access device, location, hand or port injection, and then the last, but this is the very important one, skill of person who is facing the vascular access device. So this is very important,

the skill of person who is administrating the drug. Next one, please.

Drug factors. Drug factors will have those in volume to all the way to formulation process. Osmolality and injection range. So the drug factors are several, and one has to be very careful. Next one, please.

Now, as I mentioned, that radionuclide devices as well as some other devices can cause the spiel of those and some skin injury. For iodinated contrast, that is the most common thing that you have seen, much more than other contrast agents.

Extravasation incidence has increased that you have seen it going up one to 1.2 percent. And there are some symptoms with that, usually, that go away in 24 to 48 hours.

It can cause syndrome of mechanical compression, which is called compartmentalization syndrome. There could be large, excessive volume of serum osmolality on the contrast sweep, and in the injection into the areas with less capacity for fluid increase.

So these are the issues with the contrast agent that is used for CT or for MRI process. Okay? Next, please.

Now, for RP, there are several other issues, that one of the issues is additional unique drug factors that can influence extravasation. As mentioned, that there is a contrast and then RP, but with RP, have another factor, which is the drug factor, the irradiating too. Next one, please.

Now, extravasation of diagnostic and therapeutic radiopharmaceuticals. You know, in radiopharmaceuticals, you'll have, can be diagnostic and can be therapeutic. Now let's see what other factors. Next one, please.

So radioactivity dose, emission type, emission energy, physical half-life. Together these impact the amount of energy deposited on the tissue.

The therapeutic radionuclides typically have emission type and energy that result in much greater energy deposition than diagnostic radionuclides. Next one, please.

Now, therapeutic radionuclear physical factors. This will be, there are some radionuclides. These are all beta emissions. And there is one, with radium-223, that has alpha emission.

So these are the reported case where we have seen that beta emission, as well as alpha emission, some extravasation has happened. This is

a reference of this. Next one, please.

These are positron beta plus emissions. And this is a positron-emitting radionucleus, and there are at least four of them. The FDA has seen all four, and the FDA has approved as a therapeutic radionuclide. Energies more or less all in the window of 500 keV. The same reference. Next one, please.

So these are gamma-emitting radionuclides, and there are a few of them, there, and the energy in keV, and that is all the same. And a gamma camera is needed because these are all gamma-emitting imagings. There is a reference. Next one, please.

Now, how do you calculate the dose? You calculate the dose from the energy deposited. As we all know doses energy deposited are unique. Mass or weight in kg, if the energy is in joule, then you get in dose.

So energy part DK, you use the activity, and then you get that, from the mar calculation, you get the energy part, DK, and the number of DK is the activity for the number.

So there are a few cases that I have narrated, but you see that as the tissue volume

decreases where the extravasation happens, the dose deposited is more. There is a couple of references. Next one, please.

What are the factors? Factors of -- pharmaco-factors, the pharma, but the most important thing is that these impacts are not -- is often less in extravasation RP.

And biological half-life, it also does not predict the rate available of extravasation inside. So these factors are there, but it's not that seen in the extravasation site, and it is -- the most important thing is how fast the drug goes away. Next one, please.

That's what I'm going to show you in my next slide. Yes, this is an extravasation clearance example. That's 177 lutetium, and you see the day zero, this is the image of the extravasation site, and within seven days, it goes away. Actually, even 24 hours, the decrease is very predominant.

And you really don't see extravasation in site, the drug remains inside that much. It's going away. And there is a investigational drug, not FDA-approved. Next one, please.

Then another one, I show this extravasation clearance for strontium-89, that is

used for breast therapy. And it is found that extravasation in the right arm, and you see that at the beginning, in first ten minutes, this number is pretty high, in terms of activity.

And then in 48 hours, that is reduced to insignificant number. So and that is the case for almost all of them. So this is the reference. So basically, this is one important thing, is how long it takes for the drug to remain in the extravasation site. Next one, please.

Now, tissue sensitivity factor. The skin is more radiosensitive than muscles. And it therefore the extravasation events most often affects skin. Next one, please.

Now, this is from a review paper by Jochem, et al., and this shows that for diagnostic radiopharmaceuticals extravasation reported, out of 3016, we are only seeing 3 reported extravasations which is really harmful. Next one.

If you look at that for therapeutic extravasation, yes, there's a few more reported, here. And the dose is from 10 to 40 gray, in that estimation. So can I go back to the previous slide? The diagnostic one? Yes.

If you look at this, and the case, for

diagnostic case of three, but it has caused some skin ulcers after two, couple of years from when the extravasation happened.

This is a very important case that has been reported, and we have reviewed this all. Okay, next one. Next one. Okay.

Now, these radiopharmaceutical extravasations are mostly deterministic effects, because we see it on the skin, and we have not that much information about -- it can initially increase the risk of carcinogenesis, but there is no one-to-one correspondence.

So basically, we can conclude that this is more or less a deterministic effect. Next one, please.

Now, what is the risk mitigation? Extravasation reactions are considered under the dosing and administration. So during the dosing and administration one has to be careful.

Depending on frequency and consequences of the reactions, warning and risk mitigation strategies are incorporated into labeling. Extravasation reactions and outcomes are monitored during drug dosing and extravasation reactions are also included in routine post-marketing surveillance,

and reported then.

But these are the four bullets that I have provided you. These are the ways that you can do the risk mitigation for extravasation. Next one, please.

Now, in summary, what I can say, the extravasation of imaging drugs is common. It's not uncommon. It's quite common.

But consequences depend on multiple patient infusion device and drug-related factors. And of course, the other important thing is the training of the person who is administering the drug. Our belief is from that, and that survey literature, but that is a very important part of the process.

Now, radiopharmaceuticals have additional drug-related factors not seen in other drugs, and extravasation can happen. These are nothing to do with -- extravasation has nothing to do with radiation. Extravasation is the process by which the drug spills in the skin.

But when it comes to radiopharmaceuticals with the drug, then it has other issues with the radiation dose inside of it. The most common adverse is a local tissue reactions.

As I mentioned, the tissue is the most

affected part. And most severe consequence can happen in therapeutic. Extravasation therapeutic may better concerned than diagnostic radiopharmaceuticals. That's all I have to say. Thank you.

DR. FOTENOS: Thank you, Dr. Chakrabarti. Our next perspective on this extravasation issue comes from our NRC and today's Master of Ceremonies, Lisa Dimmick. She's the team leader for the Medication Radiation Safety Team at the NRC.

MS. DIMMICK: Okay. Thank you. Kelly, could you advance to Slide 4? My first few slides just kind of restate a few things that Kish presented on what an extravasation is and a summary of that van der Pol article from 2017, citing the occurrence of extravasation and the effects that were observed and diagnostic and therapeutic extravasations.

So go back one more slide. So let's start with the 1980 policy decision. Okay, thank you. All right, so the NRC amended its regulations in 1980 to require reporting of mis-administrations.

The regulation excluded reporting of extravasation as being reported, or as a reporting as a misadministration, citing that extravasation

frequently occurs in otherwise normal intravenous or intraarterial injections.

At that time, the NRC believed that extravasations are virtually impossible to avoid, and therefore it did not consider extravasations to be a misadministration. Next slide.

So why reevaluate the 1980 policy? What's changed? Well, it has been 40 years since that policy was, you know, became a regulation for NRC. And since then, there are many new diagnostic radiopharmaceuticals in use, including the PET radionuclides, these things that weren't around back in 1980.

And also back in 1980, there were probably only a couple, if that many, injections or IV injections of therapeutic radiopharmaceuticals. So in considering all the novel therapeutic radionuclides coming down the pike, you know, we have begun to think about this policy.

So the NRC staff has begun an evaluation of whether or not extravasations should be reported as medical events.

Let me just note that back in 2002, the NRC did revise its regulations for medical use and the term misadministration was changed to medical

event. This change brought about a more risk-informed performance-based approach to regulation.

And in this change of terminology, the reporting criteria was revised to include different types of deviations from the radiopharmaceutical administration that was prescribed, such as wrong activity, wrong radioactive drug, wrong route of administration, wrong patient, wrong load.

The definition of a medical event also introduces or includes a dose threshold criteria, in addition to meeting one of the other criteria of the injection.

And that dose criteria is an effective dose equivalent exceeding five rem, an organ dose equivalent exceeding 50 rem, or a shallow dose equivalent exceeding 50 rem.

So while NRC staff was beginning an evaluation already, the NRC did receive a petition for rulemaking on May 18th. And in that petition the request was to classify extravasations that result in a localized dose, a 50 rem dose equivalent to the tissue at the injection site, to be classified as a medical event, and be reported to the NRC as such, as a medical event.

Just to note, a public comment period was

noticed on September 15th in the Federal Register. The citation is 85 FR 57148. And that comment period does close on November 30th. Next slide.

So NRC's evaluation -- and we could spend a lot of time talking about our evaluation, but we're very limited, so we're just going to give you something in a nutshell.

So the NRC staff will determine whether extravasation should be reported as medical events. And if so, what is the appropriate reporting threshold for these events?

With extravasation, tissue doses can and do exceed 50 rem at the injection site, if that dose is extravasated or some contents are extravasated. So it's really the question, is there a threshold where extravasations should be reported?

So the staff's evaluation is going to be based on -- we're looking at it through several pathways or areas. You know, is extravasation preventable with technology? Is extravasation a practice of medicine concern or a regulatory concern or both?

And then last, is the dose consequence with extravasation significant enough to merit a policy change and require regulatory reporting? Next

slide.

So the other part of extravasation is the dosimetry. Determining the dose from an extravasation is very complex. And we've started to look at this on what it might take to develop a model or associate with a model that could be used for determining the dose consequence or the dose from an extravasation.

So as I said, it's very complex. The fraction of the extravasation of the radiopharmaceutical is unknown. The volume is not symmetrical in shape, and then it's also determining how much tissue do you need to determine for the dose.

So these are important factors in the dosimetry that we'll need to consider, you know, should we require reporting of extravasation.

So all of the points on this slide, you know, characterizing the event, the fraction of the material extravasated, the radiopharmaceutical characteristics, looking at Monte Carlo modeling, biokinetics.

Again, you know, with these radionuclides, some are more soluble than others. Some have R particulates, so it's really movement from the soft tissue to the bloodstream and the

biokinetics associated with the radiopharmaceuticals.

And then identifying a dose method, and also looking at the risk hazard levels for various tissues. So all of these things will play into determining or identifying an appropriate dose model for extravasation. Next slide.

So, you can learn more about what the NRC is thinking with regard to extravasation over the coming months. The NRC is planning a stakeholder meeting to discuss extravasation, and it is tentatively scheduled for December 8th.

The NRC staff will provide its advisory committee, the Advisory Committee on Medical Uses of Isotopes, with a draft evaluation and policy options by this January. That's our target date to provide what we see as options for extravasation.

We plan to complete a technical evaluation by April. And then this will roll into a decision to accept or deny the petition for rulemaking to make a change. And we'll need to make that decision in June of 2021. Next slide.

I also wanted to note that we've had a fair amount of Congressional interest in extravasation. Our House and Senate FY '20

appropriation bills required a report on updates to injection quality monitoring, classification, and reporting requirements regarding extravasation.

That is a publicly available document that we submitted to Congress back in March, this past March. We have a similar bill that we can expect for our appropriations bill for FY '21, requiring a reevaluation of nuclear medicine at that reporting.

And then a subsequent briefing on that topic, and we've also received a number of Congressional inquiries.

So at NRC, this is a very important topic. It's an emerging topic that we are evaluating. And stay tuned. More to come. I would encourage you to be on the lookout for that December 8th public meeting to hear more about NRC's work on extravasation.

And with that, I think my next slide is just questions. So I'll turn it back to you, Anthony. So I think I made up a couple of minutes.

DR. FOTENOS: Thank you. Yes, we're running a little bit short on time. The next speaker is Dr. Anscher, a medical officer and former radiation oncologist in the Office of Oncology at the Food and Drug Administration.

DR. ANSCHER: Thank you, Dr. Fotenos. Can everybody hear me?

MS. DIMMICK: Yes.

DR. FOTENOS: Yes, we can hear you fine.

DR. ANSCHER: Okay. Good. Well, I'd like to thank the organizers for the opportunity to speak to you today.

And over the next few minutes I hope to convey to you why individualized dosimetry is important in order to optimize the safety and efficacy of radiopharmaceuticals. Next slide, please. I have nothing to disclose, so next slide, please.

So radiopharmaceuticals offer several potential advantages over external beam radiation. It may be more targeted, thus delivering a high dose to the tumor while sparing normal tissues.

Similarly, the low-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 a decay process, and this may offer the opportunity to combine imaging with therapy.

However, in reality, the targets may not be 100 percent tumor-specific. For example,

prostate-specific membrane antigen, a potential target in patients with metastatic prostate cancer, is also found in the kidneys, small bowel, salivary and lacrimal glands. So off-target toxicity may be an issue.

Depending on the isotopes used, the depth of penetration may not be ideal for the clinical situation. But unfortunately, many agents used for therapy cannot be directly imaged, and a related isotope, with decay characteristics more suitable for imaging, may need to be used with 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 agents are distributed, metabolized, and excreted becomes critical for determining dosing and dosimetry, which is different from external beam and sealed brachytherapy sources, which are not circulating or metabolized. Next slide, please.

So at the risk of insulting everyone's intelligence, what is dosimetry? When I started hunting around for a definition, in fact, there were several. The definition in the first bullet point

seems to best fit what I mean by dosimetry for the purposes of this discussion.

Dosimetry is critically important, because without knowing the dose delivered to tumor and normal tissues, one cannot properly understand the relationship between dose, safety, and efficacy, and thus cannot optimize the use of a product for the best interest of the patient. 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 dose distribution of the product throughout the target, when in fact that is often not the case, as we'll 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 that tolerances for radiopharmaceuticals are not the same as for external beam radiation, and are likely to vary by isotope.

So, 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 dose rate on cell-kill. The curve at the far left 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 and normal tissue cells. 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 equal effects of higher dose rate therapies. 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 calculation-derived data, and are not precisely known a priori for an individual patient.

We continue to refine our knowledge with these probabilities through ongoing research, but in order to do so, precise estimates of dose delivered

to both tumor and normal tissue are critical. Next slide, please.

In most drug studies, dose limit and toxicities are determining after a relatively short observation period, generally 30 days. However, for radiation therapies, the toxicity that usually drives 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 dosage delivered to normal tissues in order to accurately define tolerance doses and prevent the development of late effects. Next slide, please.

Many factors influence the therapy equation. These include patient-specific factors that might make an individual more or less likely to suffer a complication from radiation, and tumor-related factors that impact on the likelihood of controlling the cancer. 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 therapy.

But 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 more than 100 years of treating cancer with external beam radiation, is imperfect.

Probably the biggest reason for the 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 biologic risk profile, and we're a long way from being able to determine that with accuracy. Next slide, please.

Let's consider the example of prostate cancer. The most radio-sensitive organ in the immediate vicinity of the prostate is the rectum.

In the short term, radiation injury to the rectum, termed proctitis, generally manifests as more frequent, urgent bowel movements or bleeding, and it almost always resolved.

Long-term injury to the rectum can manifest as bleeding, increased stool frequency, urgent need to defecate, and even incontinence. If it occurs, it may be difficult to manage. Thus, the late effects drive the dose constraints for the rectum.

One of the problems encountered in defining tolerance doses is that the region of risk for a particular organ has been inconsistently defined between studies. This problem is illustrated in the figure above.

Should the radiation dose be related to the entire rectum, shown in green? Or only to the part receiving radiation, shown in purple? It's likely that the tolerance doses would vary depending on the approach taken. Next slide, please.

Animal models may help develop a better understanding of the biologic mechanisms leading to

radiation-induced injury. The tolerance doses vary by species, and even within species. So these dose response relationships usually can only be accurately determined in humans. Next slide, please.

I'd like to close by using the example of selective internal radiation therapy for the treatment of liver tumors to illustrate some of the issues mentioned.

This treatment involves the intravascular delivery of yttrium-90 bound to microspheres. Yttrium-90 is a low-energy beta emitter intended to preferentially irradiate tumors over normal liver. Next slide, please.

The dosimetry guidelines for these products focus on safety. The product inserts contain information and dosing guidelines. However, these guidelines assume uniform distribution of the product within the tumor and the normal liver. Next slide, please.

This figure demonstrates that the distribution is in fact not uniform. This tumor has a large area in the center, shown at the top, which would not be expected to have a viable blood supply.

This is confirmed by the images at the bottom, in which the bright areas represent

distribution of yttrium-90 and the dark region represents absence of isotope distribution.

If one calculates those based on the assumption of uniform distribution, and then recalculates the dose based on the actual distribution of yttrium-90, the dose determinations vary significantly. Next slide, please.

If one goes back to our concept of therapeutic ratio, these figures illustrate the need for individualized dosimetry for this treatment. In both figures, you can see that the probability of effect, either tumor response or liver injury, increased with increasing dose.

But the desired dosage to achieve a high probability of tumor response and a low probability of liver injury are vastly different. Next slide, please.

This study, which was reported earlier this year, demonstrates the benefit of individualized dosimetry, which was the endpoint of the trial. This trial randomized patients' treatment using personalized dosimetry or standardized dosimetry.

The inclusion criteria for patient enrollment are listed above. Next slide, please. The dosimetry results are displayed here.

Personalized dosimetry allowed delivery a much higher dose to the index tumor, shown on the third line from the bottom. It also resulted in a higher dose to the normal liver, shown on the bottom line. But still, it's in the dose constraints established for both treatment arms. Next slide, please.

The primary endpoint of the trial was response of the target tumor at three months. This table demonstrates that the use of individualized dosimetry achieved a significantly higher response rate in the index lesion at the time point. Next slide, please.

Although not a primary endpoint, personalized dosimetry also resulted in an improvement in the overall survival by 16 months over the standard dosimetry arm. Next slide, please.

So in conclusion, the benefits of individualized dosimetry are numerous, and has become the standard in other forms of radiation therapy.

Emerging data indicate that personalized dosimetry for radiopharmaceuticals holds promise to optimize dose and reduce toxicity for this form of radiation therapy, as well. Thank you very much for your attention.

DR. FOTENOS: Thank you, Dr. Anscher.

Our final speaker before lunch represents valuable industry perspectives. He's William Goeckeler and is an early development lead for targeted alpha therapies at Bayer Healthcare.

DR. GOECKELER: Thank you. And thanks for the invitation to participate today. Next slide, please.

And this just says that, as it said on the first slide, I'm an employee of Bayer. Fortunately, they pay me for doing, at least fortunately for me, they pay me for doing my job. Next slide.

So what I'd like to focus on mostly today is not the actual dosimetry-related discussions that have already been held by Dr. Anscher and others, but more focused on how we gather the data that goes into performing these dose estimates.

So Dr. Anscher made the comment about the, in the prior talk about the need for accurate information in determining dosimetry. And that's where the role of clinical trials becomes important, because it's during clinical trials, and particularly during early clinical trials, that we gather much of the source data that's needed to perform these dose

estimates.

So I'm going to talk about a few of the techniques and methods that are used to do that. I'll use an example of one that I was involved in a number of years ago with a bone-targeted beta-emitter. And then I'll turn to some of the ongoing efforts related to alpha-emitters.

So this is kind of a summary of a number of things that were done with radionuclide samarium-153 in a bone-targeted agent. And if we just kind of scan around this slide, first of all, you can see on a gamma camera image there's very selective uptake in bone. We see very little uptake in any other organ.

We can image this very well. We can quantitate images. And in part, that's related to the fact that for beta-emitters we, many of them have substantial photon components to the emissions and the administered dose levels that we use.

This was a dose escalation study. You can see on the right-hand side doses administered to patients during this study range between 1.9 and 11 gigabecquerels. So we get lots of photons. We can get very good images.

There's a number of techniques other than

imaging that we can use to obtain biodistribution information. So we can do biosampling such as blood collection, urine collection.

Also you see on the bottom left-hand side an example of a bone biopsy from one of these patients. And if you look closely, we can see that the little dark dots are localized at the surface of the bone. So we know actually at a micro level the distribution of the radioactivity. And that will become important as we'll see in the next few slides.

So, using these variety of techniques, we can determine the time-dependent organ distribution of the radionuclides. From that, we can calculate resonance times using standard dosimetry models, such as MIRD, which was used in this case. We can perform organ-based dose estimates based on the known source organ activities.

And you can see in the middle on the right-hand side, what we see is sort of dose estimates for mean dose estimates, along with some measure of precision and variability between patients.

You can see in this case the, what your eye would tell you based on the biodistribution that the most significant doses are to bone surfaces and then the immediate adjacent tissue, red marrow. And

you can see that those absorbed dose estimates are significantly higher than anything else you see on the table.

However, you can also see that based on, if you just do the arithmetic quickly, if you look at the gray per megabecquerel and you take into effect that we're administering, say, two to ten gigabecquerel, if you just do the arithmetic quickly, you can see that the dose estimates multiply to extremely high levels.

So, for instance, if you were to take the 1,500 gray estimate to red marrow, multiply that by, say, the midpoint here, 5,000 megabecquerel, you could get a very, very high number.

Obviously, if we look on the bottom table then, we see in these same patients the range of administered doses, the cumulative dose that was administered to those patients. And then we see what the actual impact on marrow was in terms of hematologic toxicity.

And so you can see that, although there is toxicity, it's certainly not what would be predicted based on the simple MIRD-based dose estimates. And we know why that is. We know that these are short-range particles. They're localized

on bone surfaces. And they do not uniformly irradiate the marrow. So this relates to some of the things that Dr. Anscher just discussed in the prior presentation.

So, on the next slide, we just see a few of the learnings that come out of studies like this. First of all, there is a variety of methods that can be employed to obtain this biodistribution data.

Administration of very high levels of radioactivity enables relatively high precision of the measurement of the radionuclides in various organs and tissues.

There is some intra-patient variability in the dose estimates. It could be up to about 25 percent. And that's in addition to whatever variability there is in the precision of the measurement.

And then finally, non-homogenous penetration of particles in target organs leads to disconnects between what we see in terms of dose estimates based on conventional models and absorb signs of clinical safety and efficacy. Next slide.

So, turning now a little bit to driving dose estimates for alpha-emitters, there's a few things I'd like to discuss.

First of all, as most people know, alphas decay largely in chains. So we're not talking about simply one emission. We're talking about multiple emissions, multiple emissions of different types.

We need to talk a little bit about the characteristics of the change and the dosimetry aspects of the daughters that are formed and the decay of these things of change. They're administered at very different dose levels. We'll talk about that.

And finally, there are some unique radiobiologic aspects of alpha dosimetry that have to do with these effects related to path length and biologic effectiveness. Next slide.

So this is an example of a couple of decay chains. On the left-hand side is thorium-227 in combination with radium-223. They actually come through the same decay chains. On the right-hand side is actinium-225. I would say these are the three radionuclides that are most frequently being explored right now in alpha particle therapy.

So you can see that there are multiple emissions for both, both alpha and beta. They both emit. They also emit photons.

But there are differences within the chain. And this relates to the relative half-lives

of the members of the chain.

So, if you look at actinium, you have a half-life of the parent of about ten days. But all the daughters that result from the decay are very, very short relative to the half-life of the parent.

And so, in that case, we end up with what we term a secular equilibrium. And the parent and all the daughters are essentially in equilibrium with one another almost instantaneously, particularly with respect to the half-life of the parent.

On the other hand, if you look at thorium-227, you could see the parent half-life is about 19 days, but the first daughter is 11 days. So, in that case, we have a transient equilibrium where the thorium leads to the formation of radium, which grows in over time and then decays with its own half-life. And we'll talk about why that matters in just a second.

The other thing is, because of the potency, the multiple decays, and the energy of those decays, these alpha-emitters are administered at administered radioactivity doses that are about a thousandfold less than for typical beta particle therapies. And that reduces the number of available photon emissions. And we'll see the impact of that

in just a minute.

And then that has an impact on the procedures used and the precision of the measurements of uptake and clearance of these radionuclides.

And then finally, these alpha-emitters typically have half-lives of 10 to 20 days. So, when we talk about the time-dependent activity, which includes both uptake and clearance, the relevant timeframes are much larger, are much longer than for shorter-lived radionuclides such as we use in diagnostics or maybe even in some of the earlier therapeutics like we talked about before with samarium-153. Next slide, please.

So one of the things that's important in considering the dosimetry of these decay chains is what happens to the daughters after they're formed.

And why that's important is when you have the decay of a radionuclide by emission of an alpha particle, there's a very large recoil energy. And the recoil energies are typically on the order of 70,000 electron volts.

On the other hand, the chemical bonds that usually were used, usually these emitters are attached to targeting molecules through chemical means. Those bonds are on the order of five to ten

electron volts.

So, typically after an alpha decay, the parent radionuclide becomes, which is no longer the parent after it decays, becomes detached from the targeting molecule. So one needs to consider not only the biodistribution of the parent but also of the daughters.

And to the extent that you have a secular equilibrium compared to a transient where all those subsequent decays occur very quickly, in the bottom right-hand corner you can see that for the example of thorium-227 and radium-223, the blue curve shows the decay of the thorium and the red curve shows the ingrowth of the radium-223. So we have two timeframes we need to be considering here.

The mathematics of doing this has been worked out for some time. And that's as indicated in the Medical Physics publication. But acquiring the appropriate biodistribution data can then be somewhat complex. Next slide.

So this is an example of imaging with alpha-emitters that illustrates a few of the points I've just made. So on the top -- and I apologize. There's a typo on this slide.

On the left-hand side, we see a

diagnostic image of gallium-68 Dotatate. And it's pretty, in liver it's what we're all used to looking at in diagnostic images.

On the right-hand side, this is where the typo is. Unfortunately, this is not gallium-68 Dotatate. But this is actinium-225 Dotatate in the same patient. So it's the same molecule labeled the same way, but it's a different radionuclide, the therapeutic radionuclide.

And this is given at a dose of seven megabecquerel. We're only looking at a confined area, the liver. But you could see, even at a dose of seven megabecquerel, the images are count-poor. They're low resolution. And there's a lot of background.

On the bottom, what you see is an example of, this is a whole, believe it or not, you can't tell by looking at it, but this is a whole body image in a patient that was administered thorium-227 at a dose of 2.8 megabecquerel. Below that it's not even worth attempting to image.

On the left-hand -- since they have their own each discrete gamma rays, which can be differentiated on imaging, on the left-hand side, you see the distribution of the thorium-227. On the

right-hand side, you see the radium-223.

And there are obviously some differences. You see in the lower quadrant of this patient, we apparently are seeing excretion of the radium-223 through the gut.

So, in situations like this, quantification of the uptake is difficult. So the gamma images are low resolution and poor signal-to-background ratios. They're difficult to quantify. And the low count rates lead to low precision in the images even when you try to quantitate them.

But there are other ways to gather data. The other point that I made before about the clearance phase being very long, these are early phase images. They only get worse over time. These images take a long time to acquire.

It's really not a good thing to ask a patient to come back time after time after time over a six to eight week period to endure, you know, an hour or two's worth of imaging over and over and over again to get this quality of data.

So we've looked for other ways to look at some of the clearance parameters. So this is an example that I've used, we're using not only in these studies, but we've used in other studies.

On this curve, you can see that, on these plots you can see the same lines we had with regard to the transient equilibrium between thorium and radium in the solid blue and red lines.

But what we see is actual patient data, in this case from a patient given 4.6 megabecquerels per cycle for three cycles of thorium-227. And in the dots, blue and red, we can see the actual clearance of the thorium separate from the clearance of the radium.

So it's just another tool that we can use. It gives us more precise data and is much more patient-friendly for the long-term kinds of needs. Next slide.

So, finally, with regard to alpha particles, there's some radiobiologic aspects of alpha particle dosimetry. And this is kind of a very new field.

As we all know, alphas have exceedingly short path lengths. So they deposit a high amount of energy over very short distances, 50 to 100 microns.

So there could be very significant inter and intra-organ issue dose heterogeneity, so-called microdosimetry, for a number of potentially important

organs, bone marrow, as I pointed out before, with a source in bone, kidney, where you may have uptake in a certain part of the kidney but not others, say, the proximal tubules for a small protein, and could even be for GI content exposure to the GI wall, as we saw in the example, say, with radium in gut contents.

So RBEs, the other important part of this is that this high LET radiation is much more lethal per unit dose of absorbed energy than are photons or beta particles. In fact, that's one of the real reasons we're very interested in alpha particles.

However, RBE is just a factor that relates the biologic effect to the amount of absorbed energy. RBEs and for photons and electrons are pretty well established at being near one. When you get the very low energy electrons, that can start to increase.

However, RBE for alpha particles, particularly for deterministic events, which are related to the safety and efficacy, are not very well known. They're thought to be somewhere between, say, three and seven. Some people would argue there's even a wider range.

And there's even less known about tissue-specific RBEs. So there's a big unknown associated

with the RBEs.

And so on the next slide, which is the final slide, I'll just kind of summarize it.

So quantification of uptake in organs to provide the source data and accurate source data is a very important component of development in these and a component of the clinical development studies.

And we've seen that there's a variety of methods that can be used. Microdosimetric effects can play a significant role for short range particles, both alphas and betas.

Alpha-emitters decay in chains. And that introduces problems with multiple radionuclides and differential equilibria.

They're administered at much lower doses. That makes quantitation a little challenging, a little more challenging. But there are other methods we can use to try to adapt to that. And RBE values for alphas are not currently well characterized.

I just wanted to end by saying, although there's a lot of challenges, this doesn't mean we shouldn't be doing this. We should be doing these things very well, but in working towards helping to characterize and understand and build clinical correlates between absorbed dose estimates and

clinical signs of safety and efficacy that Dr. Anscher talked about before.

It's really important that we have the most accurate source data we can. And that requires a number of methods that I hope we've had a little chance to look at during this presentation. So thanks for everyone's time.

DR. FOTENOS: Thank you, Dr. Goeckeler. So the bad news is, given our shortage of time, I've been asked to announce that our panel discussion, which was scheduled to begin after lunch, will start at 12:45, so in approximately 17 minutes. The good news I guess is hopefully many of us have a shorter commute to get our food.

But please return at 12:45 for the panel discussion that will last from 12:45 to 1:15. Thank you.

(Whereupon, the above-entitled matter went off the record at 12:28 p.m. and resumed at 12:47 p.m.)

DR. FOTENOS: I think we've fielded, let's see, approximately 12 questions. And I think in grouping them I thought it would make probably the most sense just to go in the order of our presenters.

And so I'll just sort of group these.

And I'll seek out the questions. And then the panelists can sort of sort which they want in turn and which they want to be reminded of.

So our first speaker was Dr. Christy John. And so we have a couple questions regarding early phase investigation. What would be a good stable isotope for safety pharma toxicity for a Y-90 compound? And then the next question is, can administration of TRT agents be considered micro dosing? So two questions for Dr. John.

MS. DIMMICK: Dr. John, you are muted. So just unmute yourself.

DR. JOHN: Thank you, Lisa. Anthony, you were breaking up. I couldn't hear the first part. Is it for, I think FM-90?

DR. FOTENOS: The first question is what would be a good stable isotope for a Y-90 compound - -

DR. JOHN: Yes, FM-90.

DR. FOTENOS: Yeah.

DR. JOHN: Correct.

DR. FOTENOS: Yes.

DR. JOHN: Honestly I must say I do not know the answer. And I have not seen, at least in submissions to FDA, anything that's somewhat, someone

else has done a study for this FM-90. So I'm sorry I'm not able to give a definite answer. Any one of my colleagues or --

(Simultaneous speaking.)

DR. JOHN: -- please feel free to chime in.

DR. GOECKELER: Hi, it's Bill Goeckeler. There's a number of stable isotopes with yttrium. I would think that you could use just stable yttrium.

DR. JOHN: 86, right, Bill?

DR. GOECKELER: 89 --

(Simultaneous speaking.)

DR. GOECKELER: Yeah, there's a number of them. I think you could just use natural yttrium, which has a number of stable isotopes. But if you're just looking to make a standard or something like that, yttrium is certainly something you can attain.

DR. JOHN: Thank you, Bill.

DR. FOTENOS: Thank you. And the next question for John is, can administration of therapeutic radiopharmaceutical agents be considered micro dosing?

DR. JOHN: Can you -- pardon my ignorance. Can you define TRT agents?

DR. FOTENOS: I'm sorry. Can you say

that again?

MS. DIMMICK: Dr. John --

DR. JOHN: What is TRT?

MS. DIMMICK: -- TRT is targeted radiotherapy.

DR. JOHN: Oh, I'm sorry.

(Laughter.)

DR. JOHN: I guess based upon the definition of micro dose, anything that is under 100 microgram or in terms of macro molecules, 30 nanomoles for antibodies, could technically be considered as a micro dose. But anything above that would not be considered as a micro dose.

So I don't think we can twist, we have too much twisting to go there with respect to the micro dose definition as fairly well defined.

DR. FOTENOS: Thank you --

DR. JOHN: I'll be happy to hear my other colleagues from FDA or somebody else.

DR. RAJENDRAN: Yeah, this is Joseph Rajendran. I think they're referring to microdosimetry that is commonly referred to for alpha particles, if I understand it correctly.

So, if it is alpha particle treatment, then it can be, the microdosimetry is used for the

evaluation of the personalized dosimetry. So that is what will be the answer for me.

DR. FOTENOS: Thank you. And this also provides an opportunity for me to introduce Dr. Joseph Rajendran, another medical officer in Division of Imaging and Radiation Medicine at the FDA with a background both in nuclear medicine and radiation therapy. So thank you.

The next set of questions is grouped around the subject, the two talks we heard on extravasation, so maybe starting with Dr. Kish Chakrabarti.

There are several, and I think some of them keep coming in. But why don't we start with the first? Are there any randomized controlled clinical trials that suggest that extravasation is a patient safety issue?

MS. DIMMICK: Kish, you're muted. Kish, can you unmute your phone?

DR. CHAKRABARTI: Can you hear me now better?

MS. DIMMICK: We can hear you. Thank you.

DR. CHAKRABARTI: Okay. I was saying that I did not see any or I am not aware of any

randomized clinical trial for extravasation possibly. Are you aware of any?

(Simultaneous speaking.)

DR. CHAKRABARTI: This extravasation is highly underreported. So part of the reason is, as I mentioned, that it doesn't stay long.

Patient many times is asymptomatic. Many times the patients do not even realize that their extravasation has happened.

DR. FOTENOS: And I just -- I would chime in as another -- another clue to findings on the randomized control trial use for registration purposes can be seen in the prescribing information, the FDA-approved prescribing information, and based on my familiarity with the currently approved therapies, at least at the level that would merit special warnings and precautions in Section 5 of labeling. Extravasation to date is not -- has not been a -- has not been reported in the prescribing information based on the registered studies.

The next question, Dr. Chakrabarti, is with respect to the dosing calculation, should the change in volume over the clearance time from the site be accounted for in the absorbed dose calculation?

DR. CHAKRABARTI: That's a good question, actually. The only change is the dose calculation would change, but my understanding is that value is calculated after immediate observation of the extravasation. And yes, with that it will change. But in the same time, you see that clearance process takes place also. It's not going to be a static process all the time that you get with those values at different times, the dynamic, at least two or three equations will follow. One is the changing the decay, changing the clearance, so it's going to be a little complicated in time.

DR. FOTENOS: Okay. Thank you. So one more question on the extravasation topic for you, Dr. Chakrabarti. Maybe discuss extravasation of radiopharmaceuticals injected intrathecally, not sure whether there were any published occurrences, but it's becoming more popular with gene therapy than their radiolabeled companions that are injected directly into the CSF?

DR. CHAKRABARTI: And in that case, could extravasation happen, is that the question?

DR. FOTENOS: I think the question is whether for intrathecally injected radiopharmaceuticals, whether there are reports of

extravasation in that clinical context.

DR. CHAKRABARTI: No. I have not seen any from the published, and I realize I gave a reference to the gentlemen, and his colleague did some early review of all applications in 2000-something, and that wasn't talked about inconsistent.

DR. FOTENOS: I would just -- I'm not aware of any. I don't believe there are any approved radiotherapies injected, you know, for administration intrathecally through an ommaya reservoir or such. But the investigation that I'm aware of, pre-imaging physical diagnostic radiopharmaceuticals for the patency of the reservoir is part of those -- is part of the extra complexity in that clinical context. But I think that at present, those -- intrathecally injected radiopharmaceuticals are investigational.

The next question was --

DR. CHAKRABARTI: But you -- Anthony, one thing in the last slide that I finished with the summary, but you will see in like the top there, three people contributed heavily on that; Dr. Marzella Dr. Masters -- Shane Masters, and Dr. All are medical officers and Dr. Marzella is a division director. They are involved in many aspects. So we are not hearing from them unfortunately, but I just wanted to

mention that they contributed heavily in that presentation.

DR. FOTENOS: Okay. Thank you. I think there was one more question submitted earlier on the topic of extravasation that Dr. Lisa Dimmick wanted to comment on. And the question was, in the approval of radiopharmaceuticals, can the FDA mandate that manufacturers and clinicians ensure or document that the prescribed dose is actually delivered as intended?

MS. DIMMICK: So I can't speak for the FDA in that regard, but I don't think that we can mandate that how the question is posed. But I will offer that in our NRC regulations, we do require that facilities have procedures or processes in place to assure that the administration was carried out in accordance with the physician's direction, the dosage and whatnot.

So there are protocols in place at facilities to assure that the administered dose is delivered as intended, but as we discussed, you know, extravasations can occur, and you're not -- you may not even be aware that they're occurring. And with an extravasation, keep in mind that we're not talking about extravasating the entire dose. There are just

maybe some contents can leak from the puncture site into the vein, so there is always some -- well, I don't want to say "always," but, you know, it's not uncommon for there to be some leakage, at least from the point where the needle enters the vein or the artery, depending on the type of injection.

But again, we do have requirements in place to assure that facilities need to assure that the administration is conducted in accordance with the physician's written directive or prescription.

DR. FOTENOS: Thank you. I guess I heard briefly from the FDA's perspective, most of our approval is based on the evidence submitted in October 21, 2020he new drug application, so any particular prescribing information, you know, would hinge on the individual product and what was necessary during clinical investigation to ensure safe and effective prescribing. So I think a lot of FDA perspectives would be product-specific and evidence based.

Proceeding to a set of questions more on the clinical perspective and the role dosimetry can play in safety evaluation may be directed first at Dr. Mitch Anscher. We have a couple of questions. First is, say a tumor is next to an organ at risk,

like the brain, the lungs, the heart, the spinal cord, etcetera -- we see this typically -- in this context, is it fair to state that proper dosimetry is a mandatory component of safety evaluation?

DR. ANSCHER: Thanks, Anthony. Well, I think that, you know, is it mandatory -- I think that goes into the development of the product and speaks to, I think, some of the things that Christy addressed and the need to determine what's being delivered to the tumor and to the normal tissues. So we would, as we're going through the development of a product, like to be able to determine that, you know, the dose that's being anticipated is actually being delivered to the tumor and to the normal tissue. So we've been asking sponsors to provide us with that information to the greatest extent possible. And I think with some of these radiopharmaceuticals, it may be different than what you're seeing with external beam radiation. We don't know -- we don't have long-term follow-up information and precise dose volume estimates for a lot of the normal tissue, as Christy John mentioned as well.

So -- and the other thing that we're seeing is a lot of these products are being developed, at least at this point, for patients with late stage

cancer so that few patients are going to live long enough to develop these long-term toxicities. However, you know, if you look at what's happened with immune checkpoint inhibitors, you know, we're starting to see long-term survivors in categories of patients who a few years ago had very short life expectancies. So we can't assume that these people are not going to live long enough to develop these late toxicities.

So I think we have to build into the studies long-term follow-up for people who are survivors so that we can learn more about what exactly are the tolerance doses for these new products.

DR. FOTENOS: Thank you. Dr. Rajendran, do you have anything to add on this topic --

DR. RAJENDRAN: You know, again -- this is Joseph -- again, each individual tumor is different for these types of systemic radiotherapy. It is not like external beam radiotherapy where you can clearly indicate that there's all the -- the administer activities going to that. It is very difficult. But again, it depends on the sensitivity of the tissue involved and also, it depends on the proximity to some extent. But they're usually not determined

based on the dosimetry because it takes a long time, but most of those patients, in my experience, we have always avoided any tumor, because mine -- my experience has been mostly in hematological malignancies, although I have done the solid tumors also, the solid tumors. The location, for example, if it is very close to some other vital organs, including spinal cord, then we routinely kind of try to reduce the volume by giving chemotherapeutic regimen prior to instituting systemic radiotherapy.

DR. FOTENOS: Thanks. And I guess on the same -- clearly, there's a distinction to be drawn between dosimetry that's specified in the -- as the requirements explicitly in multiple areas of our regulations for group measurement so that there would be at least small group estimates of organ at risk dosimetry acquired during premarketing investigation. And that is sort of a mandate, I guess, in the language of this question. But currently, going beyond that in terms of any existing regulation for personalized per patient dosimetry prior to -- you know, to guide individual patient dose, that does not currently exist. But Dr. Anscher, in your presentation, you highlighted the promising results from the phase two Dosisphere study for the

administered microspheres, and I guess assuming those are confirmed with additional investigation, how big do you think the gap is for extrapolating the evidence from that trial in support of individualized dosimetry for intravenously- administered therapy?

DR. ANSCHER: well, I think we would have to, you know, do the same type of demonstration, but one could envision where you would see the same thing. I mean because we know that tumors rapidly outgrow their blood supply, and that it's -- once they get beyond about 150 microns in size, they start to develop areas of no blood supply. And so to assume that there's uniform distribution of compounds that are administered intra venously I think would be -- we'd be fooling ourselves. But we would need to actually, I think, see that demonstrated and then once we see it demonstrated, I think the next step would be to do studies that either demonstrate or refute that it matters whether the dosimetry is individualized, similar to what was done in the dose of Dosisphere study. I think that will be very important information.

DR. FOTENOS: Thank you. I had a question for Dr. Bill Goeckeler, and I guess try and sort of connecting the dots from the sessions that

Dr. Bergeron and from NIST in the earlier session provided, I thought, you know, enviable findings on the degrees of precision for estimating, you know, administered activity with variability ranges in the less than half percent range. I noted in your slide, you referred to sort of the 25 percent inter-individual variation for causing that, and I think you even mentioned that on top of that, there was -- you know, there'd be measurement variation. My question was with respect to alpha dosimetry, do you have any estimate of the magnitude of measurement variation?

DR. GOECKELER: Yes. It -- that's a great question. So because of -- the best estimates we have so far is that because of the -- it's really the precision appears to be limited by the available number of photons. And I mean you saw what the images looked like. It looks like the -- a lot of work and you image for a very long time. Currently, the best you can do is about plus or minus 30 percent or so in terms of just the precision of the measurement itself. And think about the image I showed you of the 7 megabecquerel of actinium just in a liver lesion and kind of extrapolating to the whole body, one of those whole body images that I showed you, and what they

look like. So that's not to say that can't improve or that we won' use higher doses or that there aren't other methods. It just kind of reinforces the sort of compounding of uncertainties that are involved in some alpha-emitters and even some beta-emitters, short-range beta-emitters.

DR. FOTENOS: Thank you. And I guess with the few minutes we have left, following up on that response, maybe for any members of the panel, if you were -- you know, if you had to speculate on sort of one leading methodological target for reducing preventable variation in these estimates to drive the science forward, what sort of single methodological target would you identify, you know, for the community to aim for in improving the precision of these dosimetry methods?

DR. GOECKELER: Well, this is --

DR. FOTENOS: Maybe Dr. Goeckeler --

DR. GOECKELER: -- Bill Goeckeler. Yes. I'll take a crack. So I think one thing that's important, and it comes out when you actually start to look at this data. You can gather a lot of data but for most targets, there's a main source of exposure. The other thing -- and you raised it a minute ago about inter-intra patient variability,

right, so many of these patients with advanced solid tumors, it's not just a tumor. They have lesions all over their body. So I think that part of -- to the first part of your question is if you look at, for instance, for most of these -- for most of the drugs we're developing right now, bone marrow toxicity seems to be limited. It's not to say that it's the only one, but it's the one that's most clinically acute.

So if you look at that, there may be a couple source terms that predominate the correlation with clinical -- it may be just circulating time and blood. It may be something else and identifying what those are is really important, because some things, like blood sampling and other kinds of sampling, you can do with much more precision than just with gamma camera imaging. And so I think focusing in on what's most critical to measure and what's going to introduce the biggest part of the source component and then figuring out what's the precise -- most precise way to measure that could really help.

DR. MARIANI: Can I -- I don't know if I can contribute to the -- this is Maurizio Mariana -- I -- can you hear me now?

MS. LOPAS: Yes, I can.

DR. MARIANI: So I think that we should -- so I think with the last comment from William, I think that yes, we should remember that those images a lot of limitation. So it can only give us a ballpark in terms of the potential exposure to normal organ, and in our experience, we -- you were asking about the example experience. The marker -- biochemical methodological marker of toxicity were indeed the most effective in telling us if the exposure was in a range of safety that was acceptable.

Also in our experience, the uptake in the various lesions in the -- in a given patient, the uptake in the various lesions is quite variable. So that led us to think that the real marker of a good therapy is a marker of toxicity of normal organ. So when you have a marker of toxicity, that tells you that you are close to a -- the level in which you have limited in terms of the dose. And this is also a way to track maximize the exposure to a given patient.

It's difficult to have a dose evaluated on exposure of a single or multiple lesions, because this is, by definition, very variable. So yes, the -- my comment is essentially that dosimetry is valuable. It may be used to check or to approximate

which is the range of potential toxicity for normal organ. It's much more difficult to assess which is the contribution of lesions that are close to normal organs and then induce and direct exposure to the -- to the -- to an organ that is in a close proximity of (audio interference) unless it is a brachytherapy approach.

But for the administration that's intravenous for a carrier molecule, like if you had given receptor, for example, that is treated.

DR. RAJENDRAN: Yes. This is Joseph Rajendran. I know that dosimetry is not 100 percent perfect. See, the -- when we do the exploratory studies, as you mentioned -- as Dr. Mariani mentioned -- that the dosimetry is done to determine the dose to the organs of toxicity where toxicity is expected. But the intravenous methods are, again, not very perfect like a direct brachytherapy approach as you do it in liver therapies, like SIR-Sphere and other things.

It is important that we have an idea about where to focus on our toxicities because, for example, the toxicity really is based on what the radiopharmaceutical is used, and bone marrow was mentioned as one of the toxicities. That can be a major toxicity. That can be -- we can do a number of

ways in which you can estimate the dose to a patient receiving systemic radiotherapy. For example, in radioimmunotherapy where the treatment is done by labeling the normal situations, like, for example, anti-CD45 is antibodies used to target anti -- to target CD45 receptors. There is -- a lot of uptake can be in the bone marrow, but in situations where we can estimate, we do a bone marrow biopsy and adjust the dose, the circulating dose and also the dose estimated to the bone marrow by the level of uptake.

There are various ways to improve the deficiencies in patient organ-based dosimetry.

MS. DIMMICK: Okay. I think we're going to go ahead and need to end there. Thank you very much, Dr. Rajendran, for your additional comments. We need to go ahead and move on to Session IV. So again, thank you Session III and the Session III panelists and for the discussion. It was very good.

And so for questions we weren't able to get to, again, we will try to provide responses to the questions that have been submitted to the chat.

Okay. With that, we'll turn it over to Session IV, which is, "The Evolving Landscape of Radiological Devices." The moderator for this Session is Ralph Lieto. Mr. Lieto is Chair of the

American College of Radiology Medical Physics Government Relations Committee. Mr. Lieto has been a medical physicist for over 50 years -- I'm sorry, Ralph -- 40 years. Thank you and welcome.

(Pause.)

MS. DIMMICK: And Ralph, you were there. You're on mute, Ralph, or maybe we need to unmute Ralph.

DR. LIETO: Let's try this. Is that better?

MS. LOPAS: Yes, that's better. That was very good. Thank you.

DR. LIETO: Okay. Sorry about that. Okay. Thank you for the introduction, Lisa, and the correction on the time because I still think I'm younger than what I am. Just a reminder to attendees, submit your questions you have for the speakers by selecting the "chat," which is a bubble in the lower right-hand side of your Webex screen. Be sure to select "all panelists" for your questions, because some of these are going to a private chat.

Speakers, please adhere to your time allotment. Our first presentation is entitled "Radiological Devices: Total Product Life Cycle," which will be given boy Julie Sullivan. Dr. Sullivan

is currently an Acting Branch Chief in the Division of Radiological Health within the Food and Drug Administration's Center of Devices and Radiological Health, which regulates diagnostic imaging and radiation oncology devices. Dr. Sullivan.

DR. SULLIVAN: Thank you. Can you hear me okay?

DR. LIETO: Yes.

DR. SULLIVAN: Okay. So I do want to mention up front that the examples that will be used in this presentation are not to be considered FDA endorsements of those products or companies. Next slide, please.

So today I'll be discussing the regulation of radiological medical devices with a focus on their premarket regulation. Next slide, please.

To start, I'd like to discuss the scope of FDA's regulation of medical devices. FDA regulates the manufacture of the equipment and the equipment itself. Other state and federal agencies are responsible for regulating the use of radiation-emitting devices through recommendations and requirements for personnel qualifications, institutional quality assurance programs, and

facility accreditation. Next slide, please.

The Medical Device Amendments of 1976 are laws that require medical devices to be both safe and effective and the definitions for these terms are shown here. To summarize, safety is the reasonable assurance that the probable benefits to health and the use of the device for its intended uses outweigh any probable risk. Effectiveness is the reasonable assurance that the use of the device for its intended use and conditions of use will provide clinically significant results. Next slide.

The FDA takes a risk-based approach to device regulations. In the FD&C Act, three classes are established for medical devices, and devices are placed into one of these three classes based on the degree of control necessary to assure safety and effectiveness. Class I devices are the lowest risk devices and are subject only to general control such as good manufacturing processes. Most, but not all, Class I devices are exempt from premarket notification. Some examples of Class I devices are toothbrushes, tongue depressors, and hospital beds.

Class II devices are products for which the FDA has determined that general controls alone are not sufficient to ensure a reasonable assurance

of safety and effectiveness and so special controls are needed. A few Class II devices are exempt from premarket notification via the 510(k) pathway, but the vast majority of Class II devices require premarket review and FDA clearance prior to being put on the market. The majority of medical devices are Class II. This includes most radiation therapy devices and devices such as patient positioners, HDR brachytherapy systems, and proton therapy systems.

Finally, Class III devices are the highest risk devices. These are life-sustaining or life-supporting devices such as cardiac pacemakers, or devices or new technologies that we don't know enough about to regulate as Class II. Either special controls or general controls cannot provide reasonable assurance that the device is safe and effective for its intended use, or the technology is new enough that we can't identify all the potential controls needed. These devices are subject to premarket approval by the FDA. Some examples of radiation therapy devices that are Class III are radioactive microspheres.

Generally, if an existing regulation cannot be identified for a new device, it is classified into Class III by default. The exception

is if FDA feels the device is low enough risk and is well understood enough to write special controls. The process of creating a new Class II regulation for such a device is called de novo. Next slide, please.

Both general controls and special controls are used by FDA to help provide a reasonable assurance of safety and effectiveness. On this slide are examples of both general and special controls. The types of controls a device is subject to can be found in the classification regulation for that device. All medical devices are subject to general controls unless exempted by the regulation. Special controls are usually device specific and may include controls such as premarket data requirements or special labeling requirements. Next slide, please.

How FDA determines what a device is meant to do or how it is meant to be used is by both its intended use and its indications for us defined here. Understanding these help FDA determine how the device is regulated. Note that the intended use and indications for use for a device may be the same for devices with a general indication that do not specify a disease, condition, or population. The intended uses of many radiation oncology devices can be very general. An example of this is for a linear

accelerator where both the intended use and indications for use may be to deliver radiation to the body where radiation is indicated.

As I mentioned earlier, most radiological devices at Class II devices that require a 510(k) submission to FDA. We'll talk more about this type of submission next. Next slide, please.

The premarket notification, called a 510(k), is the pathway to market for most Class II devices such as radiation therapy devices. A device that has gone through the 510(k) pathway is said to have received FDA clearance. Manufacturers must submit a 510(k) when introducing the device into commercial distribution for the first time or when making a change to a currently marketed device. A new 510(k) is needed when the change could significantly affect the safety or effectiveness of the device or when there is a major change in the indications for use of the device. Next slide, please.

The 510(k) premarket notification establishes a pathway to market based on substantial equivalent. To gain market access via this pathway, a manufacturer must demonstrate that the new device they intend to market is substantially equivalent to

a predicate device. This is done by comparing the new device to the predicate device and demonstrating that the new device is as safe and as effective as the predicate device. FDA establishes substantial equivalence by comparing the intended use and technological characteristics of the two devices. Next slide, please.

The substantial equivalence is demonstrated when the new device has the same intended use and the same technical characteristics as the predicate device or when the two devices have the same intended use and different technological characteristics but do not raise different questions of safety and effectiveness. Next slide, please.

To evaluate the different technological characteristics between devices, FDA reviews the scientific methods used to evaluate the difference in technological characteristics and the resulting performance data. The types of performance tests necessary to establish substantial equivalence are dependent on the complexity of the device and its intended use and indications for use. The performance testing may include bench, animal, or clinical test data. FDA uses information from previously cleared or similar device types to

understand where the failures may occur in the newer modified device. We use this information in a total product life cycle approach where the same reviewers that are evaluating the post clearance issues with the devices are also the reviewers performing premarket review of the devices. On the next slide are some examples of radiological devices and their classifications. Next slide, please.

Regulations for radiological devices are divided into diagnostic devices and therapeutic devices. An example of a radiological diagnostic device regulation is 21 CFR 892.1200, which is for emission tomography and is a Class II regulation. The regulation contains multiple product codes that include devices such as PET, PET CT, and PET MR devices. The product codes are generally an internal FDA method for bucketing devices within the same regulation. Next slide, please.

The therapeutic radiological devices are found in subpart (f) of 892 and include approximately 15 regulations. Examples of common radiation therapy regulations are shown here. On the next couple of slides, I'll give some examples of Class II devices that were cleared using the 510(k) process. Next slide, please.

The first example is for the Varian Bravo system that falls under the regulation for remote controlled radionuclide applicator system. And this regulation also includes things such as the actual applicators that are used for the HDR system. The predicate device used in this case was a previous version of the Afterloader device. Next slide.

The second example of a 510(k) clearance was for the CivaSheet from Civa Tech. This device was found substantially equivalent to a predicate device from the same company that was also used for low dose rate brachytherapy. It just was seeds on a string versus seeds in the resorbable matrix shown here.

So now that we've discussed Class II devices and the 510(k) process, I want to differentiate this from a PMA process that is used for Class III devices. Next slide, please.

So if you remember from earlier in the presentation, a Class III device is considered the highest risk category. It is one that supports or sustains human life and is of substantial importance in preventing impairment of human health or has the potential for an unreasonable risk of illness or injury. We are also unable to solely rely on general

and special controls to assure safety and effectiveness. Next slide, please.

A PMA, or a premarket approval, is the review process for a Class III device. The PMA approval process does not rely on the use of a predicate device, so there is no substantial equivalence determination. A PMA application must contain sufficient scientific evidence to provide a reasonable assurance that the device is safe and effective. In the review, FDA weighs any probably benefit to the health from the use of the device against any probable risk of injury or illness from such use. Next slide, please.

Examples of the types of benefits, risks, and additional factors that are weighed during the review of a PMA are shown here. For more information, you can look into this guidance document on the slides that are sent out. If not, it's entitled, "Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and De Novo Classifications." But in general, we're looking to understand the type, magnitude, duration of benefit and compare that to the probability and duration of risk. And in addition, we take into account the additional factors shown here. Next slide, please.

PMA submissions must include valid scientific evidence to support the reasonable assurance of safety and effectiveness of the device for its intended purpose. Some important components that are part of a PMA submission are shown in the table on the slide and include information such as clinical trial results, proposed labeling, and manufacturing information. Next slide, please.

In the last slide, I mentioned the term "valid scientific evidence" when discussing the type of evidence needed to support the reasonable assurance of safety and effectiveness. Some examples of valid scientific evidence are shown here. I want to note that FDA does not consider isolated case studies, random experience, unsubstantiated opinions, or reports lacking sufficient details to permit scientific evaluation to be valid scientific evidence. Next slide, please.

On this slide are a couple examples of post approval controls that PMAs have. These may not also be prevalent in 510(k) submissions. Next slide.

So an example of a Class III radiologic device is the Sirtex SIR-Sphere device. These are Yttrium-90 labeled microspheres that are indicated for the indications shown at the bottom of the slide.

So now that we've discussed the classification process, I just want to provide a few tips for successful submission with the Division of Radiological Health. Next slide, please.

So the Division of Radiological Health, or DRH, is a huge proponent of the use of the pre-submission program. This process, which is often called the Q-sub process, allows you to ask questions about the development and regulatory pathway for your device. For example, it can help in identifying performance tests as needed based on the intended use of your device before you start testing.

Other key tips are to make sure you provide a clear description of your device, what it does, and what it is used for. Remember while you have spent years developing your device, we may be learning about it for the first time, and we really need to understand what your device does before we can properly evaluate it.

Additionally, it's beneficial to focus on the why in addition to the what. You had a reason for performing the testing you did or for providing that data to FDA. We want to understand the rationale. Next slide, please.

We can probably skip this one. This just

says that we talked about the regulation of radiological devices. Next slide.

And then here are some helpful resources for preparation of a submission. CDRH Learn has many videos about compliance and premarket submissions, Device Advice is a CDRH website that contains helpful information about all regulatory pathways in CDRH. And the Division of Industry and Consumer Education, or DICE, is a great place to start if you have any questions about the development of a medical device. Next slide.

And just to say additionally, you're free to contact the Division of Radiological Health directly if you have any questions. My email address is provided here, and thank you for you time.

DR. LIETO: Thank you, Julie. Our next presentation is entitled, "Sealed Sources and Device Registry." Our speaker is Tomas Herrera. Mr. Herrera serves as the Sealed Source and Device Team Leader in the Material Safety and Tribal Liaison Branch of the Nuclear Regulatory Commission. Mr. Herrera.

DR. HERRERA: Thank you, Ralph. Good afternoon, everyone. As Ralph mentioned today, I'm going to be providing an overview of the sealed source

and device review process. Next slide, please.

The purpose of our sealed source and device evaluations is to ensure that sealed source and devices containing radioactive material will maintain their integrity during normal use and likely accident conditions. We're not evaluating the efficacy of the devices or sealed sources. What we are is looking specifically at safety. And our review allows for the registration of the product with one entity, whether it's the NRC or an agreement state, and that review is reciprocal and accepted by the NRC and agreement states and vice versa. Next slide, please.

The sealed sources and device registration certificates that are issued after the device and sealed source have been reviewed are maintained in a national registry. The national registry is a composite of all the sealed source and device registration certificates issued by the NRC and agreement states. And the registration certificate is essentially an evaluation of that sealed source or device that's been reviewed and information regarding licensing and any kind of special conditions of use. That registration certificate, the registry includes certificates for

industrial, medical, and consumer products, and it is maintained by the NRC. Next slide, please.

And during today's topic, these discussions, I wanted to highlight some o the specific areas that I think would be of most interest to the attendees, specifically, the NRC uses a guidance document, NUREG-1556 Volume III, for its reviewers as well as for applicants. And it is available publicly and it's a very good document in terms of when somebody's preparing an application. In today's slides, we'll be discussing what we review in terms of the design, prototype testing, operations, instructions of use, external radiation levels, and quality assurance and control. Next slide, please.

As part of our design review, what we're looking for in terms of an applicant's submission is looking for an overall understanding of the product, the dimensions, the size of the product, the materials of construction in terms of what kind of shielding will be used, what types of material would the actual product or sealed source it would be made from, also how the device is actually manufactured in terms of how it's put together, with fasteners or screws or in terms of welding. Also, we want to understand how the actual device functions and works. And also, any

kind of safety features that may be included with the device, especially if there's a loss of power and if the source -- sealed source will be returned to a safe position in the event of a power loss. Also understanding how the on/off mechanisms work and if there's any indicators to indicate if the product is in the on or in the safe position, labeling to be able to identify the distributor of the device as well as the maximum -- the activity levels in the isotopes and the product and as well is any kind of assumptions or approximations or any type of calculations that are provided will ensure -- to make sure that that that's been submitted does make sense to us and is clear. Next slide, please.

For the prototype testing aspect of the sealed source and device review, we, the NRC and the agreement states, do accept four different types of prototype testing submissions. This includes actual testing of a product, the comparison to a previously reviewed product, and by that, I mean if the applicant has a previously-reviewed product, if they compare it to something they had previously registered, the operational history of the device, and in some cases, we do receive applications from outside of the effort, products that had been distributed outside the United

States, and if they had a significant amount of operational history, we will review and potentially accept that as well as a potential engineering analysis.

And what we're looking for as part of the prototype testing evaluation is that if the actual product that's tested, it may actually be tested without the actual sealed source containing radioactive material while preventing unnecessary accidents. We're looking for if there are moving parts, have those been tested. Has the testing exceeded the actual normal conditions in adverse environments? So basically, as I mentioned before, the whole purpose of this is ensuring that the product will maintain its integrity during normal use and likely accident conditions.

Ad as I mentioned earlier in the slide, if the applicant is comparing to previous product that had been registered by that same applicant, we will evaluate just to ensure that it's substantially similar to that previously approved product. Next slide, please.

We're also looking at understanding the operations and instructions to users, understanding what the normal operation of this product is, how

it's going to be installed, and what kind of environment it's going to be installed in, how the product will be leak tested or there's on and off testing, how the source exchange will occur after the source -- if it has a short half-life, how that will take place, if there are any kind of special servicing requirements or what kind of agreements that the applicant, what type the manufacturer will perform, if there's going to be any special conditions or any other limitations of use, particularly if there's a certain temperature range that that product should be used in or should not be used in, and maintenance, what kind of special maintenance will be performed for that device to ensure that it'll maintain its integrity. Next slide, please.

And for the purposes of external radiation levels, what we're looking for is when the applicant submits the dose rates, we want to make sure -- we'll review to make sure that they seam reasonable. Also what we're looking for is that the applicant will submit the maximum activity -- the dose rates and the maximum activity their requesting for, so in a sense, that if they're requesting for a device to use 12 curies of iridium-192, we want to see that dose rate for this 12 curies as well as if

there's any additional tolerances; if there would be a plus or minus 5 or 10 percent, we'll want to make sure that that is all included as part of our evaluation to understand what the maximum activity or the maximum dose rates for that device might be.

And so in some cases, devices may use -- or sealed source devices may use different radionuclides, so we would want to see the maximum -- we want to see the dose rates for each of those radionuclides and if there's different models of -- different models in that applicant's submission, we want to make sure we have an understanding of what the radiation -- the dose rates would be for each of those models. Next slide, please.

And then we also perform an overview of the quality assurance and quality control programs. Essentially, what we want to verify is that the applicant has a program in place to ensure that the sealed sources and the devices that are manufactured and distributed will meet the approved specifications before it's going out the door. We want to make sure what's been submitted to the NRC is actually what is actually going to be distributed. We also want to verify that if there's any safety features, that those have been tested prior to distribution, that the final

radiation profiles of external dose rates are as they were submitted to the NRC and making -- verifying that the product is leak tested when it's distributed.

So that's all the information that we'd require as part of our quality assurance review as well as reviewing the overall program. Next slide, please.

And for medical products, which I think is of most interest to the attendees today, the NRC policy is that if there's a -- if the product requires FDA evaluation, that we would not issue a registration certificate until we received one of those. In the previous presentation, one of the most popular that we see are the 510(k), but the NRC would accept a PMA, HDE, or IDE. So again, we might review it in tandem, but the registration certificate, from the NRC's perspective, would not be issued until we receive that final approval. Next slide.

For the registration certificate itself, the final issuance of the registration certificate is just the final culmination of the NRC or agreement states' review. It's a summary of the information that has been provided as part of the application, and in the registration certificate, there is a statement that the source or device has been reviewed

and based on the information has been approved for use and licensing. And each registration certificate has a unique number. As you see, I had an example. So the first two digits of the registration certificate represents the entity that issued the sealed source and device evaluation. In this case, it's NR. That's the abbreviation for the NRC. If it was issued by California, it be CA and so forth. The next four represented by the "X" are the vendor, specific vendor code. There's a specific vendor code with an applicant. Next letter, "D," represents if it's a device or a sealed source. If it was a sealed source, it would be an "S." And the "YY" would be a series of numbers to indicate how many registration certificates that applicant has. The normal numbering process would be to start at 101, 102, 103, and so forth. And the last letter represents who can actually use the actual device. In the case, that "S" represents that someone had required a specific license to use it.

Now for format purposes, as I mentioned, the NRC and our agreement states both issue registration certificates. Now the standard --the format is pretty standard. There might be some differences in terms of thought, but the information

that's contained in both registration certificates issued by the NRC and agreement states are the same. The guidance document I referenced earlier, NUREG-1556, does provide templates and that's what's used. Next slide.

And for the certificate sections, the certificate sections have the descriptions, provides an overall summary of the product, labeling -- it describes the labeling that are on the products; a diagram -- it includes the attachments that may be included with the registration certificates; it's usually a good drawing or a picture of the actual sealed source or device. Conditions of normal use; this is a summary of what the normal proposed conditions would be, whether it's temperature, vibration. The quality assurance is a summary of the quality assurance and control program. And limitations and considerations of use, this is a high-level discussion of what limitations are on the product and whether or not there's any special conditions that must be met. And then for medical products, there is a summary of the DA approval. And then finally, it's the safety analysis summary for the actual sealed source and device. This is where the confirmation of the product has been reviewed and

validated and approved by the NRC or agreement states.

That concludes my discussion for today. I'll turn it back over to Ralph. Thank you, Ralph.

DR. LIETO: Thank you, Tomas. As a past RSO, I really recognize the importance of these certificates.

Our next speaker and presentation is entitled, "Gamma Knife and Microspheres: An NRC Perspective," that will be given by Katie Tapp. Dr. Tapp is a medical physicist on the Medical Radiation Safety Team of the Nuclear Regulatory Commission. Dr. Tapp.

DR. TAPP: Thank you, Ralph. Today I'm going to talk about gamma stereotactic radiosurgery units and microsphere brachytherapy and other emerging technologies the NRC regulates.

Next slide, please. When the NRC learns of a new emerging medical technology, we evaluate it to determine if it can fit into the current regulations in 10 CFR 35, Subparts D through H.

If a technology is not specifically addressed in 10 CFR 35, Subparts D through H, with specific requirements, the staff will develop licensing guidance that describes regulations and specific conditions the Commission has evaluated and

considered acceptable for the specific technology so that it can be licensed under 35.1000.

Next slide, please. First I'll talk about gamma stereotactic radiosurgery units.

Next slide. Subpart H for 10 CFR 35.600 provides regulations for teletherapy, remote after loaders and gamma stereotactic radiosurgery units. Specific requirements include safety procedures and precautions, full calibrations, periodic spot checks and training experience for authorized users.

These specific requirements are outdated for many of the new gamma stereotactic radiosurgery units that are being developed today. But they are still being used for the gamma knife Model C, which is licensed under 35.600.

Next slide, please. As I just mentioned, the recent GSR units are unable to meet most of the specific requirements listed in 35.600 today. These include calibration and periodic spot checks of the relative helmet factors, comet micro switches and trunnions as well as the regulations did not consider fractions, moving sources, frameless options and dynamic treatments when the regulations were first developed.

Next slide, please. I'm going to go

through some of the modalities that currently have licensing guidance under 35.1000 to demonstrate why they're in 35.1000 and some of the things that the NRC evaluated and has listed in their guidances for licensees to consider.

First, we have the Elekta Perfexion/Icon. This is licensed under 10 CFR 35.1000 because it does not have a helmet. The sources are in a movable sector to adjust for collimation without changing the helmets and the Icon has a frameless option.

Next slide, please. In the current 35.1000 licensing guidance, the specific licensing conditions for the Perfexion/Icon, this includes unique written directive condition, which must include a patient name, date and treatment site, gamma angle and target coordinates and sector settings for each slot and for the Icon requires dose per fraction and number of fractions.

The licensing guidance also has commitments to verify patient fixation prior to the treatment, pausing and checking locations in case of movement and visually checking patient setup if a gamma angle is changed.

It also has modified physical presence requirements and modified period spot checks in full

calibration conditions.

Next slide, please. It also allows the use of manufactured procedures where there's no published protocols accepted by nationally recognized bodies and has updated training and experience requirements for the authorized users, authorized medical physicists and RSOs.

Next slide, please. The ViewRay is another GSR unit that is licensed under 35.1000. It is licensed under 35.1000 because it has a rotating gantry assembly, an integrated magnetic resonance imaging for real-time image guidance, multi-leaf collimation and gating. These are all features that were not considered when regulations in 35.600 were developed.

Next slide, please. The licensing guidance for the ViewRay has licensing conditions, again, specific to the ViewRay.

The written directives must include a patient name, total dose, dose per treatment and number of fractions. It also must include isocenter and gantry angle positions and treatment sites.

The procedure will include validation of geometric and dosimetric accuracy for each patient's treatment. Again, it has a modified physical

presence requirements and modified periodic spot check in full calibration conditions.

It allows the use of manufacturer procedures when there is no published protocols accepted by a nationally recognized body and has specific training and experience requirements similar to the Perfexion/Icon.

Next slide, please. The Gammapod is an additional GSR Unit. This unit is used for breast cancer treatment and is licensed under 35.1000 because of the rotating sources and collimator carrier, table movement during treatment and a vacuum-assisted breast cup immobilization and stereotactic localization system.

Again, these are features that were not evaluated during the development of 35.600 regulations.

Next slide, please. The Gammapod licensing conditions are listed on this slide. First the written directive requires a patient name, total dose, dose per fraction and number of fractions, the treatment site, including the planning target volume and inner and outer cup sizes.

It also includes modified physical presence requirements, modified periodic spot checks

and full calibration conditions to account for differences due to the breast immobilization and location systems and source and collimator movement and dynamic treatments.

It allows for the use of manufacturer procedures when there are no published protocols accepted by nationally recognized bodies and, again, has specific training and experience requirements for the authorized users, authorized medical physicists and radiation safety officers specific for the Gammapod.

Next slide, please. One thing I would like to highlight is for all the GSR units and all the emerging technologies, the NRC appreciates when manufacturers, early users and FDA work together to help create these licensing conditions that are listed above.

There is some question why there is differences between GSR units. And working with the manufacturers and the early users is generally the reasons for these differences. It is we're really trying to make it specific to those units and these licensing guidances.

I'm going to move on now to the microsphere and particle brachytherapy.

Next slide, please. Microspheres are closer to Subpart H in 10 CFR 35.400. This provides the regulations specific for manual brachytherapy using sources either approved in sealed source and device registries for manual brachytherapy or used in research to deliver therapeutic doses for medical use in accordance with an active investigational device exemption

The specific requirements in 35.400 include calibration, brachytherapy source accountability, authorized user training and experience, patient surveys and safety instructions and precautions.

Next slide, please. Yttrium-90 microspheres were classified by the FDA as brachytherapy devices. It was the original 10 CFR 35.1000 modality to have a licensing guidance, which was issued in 2002. It was licensed under 35.1000 because of the unique delivery system and the size and large number of spheres that are delivered for treatment.

Next slide, please. The Yttrium-90 microsphere licensing guidance includes training and experience specific for Yttrium-90 microspheres. It's a combination of radiopharmaceutical and manual

brachytherapy training. The training is allowed after authorization, which again is unique for the Yttrium-90 microspheres.

The medical event criteria excludes reporting of known medical risks such as underexposure due to stasis and wrong treatment site delivery due to shunting when pretreatment assessment is done in accordance with the manufacturer procedures.

This is, again, specific to Yttrium-90 microspheres due to the unique delivery of this device. It also has specific inventory and waste concerns listed that licensee should be made aware of and further guidance and has leak testing information available.

Next slide, please. Particle brachytherapy in addition is permanent implant brachytherapy, but it's similar to microspheres in the sense there is a large number of sources being implanted and they're of small sizes.

Therefore, particle brachytherapy, such as Phosphorous-32 used in Oncosil, is likely to be licensed under 10 CFR 35.1000. And depending on the applicator might not need -- these types of devices might not need a sealed source and device registry as

Tomas' previous presentation just went over.

Next slide, please. Now we'll quickly cover the proposed emerging technology rulemaking.

Next slide, please. The NRC staff is developing a rulemaking plan that provides options for codifying requirements for emerging technologies.

Codifying the requirements would mean that some of these technologies would be licensed without the need for being in 10 CFR 35.1000. Instead they would be licensed under the specific subparts that I mentioned before.

Potential rulemaking options include codifying requirements for the current GSR units and microspheres or the option is to have a broader rulemaking that would codify more approved emerging technologies and add greater flexibility to accommodate future emerging technologies.

The rulemaking plan with these options will go to the Commission in December 2020 for the determination if the staff should pursue this rulemaking for emerging medical technologies.

Next slide, please. And that concludes my presentation, and I'll turn it back over to Ralph.

DR. LIETO: Thank you, Katie. Our last presentation is entitled Industry Experience in

Regulatory Process for Radiological Devices, which will be given by Diana Thompson. Ms. Thompson is a radiation safety scientific advisor at SIRTeX Medical. Diana?

DR. THOMPSON: Hi, everyone. Can you hear me okay?

DR. LIETO: Yes, you're good.

DR. THOMPSON: Excellent. I want to thank the NRC medical team for the invitation. This has been a star-studded lineup as well as attendance. I'm very humbled to see many of my friends and colleagues during these weird times here in the chat box so kind of united over something that we are really passionate about, which is radiation physics. So on with the presentation.

So industry experience and regulatory process for radiological devices. Next slide, please. This is just a disclaimer that this is my own personal experience working at SIRTeX Medical.

In addition to my regulatory team, Marylou Stroumbos as well Jeffrey Cyr, we've all reviewed this presentation and they are present on the call with us if we have any questions for them.

Next slide, please. I also wanted to highlight and focus my presentation on what the agenda

was for this call, which was to basically look at supporting the timely access for patients to emerging technologies, especially when we're looking at life threatening medical needs, right?

So I'm going to go through our approval process and when and how we were approved by the different regulatory bodies as you saw. Because we are a medical device that's radiological, we are going to have a lot of approvals that we have to juggle and how that affects how our users and patients are treated.

Next slide, please. This is a description of our device. It's been brought up a couple of times, but this is from our instructions for use specifically.

It talks about we are microsphere between 20 and 60 micrometers in diameter. So we're pretty small with the Y-90 bound to that microsphere. It is implanted permanently using a catheter that is placed in the hepatic artery. We'll have an image on the next slide to kind of visualize what that looks like, how that implantation works.

It's similar, like Katie Tapp was saying, to that manual brachytherapy except for you can't really see our particular brachytherapy devices.

Our Yttrium microspheres are shielded using acrylic and implanted using a Class 1 accessory. So these Class 1 accessories are also part of our FDA approval.

They are not radioactive, but they are part of our sealed sourcing device registry as well, and they facilitate the implantation of the microsphere as well as providing beta radiation shielding.

Next slide, please. This is the image of our Class 1 accessories that are a part of our SSD application or SSD approval. If you look on the left-hand side of your screen, you'll see the acrylic that is used to shield the beta radiation from the Y-90 and then this is our acrylic delivery box on your right-hand side.

It is delivered by a pressure. So the doctor here is gloved, and he is using pressure on the syringe to then force D5W, or sterile water, into the V Vial, as we call it. And then that forces the spheres out and then to the right will be the patient that is attached by a catheter, right?

So those spheres are going into the patient via that catheter that is attached to our delivery device and the actual microspheres are

suspended in the liquid that is in the vial because they are so small.

I think one thing for us to highlight as physicists is that as the beta is shielded in the acrylic, it does still produce a little bit of X radiation and that is characterized in our sealed source and device registry, those radiation levels around our devices.

Next slide. This is to help visualize how our sealed source is implanted into the patient. So if you can imagine, the catheter is inside one of these vessels. And then when the authorized user or interventional radiologist, who may not be the authorized user, which we will continue on in the next section, then implants these spheres. They use that preferential blood flow to go into -- to treat the tumors that are being selected for treatment.

This is also how we essentially map. So we talked a lot about dosimetry. This is how we map where we want those spheres to go as well. So prior to the implantation as part of our instructions for use, we do use that technetium-99m MAA to verify where our spheres would go prior to implant. And then you implant them in that same location.

Next slide, please. So our initial PMA

approval was issued in March 2002. This is going to be an important date to remember as we go through how that impacts our other approvals and access for our patients and users to our device in the United States.

The important thing that I wanted to highlight here is that it was approved as a medical device because it -- and I copy pasted this regulation, regulatory definition, as it was approved in 2002 as a medical device. This kind of caused a little bit of conflict with the NRC definition of sealed source, which in 35.2 we don't meet those requirements of that sealed source, but we have a sealed source and device registry.

Part of that is because we are a medical device, and we do not use any chemical action within the body. The actual implant is implanted into the tumor and that's where we are imparting our active intended purpose of treatment.

Next slide, please. Part of that FDA PMA approval, as Ms. Sullivan was describing in that first part of our section, is that we do have this additional requirement for the training, education and certification program, the TEC program as we call it.

This requires our physician proctor to go

out for every treating physician and that is the interventional radiologist. This is to ensure that they understand where the catheter goes, how that affects treatment, how to select patients and how to perform mappings and how that relates to treatment.

This is part of the safety that we have that we put physician proctors that have done hundreds of cases with our new users to go through this process.

A user cannot order our product without having completed the TEC process and be certified by one of our physician proctors that they understand the safety and efficacy of our product.

This is also highlighted again in our instructions for use that we specifically state that unless you have a license pursuant to 10 CFR 35.1000 and have completed the TEC process, we will not ship our device, which is our safety promise, right?

Moving on to the next slide. As well just to highlight, you know, our industry experience, this was to note that we do have a supplement 004 that we did get approval in January 2008 to manufacture and distribute our own product in the United States in Wilmington, right outside of Boston.

This is an FDA supplement but we also

have two additional state licenses for possession and distribution of the radioactive material. So that did require a radioactive materials license.

They are from the state, the agreement state, because Massachusetts is an agreement state.

Continuing on to the next. This is highlighting Dr. Tapp's excellent work. We do have the guidance, which tells our clients what they need to do in order to use our product safely.

The things that I wanted to highlight that have the stars here is that the first guidance came out in October 2002 whereas our first PMA approval as well as our SSD approval came out in March of 2002. So between March and October, there was really not access to our product in a completely compliant way because as she highlighted under 35.400, you can't really count our microspheres as you're doing the implant and so what were our users to do?

The broad scopes that were doing research type applications and trying to get the initial patients treated in the country were working with us and with Katie Tapp's group in order to develop this guidance so that we could have these set guidelines for safety for everybody. So that's part of that

collaboration that we have with the NRC that we greatly treasure.

In October 2002, again in line with that manual brachytherapy and the fact that we are a micro brachytherapy, the radiation oncologist was our authorized user whereas the interventional radiologist was the person that was actually implanting the device and the person that we were training as part of our TEC process required by the FDA.

So we had a little bit of disconnect, but we kept that as a team approach in the guidance document.

Moving on into 2017, that's when the nuclear medicine physician could now become the authorized user, which is important for our product because the nuclear medicine technologists are the ones that are actually preparing the patient dose.

So the radiation oncologist was the authorized user. The interventional radiologist is the treating physician and the nuclear medicine technologist is actually preparing the dose.

So we added the nuclear medicine physician as a potential authorized user. But there's still no pathway for that interventional

radiologist to become that authorized user on the license that can actually sign the prescription for our device.

Here in 2011, that's when we finally aligned, right? So the TEC process that the FDA kind of observes for us and then the NRC guidance, we matched. The interventional radiologist is now able to become an authorized user. And they're kind of congruent.

So this was a really great -- this was when everything was in congruency. And now in March 2020, we have a new guidance that was issued where the authorized user and the TEC process is again separate.

And in all of these revisions, we do work with our clients as well as the NRC to make sure that we understand the requirements so that our product is used safely and that our clients understand that they must be compliant with NRC regulation because the most important thing is the safety of our patients as well as our users.

Next slide, please. So here was just another thing to highlight about keeping things in congruence is that we did have a PMA Supplement Number 7, which required an update to our SSD application

when we added the optional use to use D5W as a non-ionic solution.

Prior to that it was only sterile water, and we did have to juggle both of those approvals. And if they were not in congruency then our users had to live in a gray area of compliance until we could realize both those approvals at the same time.

And then the last slide, please. And that's basically my ending comment is that we have quite a few approvals, the PMA Class 3, the Class 1 for our accessories, the sealed source and device registry as well as all of the NRC guidance.

I welcome any questions. And I want to thank the team again for having me and having us on the agenda. Thank you very much.

DR. LIETO: Thank you, Diana. I want to thank all four speakers for their really nice, concise presentations. And as a moderator staying within your time allotments makes you all the rock stars.

We do have a few questions. I'm going to -- we have kind of a very long one here. Let me see if I can paraphrase it.

It has to do with the Y-90 microsphere licensing guidance, which has been interpreted by some licensing agencies to not allow centralized

nuclear pharmacies to put this on their license to allow them to prepare the dose in a vial for their licensee customers.

Evidently, this would require a change in the sealed source device safety evaluation and thus precludes this being done by a nuclear pharmacist. Do any of the panelists want to comment?

DR. HERRERA: Ralph, I'll try to take part of it. From my perspective at least in the sealed source and device evaluation processing, the microspheres themselves were registered as part of the device, I think, as Diana mentioned. They really didn't meet the definition of a sealed source, per se. Usually when you think of a sealed source, you think of a piece of metal with some metal slugs in it.

So in this case I think I agree with that statement in that if they're going to be using other microspheres, I think if my understanding is correct that they're distributed as part of the product, then, yes, there would be a necessity to seek a different sealed source and device evaluation.

But I'll let one of my colleagues maybe expand on the licensing questions part.

DR. THOMPSON: Katie, do you have this?

Because I think we've spoken about this in the past as well.

DR. TAPP: Yes. I agree with Tomas. If someone would like to use a different microsphere with a different device or mix and match, that would require another evaluation. I'm not sure exactly if that's the question or not.

If the question is to use a microsphere and draw it up and then use it as part of the device, I do not think that's what the licensee guidance is trying to specify here.

It's really trying to specify don't use one microsphere with the other device or vice versa or something new without doing a formal evaluation.

DR. LIETO: I was interpreting this to mean that the centralized pharmacy would get the vial and then adjust the amount to the patient specific requested dosage. Does that require a change in the sealed source device registry?

DR. THOMPSON: No, Ralph, that doesn't for us because that is specifically how our product is used. Our product comes as a single vial at a specified activity. And the nuclear medicine technologist or the pharmacist would draw up the dose from that sourced vial and put it into that V Vial.

So we don't -- that's how our product is supplied and how it has worked since its inception in 2002.

DR. LIETO: Okay. Thank you. There's a question here about the about the new SIR-Spheres delivery system that I guess is under evaluation. Has this been approved for use?

DR. THOMPSON: Correct. It's on our sealed source and device registry. And that has been approved through the Massachusetts Sealed Source and Device Evaluation Group. And it is on the same certificate. You can use the SIR-Spheres with either the SIROS delivery device or the current box delivery device, correct.

DR. LIETO: This --

DR. THOMPSON: This was reviewed in March 2020.

DR. LIETO: Thank you. Maybe this one is also aimed at you, Diana. It's a clinical question. Do the spheres settle into the bottom of the vial. And I'm wondering if physicians must take this into account when administering the treatment dosage.

DR. THOMPSON: So they do settle, and they settle quickly. Any of the nuclear medicine technologists on the call that have done this, they

will see the number change as it's in the dose calibrator, right?

But that's the entire purpose of the delivery device is to resuspend the spheres so that they can be administered.

So they do not need to take that into account during administration in the sense that the administration device or apparatus is meant to suspend them again so that they can be administered.

Additionally, as part of the guidance, every user has to estimate the residual activity and ensure that that's within the plus or minus 20 percent that requires a medical event report, right?

So if for some reason there would be some residual in the device, that would be captured during that time as well.

DR. LIETO: The next question that has to do with USP 825 and how does this affect the preparation of SIR-Spheres for preparing dosages for customers? It might be in your wheelhouse here, Diana, also.

DR. THOMPSON: Sure. Absolutely not a problem. So USP 825, they did -- the USP did go through, I think, appeals on this. And so right now it is an informational standard that's not

compendially applicable as stated by the USP. But it really does depend on your local regulator because the local regulator, which usually is the Board of Pharmacy, can implement that in your state via regulation.

So I would look to the Board of Pharmacy to see if they've actually implemented it as a not informational but required standard. And if it is still informational then it is up to your facility whether or not they want to implement that.

And for me when I was an RSO that was through the environment of care. We would talk with our accreditation group and see if this is a standard that we can adhere to, how and why to ensure that we mitigate our risks. And if anybody needs to talk about that they can feel free to call me as well.

DR. LIETO: Okay. And maybe this is a clarification -- excuse me -- of that question about can a commercial or centralized radiopharmacy draw the prescribed Y-90 microspheres and place them in the V Vial and then deliver the V Vial to the customer?

DR. THOMPSON: Yes. Yes, Katie, go ahead.

DR. TAPP: One thing I would like to comment on this is that the licensing guidance itself

was not that -- the commenter referenced the clause in the licensing guidance, which was talking about the sealed source and device registry.

And that clause in the licensing guidance is really for -- you cannot mix and match microspheres and the delivery system. Those have to be together, and it has to be the approved sealed source with the delivery system.

A specific question regarding specific commercial radiopharmacies and what they're able to do for their license really should go to their licensing agency whether an agreement state or NRC.

And if they still have questions from the state, they could go ahead and contact me. I don't want to speak in general what every state out there is licensing.

DR. LIETO: Thank you. I have a couple questions here that relate to dosimetry methodology, in other words is there FDA approved or recognized methodology to determine the personalized dose for the Y-90 microspheres? And does that type of methodology require any type of regulatory approval? I'm assuming probably by the NRC.

DR. THOMPSON: So the way that I interpret this to be is that our insert has the BSA

method. The body surface area method is in our package insert in our instructions for use for users to estimate the dose to be delivered to a particular patient.

The authorized user will use this dosimetry method in order to determine what should be on the written directive. The written directive is what the nuclear medicine technologist then uses to draw up the dose as well as what they compare to for medical event criteria.

As far as doing any other type of dosimetry, that would be an FDA question. It would not be part of our legal views.

DR. LIETO: Okay.

DR. SULLIVAN: Yes. To expand on what Diana said, what we've cleared or approved has been used what's currently on label with SIRTeX. Anything else, if you have questions, please contact us.

DR. LIETO: Okay. Yes, I think the questions were kind of like aimed at sort of the radiation therapy treatment planning concept where there was maybe an FDA approved methodology that's been submitted or reviewed or recognized. And it sounds like that is not the case. The next question that I see here is, can you comment on the DAVYR

application? I'm not quite sure what the DAVYR application is.

DR. THOMPSON: The DAVYR application. It is an app that's available, I think, for iPhone and Android users, and it does dosimetry calculation using several different methods based on input.

It is not endorsed by us, I think, and it's also not approved by the FDA. It does have a disclaimer on that app that it is for informational purposes only.

DR. LIETO: I have a question for Tomas. Tomas, a licensee cannot use or receive a sealed source unless he has a sealed source registry certificate. And is that correct?

DR. HERRERA: I'm sorry, Ralph, you're breaking up a bit. I didn't catch all of that.

DR. LIETO: Okay. A licensee cannot receive or use any sealed source unless a sealed source registry certificate exists and has been approved. Is that not correct?

DR. HERRERA: Okay. So as I understand it, basically someone cannot use a sealed source or device unless the sealed source has been registered by a state agency or the NRC. Is my understanding correct?

DR. LIETO: Yes.

DR. HERRERA: Well, I think there are certain stipulations, particularly if it's a broad scope licensee. There are other instances where the licensee, if they could actually add or request that sealed source device be added as part of their license but then they would have to submit that information, the device information, the sealed source device information, that we would typically evaluate to the licensing authority.

So there are ways to obtain a sealed source device that may not be registered, but they would still need to be licensed and they would still need to be evaluated.

DR. LIETO: But that registry, assuming, you know, it's a specific licensee and not your broad scope, which is, you know, your 90 percent licensees, they do not have access to the registry any longer. That's true, right?

DR. HERRERA: That is unfortunately correct. Following the events of September 11, the registry -- it was publicly available but it was taken down.

We do ask that if somebody is trying to obtain a sealed source device registration that they

reach out to the manufacturer and distributor. So there is that allowance for the distributor to provide the certificate, but the registry is currently down.

DR. LIETO: Okay. So if they requested it, it is provided normally?

DR. HERRERA: Right.

DR. LIETO: Okay. Thank you. I have a question here, the question here on --

DR. HOWE: Ralph?

DR. LIETO: Yes?

DR. HOWE: I just wanted to add to the answer to the last question. In our regulations, we also permit licensees to use devices that are under an IDE. So that would be a device before it's gotten a sealed source and device registry. So that's another avenue for getting a device.

DR. LIETO: Okay. Thank you. I'm not too sure how this relates to ours, but I'll ask it anyhow. It says the NRC requires a medical event report if the therapy dose is not administered to the patient due to a device failure or a human failure which prevented the dose from being placed into the patient.

Does the NRC want to comment on that?

DR. TAPP: Sure. The NRC requires

medical event reporting to help prevent recurrence. So when an event reaches the criteria set in the regulations, it is helpful for the NRC to see these events. They do not always mean that there was a device failure or human failure. It can sometimes be -- a medical event can just occur due to limitations and practice of medicine.

The NRC uses this information to determine if there was some sort of incident that could be corrected and then we alert that individual licensee for corrective actions and make sure they follow through to prevent it in the future as well as if it's something we could alert other licensees or the manufacturer to prevent recurrence at other licensees.

So, again, it does not always mean a failure. Sometimes medical events just occur. But the NRC uses them to try to prevent recurrence in the future.

DR. LIETO: Do these device failures get reported to the FDA or is the licensee required to report to both agencies?

DR. TAPP: The FDA does have access to the NRC's medical event reporting system. So they would see if it's reported to the NRC. And I'll let

Julie respond for reporting to the FDA if she wants.

DR. SULLIVAN: Sure. So FDA sees reports of device failures when it's the device itself or the use of the device that has failed versus something like a mis-administration.

DR. LIETO: Thank you. A follow-up question regarding dosimetry methodology for Y-90 microspheres. There is a software dosimetry from MIM Software Incorporated for Y-90 microspheres treatment that was approved by the FDA. Is that true?

DR. SULLIVAN: Yes. So there is a MIM software device. You can find the information in our 510(k) database. On our 510(k) summary should say what it can be used for.

What I should note is we have no pre-treatment dosimetry methods other than what is on the SIRTeX with the therapy labels that have been approved or reviewed.

The MIM software is specifically for determining post-treatment dosimetry and is labeled as shouldn't be used to make decisions on whether a patient should be retreated.

DR. LIETO: Thank you, Julie. We have a question unrelated to this. But I was trying to understand why the Y-90 microspheres are a Class 3

device but devices like an HDR or LINAC teletherapy are Class I? You may have touched on the nuances there, but I'm just trying to understand why that's a higher risk than say those devices.

DR. SULLIVAN: Sure. So when you get into classification of radiological devices, part of it may depend on when the device was first developed or used. Things that were in clinical use prior to 1976 are considered pre-amendment devices and that could affect the classification.

As Diana mentioned, SIR-Spheres came on the market in 2002. And while that predates me, or predates my time at FDA at least, that means that we felt that the risk associated with the use of the device couldn't be mitigated only using general and special controls.

DR. LIETO: Okay. Thank you. I don't think -- I don't see any other questions coming into the chat here. Does anybody have any clarifications or further comments because I think we still got a little bit more time here for questions. And if people want to submit them, I would be glad to -- oh, here's one.

Post-treatment Y-90 dosimetry, really on the Y-90 dosimetry questions, presumably provides

more accurate dosimetry but opens up the clinic to medical event risk. Classic medicine may calculate an acceptable case, but careful voxel dosimetry may demonstrate a medical event. Does the NRC have a comment on that?

DR. TAPP: Yes. Post-treatment adjuvant dosimetry can identify medical events. As I mentioned earlier, these medical events do not always indicate there was an actual fault. They're an event that happened that meet the criteria but they do not always meet a fault. They can just be something that we want to know about and learn from going forward.

At this time, we do know post-treatment dosimetry is identifying some events that we didn't see before. And we're keeping an eye on them and appreciate the reporting on them.

Ralph, I did have a question from Session I.

DR. LIETO: Sure.

DR. TAPP: I'm trying to find it. But the question came up, what does the NRC -- does the NRC allow latencies just to not do the technetium-99m pre-treatment imaging? And I'd like to comment on that.

The NRC does not require the pre-

treatment imaging. That is not the NRC's role. The only thing is per the licensing guidance if the licensee chooses not to do the pre-treatment imaging, it is their choice. But they are no longer following the current manufacturer recommendations. And that is the only way to see the lung shunting. So if they choose not to do it, they would be required to report if they have unexpected lung shunting to us.

This for us is a learning tool so we could identify if there is increased lung shunting if someone decides not to do those pre-treatment imaging. But at this time, we do not require the pre-treatment imaging per NRC requirements. So I just wanted to comment on that.

DR. LIETO: Thank you. I think this is aimed at Diana. What is the most misunderstood item that is discovered during the proctoring of new authorized users, yes, I guess, if known?

DR. THOMPSON: Yes. I think it's going to be pretty variable depending upon the proposed user's background. So I don't know that I have an answer to that question, but I'll think about it and report back. I don't think we have, like, a total dive.

DR. LIETO: Okay. I think this was just

a request. Can you have a CMC specific presentation on regulations of radiopharmaceuticals conjugated to monoclonal antibodies? I guess that's a request. The question here is: Is extrahepatic activity in the stomach, I'm assuming from Y-90 microspheres, considered a medical event?

DR. TAPP: Per the licensing guidance from the NRC that would not be a medical event if it's due to shunting and if the licensee did manufacturer's pre-treatment imaging and other techniques to try to avoid shunting.

You should be cautious there as some states do not adapt that clause and may require reporting. So it's important to check with what your state -- the state's licensing guidance for medical event criteria. But per the NRC's licensing guidance if it is due to shunting and if that shunting was evaluated prior to treatment, then it would not be a medical event.

DR. LIETO: Does SIRTeX plan to produce unit dosages?

DR. THOMPSON: This would be a question that would require quite a bit of work through our FDA colleagues. It would be a change to our labeling.

DR. LIETO: Okay. I don't see any other

questions coming into the chat room here. I guess I don't know if -- Sarah, do we want to turn this over a little bit early or --

MS. LOPAS: Yes, Ralph, I think that's fine.

DR. LIETO: All right. Here's one. Does TheraSpheres require IRB approval but SIR-Spheres do not?

DR. SULLIVAN: Sure. So TheraSpheres are currently, at least in the U.S., are approved under a humanitarian device exemption whereas which an HDE, or a humanitarian device exemption, is a device is safe and probably effective. So it's shown probable effectiveness but hasn't gone through the same type of either clinical trials or shown the same clinical evidence as something that would be needed for a PMA level of approval.

SIR-Sphere is a PMA approved device. Note though that the two devices, even though they're very similar, have two different indications, one for metastatic colorectal cancer and one for primary hepatocellular carcinoma. So that's the difference between those two.

And then I see there's another question about information presented in the Dosisphere trial.

What would be needed, come talk to us. But why aren't they cleared? If people haven't come in and presented us with data, then we can't clear things.

DR. LIETO: This last question is a little perplexing. I think it's just in general. It says is there a difference in medical event depending if the authorized user is a radiologist nuclear med physician or a radiation oncologist.

I think they're all equal opportunity offenders. But I'm assuming maybe are they looking at maybe the question is which one might provide a higher number shall we say or more frequently occur with medical events?

DR. TAPP: You're correct that there would be no difference in the criteria. And is there a different number of events? I do not believe we have seen that. We do not always know who is the authorized user when we go back and trend the data. But we have not seen an indication that one versus the other authorized user per our inspections create more than the others.

DR. LIETO: Okay. I think just in general, and correct me if I'm wrong, Katie, but I think in looking at the types of events that occur, I think there are more Y-90 events than say, medical

device like HDR, which I think is the number one device -- well, I should say therapy device number of events. It wasn't so much the case maybe a few years ago, but I think that's the case now in terms of numbers.

DR. TAPP: Yes. That is true.

DR. LIETO: What are the requirements for AUs to stay "on label" in Y-90 treatments. That is, are there regulatory issues with planned very high dose segmentectomies? It might be aimed at you, Diana or Julie. But I'll just throw it out to the whole panel there.

DR. SULLIVAN: So from the FDA perspective, FDA doesn't regulate practice of medicine so if the device has been found to be safe and effective when used in accordance with the approved labeling. However, if the physician decided that that was in the best interest of the patients to use it in that manner that would be their decision in accordance with probably their hospital or facility.

DR. LIETO: Okay.

DR. TAPP: And for the NRC, we're very similar. The AU has the choice for the written directive and what their prescription is. We do not require them to stay on labeling as well.

DR. LIETO: Okay. Well, I think we've reached the end of our time for this session. And I'm going to turn this over then to Sarah Lopas so that she can do any announcements and, I guess, take us into a break.

MS. LOPAS: Yes. That's great. Thanks, everybody. That was a great panel. We are on time so everybody gets a proper 15 minute break. We will reconvene at 3:00 p.m. for our final Session V panel. So just hang tight, and we'll be back right at 3:00 p.m. to get started. Thanks, everybody.

(Whereupon, the above-entitled matter went off the record at 2:45 p.m. and resumed at 3:00 p.m.)

DR. HSIAO: Okay. Well, thanks, everybody, for coming to this Session Five. It's on Clinical Trial Design Considerations for Radiopharmaceuticals.

So, the first speaker will be Dr. Denise Casey. Dr. Casey works in the Office of Oncological Diseases. And so, I'll just let her tell us more about what she is working on. Thank you.

DR. CASEY: I will be referring to three agents that have been approved for oncology education for the case example throughout the talk.

Radium-223 dichloride, or Xofigo, was a first-in-class alpha-emitting radiotherapeutic approved in 2013 for the treatment of patients with castration-resistant prostate cancer, symptomatic bone metastases, and no known visceral disease. And this approval was based on an improvement in median OS versus placebo and some supportive evidence showing that patients who received the radium 223 dichloride had a delay in time to their first symptomatic skeletal event; for example, palliative radiation use for bone pain or new pathologic fractures.

Lutetium-177 dotatate, or Lutathera, is a radiolabeled somatostatin analog approved for the treatment of patients with gastroenteropancreatic neuorendocrine tumors, or GEP-NET, based on demonstration of an improved progression-free survival primary endpoint as compared to long-acting octreotide. And there's also an improvement in overall survival in the data that was submitted in the original application.

And then, the iodine-131 labeled iobenguane, Azedra, also approved in 2018 for patients 12 and old with inoperable pheochromocytoma or paraganglioma. And this product was approved

based on patients having a reduction in the need for antihypertensive medications that were durable. And there was also a tumor response rate of 22 percent in their single-arm registration study.

These products are good case examples, not only because they are recent approvals, but, also, because they are indicated for patients who in some cases have indolent tumors and are likely to live for several years after treatment. So, it makes long-term safety a key component of the benefit-risk assessment we make on these products for approval.

Next slide. And next slide.

So, the bone marrow is the dose-limiting organ in most types of radionuclide therapy. Acute myelosuppression can, obviously, occur in the first days to weeks after treatment, and the later adverse events, such as myledysplastic syndrome and leukemia, can occur up to years following treatment.

Next slide. And, first, we'll just walk through some of the more common reversible acute and subacute effects on the marrow. As you know, bone marrow is radiosensitive due to the presence of stem cells that are rapidly dividing. A maximum absorbed dose of too great of bone marrow is generally accepted, and this value is based on older data from

radioiodine studies in metastatic thyroid cancer.

And it's important to remember that these are estimates and the calculation may not account for all factors that contribute to bone marrow radiation exposures, such as potential binding of the radiopeptide, which is the same target that may exist in stem cells.

The short-term myelosuppressive effects are generally tolerable. Most patients recover prior to the next cycle of treatment. Factors that are associated with higher frequency of severe toxicity are listed here. Age and prior chemotherapy are important and prior renal impairment.

Next slide. Now we'll just go on to some of the data from these recent approvals. For radium-223 dichloride, we have safety data for 600 patients with metastatic castration-resistant prostate cancer. About 60 percent of the patients received prior docetaxel, and 2 percent, or 13 patients on the treatment arm, experienced bone marrow failure or ongoing pancytopenia compared with no patients that were treated on the placebo arm. And these included two patients with fatal events, seven requiring transfusion support, and seven with ongoing pancytopenia at the time of death, but not necessarily

the cause of death. Four percent of the patients required permanent discontinuation for either anemia or thrombocytopenia, and severe thrombocytopenia was higher in patients who had prior chemotherapy, as would be expected.

The CBCs for the registration trial were collected every four weeks and prior to a dose. So, the nadir was not all that well-characterized. But review of a separate single-dose study showed that neutrophil and platelet counts nadired at approximately two to three weeks and recovery occurred at approximately six to eight weeks after a dose.

Next slide. And here you see the lab abnormalities. This is Table 4 in the package insert for this product. And some of the uncertainties that are discussed in our review of this safety signal and of the application were patients' ability to tolerate subsequent cytotoxic chemotherapy, the optimal sequencing of treatments based on the effects on the marrow, and what portion of myelosuppression is actually drug-related versus related to bone marrow infiltration.

Next slide. So, I-131, iobenguane, approved in 2018. The main safety data for this

approval was from a single-arm trial of 88 patients with pheochromocytoma or paraganglioma. Hematologic toxicity was common. As you can see, about half of the patients had Grade 3-4 thrombocytopenia and more than half had Grade 3-4 neutropenia at some point during the study. About 5 percent of the patients had febrile neutropenia, and the counts generally nadired between four and eight weeks following treatment, with a median time to recovery of about two weeks for white cells and for platelets.

A quarter of the patients required red cell transfusion, and about 16 percent receive platelets. And almost 10 percent received G-CSF for an erythropoietin study.

Next slide. And then, for lutetium-177 dotatate, also approved in 2018, the key trial supporting the approval was NETTER-1. It included 223 patients with midgut carcinoid tumors randomized to receive either the lutetium-radiolabeled product or a long-acting octreotide. Again, you see hematologic toxicity was common, but it was usually low grade and recovered by the next treatment cycle.

And here is a section of the product label. While more than half of the patients had any grade anemia or thrombocytopenia, and about a quarter

of them had some level of neutropenia, the Grade 3-4 toxicities were relative uncommon.

Next. So, if we move on to the longer-term effects or the long-term marrow toxicity, the two risks we worry about are later development of myelodysplastic syndrome, or MDS, and acute leukemia. Risk factors cited in the literature include duration from first to last cycle of therapy, and this may be indicative of a continuous bone marrow insult; prior chemotherapy or radiation therapy; platelet toxicity during therapy, and obviously, tumor invasion of the marrow.

For lutetium-177, across two studies, NETTER-1 and ERASMUS, data that were reviewed for the applications, with a median duration of follow-up of 19 months and 35 months, respectively, for the two studies, the risk of acute leukemia was less than 1 percent and the risk of MDS was between 2 and 3 percent.

For I-131, iobenguane, six of the 88 patients developed MDS or leukemia between nine months and seven years following treatment. But, for these patients, it was the confounder of prior therapy, including alkylating chemotherapy or radiation, in all cases.

Next. Next slide. So, Bergsma, et al, published an interesting of long-term hematologic toxicity in 274 patients with GEP-NET that were treated with lutetium-177 dotatate between 2000 and 2007 at Erasmus Medical Center. And the authors defined persistent hematologic dysfunction as a diagnosis of either myledysplastic syndrome, acute myeloid leukemia, myeloproliferative neoplasm, or an otherwise unexplained cytopenia that lasted for more than six months.

And they used comparative data from the Netherlands Cancer Registry study for their analysis. And they looked at a number of risk factors, including gender, age, bone metastases, prior therapy, hematologic toxicity during treatment, estimated bone marrow dose, and renal function.

And while the study concluded that there was an increased risk for late hematologic toxicity in patients who received lutetium-177 dotatate, with 4 percent of the patients in the study population experiencing a late toxicity, mostly MDS, and a relative risk of 2.7 compared to the registry data, there was still no correlation with any single or grouped risk variables that were tested.

So, this table here on the left

summarizes the 11 patients who experienced what they defined as PHD. And this graph on the right is data from one patient. And you can see this patient at exactly five years after completing for cycles of Lutathera developed MDS, and the red line is indicating the hemoglobin decline that is consistent with the blue line, indicating the rise in MCV over time.

Next slide. So, we move on to the risk for renal toxicity with radiopharmaceuticals, as you know, the kidney is considered a dose-limiting organ, so PRRT. Hydrophilic radiolabeled peptides are excreted via the kidneys, but, then, they can be partially reabsorbed at the level of the proximal tubule, and the renal retention of the radionuclide can cause a relatively high radiation dose to the kidneys. And this is just an illustration to show the reabsorption at the receptors that line the proximal tubule cells.

Next slide. So, a couple of points regarding renal toxicity using the example of radiolabeled somatostatin analogs. Acute renal toxicity can occur within the first few weeks or months after treatment, and often manifests as changes in blood pressure or asymptomatic

proteinuria. But chronic kidney damage is much less common and may reflect the failure to regenerate functional tissue after the initial injury.

Risk factors for radiation nephropathy include baseline anemia, hypertension, and diabetes. And it is important to note that the risk of radiation nephropathy depends, partially depends on the choice of nuclide. For example, yttrium-90, because of its higher energy and longer penetration range, can irradiate the renal tubule more extensively than lutetium.

And to mitigate risk for renal toxicity, it's standard to use the co-infusion of amino acids, which work at the level of the proximal tubule of competitive re-activaters. And for the lutetium 177 NETTER-1 data example, from what we had in our review, at Grades 3 and higher, renal toxicity was relatively uncommon at 1 percent, and at the median duration of follow-up of 19 months, it didn't look like there was a difference between the two study arms for creatinine clearance rate, but, obviously, longer follow-up is ongoing and required.

Next.

And very briefly, since radiolabeled metastatin analogs are used to treat neuroendocrine

tumors, it's important to be prepared for carcinoid crises with PRRT, as with any other procedure or treatment that may manipulate the tumor and lead to an acute release of active immunes. There is literature describing this acute toxicity with PRRT, and acute hormonal crisis is a labeled warning and precaution for the lutetium-177 dotatate package insert.

Next slide. So, in terms of risk mitigation practices, we already mentioned that different radiopeptides carry different risks to tissue. Patients should be screened prior to treatment for adequate marrow reserve and renal function. Individual dosimetry may mitigate risk. Obviously, safety monitoring is important during infusions and between cycle. Co-infusion with amino acid solutions and standard supportive care guidelines are important for antimetics, for transfusion and stem cell infusion protocols. And importantly, long-term follow-up with the patients to follow their bone marrow and renal function for months and years after treatment is key.

Next.

Sorry, I don't know why the slide is not all filled out, but this might have been a prior

version of the slide deck.

But what I wanted to get across here is that possible informative product labeling can really help mitigate risk for short- and long-term toxicity associated with each radiopharmaceutical. And for all these products, Section 2 generally includes information on radiation protection; dosimetry; imaging guidelines; dose calculations, when relevant, and critical organ limits.

And then, Section 5 of the label will include our warnings for radiation exposure; secondary malignancies; myelosuppressive, and renal toxicity, and precautions that go along with each one.

Section 6 will describe the safety in the intended-use populations.

And Section 8 of the label, not listed there, but it is used for specific populations. For example, one special population in the iobenguance 131, Section .4, is a discussion of the pediatric use.

Next slide. So, our job at FDA is to expedite the availability of lifesaving drugs to patients. And post-marketing requirements, or PMRs, and post-marketing commitments, or PMCs, are tools

that allow FDA to sort of contract with companies to collect additional safety data post-approval that may have implications for how the drug is dosed or the monitoring practices that should be in place for patients receiving the drug.

And all three of these products discussed have PMRs for cumulative safety analyses after five and ten years of follow-up to better track long-term risk.

Next slide. And to conclude, I wanted to point out that radiopharmaceuticals is certainly an active development space. This table from a paper in Nature Reviews is from earlier this year that looked at various products that are either approved or under development.

And the slide was originally animated, but I've got these according to where they are in development. So, the first box you see on the left are products that are approved, including the three we discussed. And then, the second box are products that are in phase 2-3 studies. And then, the box on the upper right are the phase 1 studies. And then, the lower right corner are the products that are in pre-clinical development.

And this list is not exhaustive, but I

just wanted to point it out because this is an active development space and FDA is involved from pre-IND onward to discuss and advise on these development programs and trial design. We really do encourage sponsors to request meetings, especially pre-IND meetings, to discuss these products or new products.

Next slide. And so, in summary, radiopharmaceutical development is an active and growing field for the targeted treatment of various cancers.

Certainly, long-term toxicity must be considered in the benefit-risk assessment for these products.

Standard clinical practices have evolved to safely administer the products while mitigating risks for acute and chronic radiation-associated toxicity.

And FDA does recognize the need for patient access to effective treatments and we'll continue to work closely with sponsors to strategize on how to enhance dosing while minimizing radiation-associated toxicities.

Thanks.

DR. HSIAO: Thank you very much, Dr. Casey.

So, I know that a question already came in through chat. Please hold onto your questions, and for the interest of time, we'll proceed to the next speakers.

The next speaker will be Dr. Sue-Jane Wang. Dr. Wang is a biostatistics liaison to the Office of New Drugs for the CDER Biomarker Qualification Program. And her topic is about Efficacy Considerations for Theranostic Pairs.

Please, Dr. Wang.

DR. WANG: Thank you for the kind of introduction. Can you hear me okay with the volume?

DR. HSIAO: Yes.

DR. WANG: Okay. Great.

So, I will be speaking about the Efficacy Considerations for the Theranostic Pairs.

Next slide. So, this is the outline. I will start with the current regulatory practice and propose a paradigm known as in-parallel-with-leveraging paradigm, followed by some examples, and showing the efficiency of this new development paradigm, and followed by the interim remarks.

Next slide. So, for the theranostics, I will focus on the nostics portion. We know theranostics is a combination of therapeutics and

diagnostics. For the nostics component, it is an imaging version of a radioactive drug. We call that radiopharmaceutical that identifies a patient with the presence of certain proteins, such as the one that everybody's presenting today, which is an SSTR receptor, in a disease such as neuroendocrine tumor, NET, where the SSTR receptors serve as a target for the cancer drug. And the therapy is a therapeutics version of it.

The example that I am going to use throughout is one known as Lutathera, approved in 2018. The indication statement of Lutathera mentioned that it is treatment in adult patients for a gastroenteropancreatic, NET, tumor with SSTR present, which is identified through Octreoscan.

Next slide. So, we can see that the approval process in this particular example is a sequential approach. The Octreoscan was approved first, followed by Lutathera. Here, we would like to articulate a better approach, which is in parallel with leveraging. And the interest there is to leverage therapeutic trials by aiming to reduce the combined development time, improve the design efficiency, and make additional imaging indications feasible for the marketed diagnostic imaging drug or

for the investigational nostics imaging drug.

Very important, establishing test reproducibility with a local characterization, as needed. A substudy, an imaging substudy may be needed.

Next slide. So, with Lutathera, approved in 2018, I will spend time now talking about the Octreoscan. In the indication statement, it says it is a scintigraphic localization of primary and metastatic NET bearing somatostatin receptors. So, after its approval in 1994, the label describing its diagnostic performance is showing the diagnostic success of about 86 percent. And in a small group of subjects, the tissue confirmations were available. So, one can estimate sensitivity and specificity. What's shown on the label was the sensitivity is about 86 percent compared to conventional imaging, CD/MRI, of 68 percent. So, that's definitely an improvement.

In addition, on the specificity, the Octreoscan has a specificity of 50 percent compared to conventional imaging of 12 percent.

So, that was the imaging a nostics component in the nostics development of Lutathera.

Relevant clinical studies, as mentioned earlier, include the following three studies. I will

focus on the first study, the main study, NETTER-1, to illustrate the potential benefit with the new paradigm that we are proposing.

So, NETTER-1 is a two-arm active controlled trial. The primary efficacy in point is progression-free survival. Of the 229 subjects -- next slide -- as you can see here, the top figure is extracted from the label. The test arm has 116 subjects, and the control arm as 113 subjects. And you can see the separation in the survival curve as early as three months, and then, continues to separate and get wider and wider over time to two years out and two and a half years.

The study was stratified by tumor uptake score with a Grade 2, 3, 4, and the length of time that a patient is on constant dose of Octreotide, which is a control arm dose of drug, and whether they are in a stable, constant dose of less than six months or more. With a stratification, one can do a statistical analysis based on a stratified log-rank test or unstratified log-rank test. The unstratified would be more conservative in the sense it did not further adjust the stratification factor.

But, either way, we see the produced hazard ratio is .18 with a 95 percent interval of 11

percent to 29 percent. So, the 18 percent translates into 82 percent hazard reduction. This part of the table is extracted from the FDA Multidisciplinary Review and Evaluation.

So, it clearly shows that Lutathera is effective through this experience.

Next slide. Oh, sorry, can we go back to the previous slide?

I forgot to mention that the overall response rate was 13 percent in the Lutathera arm and 4 percent in the control arm. And that difference is the 9 percent. To be more accurate, that difference is 9.4 percent.

Next slide. So, in the imaging drug of the diagnostic imaging, we often see drug labels show clinical performance characteristics, such as the sensitivity, specificity, accuracy, percent agreement, et cetera.

As shown, for Octreoscan, we had a sensitivity about 86 percent and specificity about 50 percent. So, assuming the prevalence of subjects with STTR positivity is 70 percent. Then, if there is no imaging used, just based on the prevalence, we will be able to identify 70 percent of the patients who are SSTR positive. If we now bring in an imaging

that has good clinical performance characteristics, we are going to increase the chance of identifying patients who are STTR positivity.

And in this example, with the sensitivity, specificity, and prevalence, one can easily calculate that that positive predictive value is 80 percent, which means that we are able identify an additional 10 percent of the patients who are STTR positive if we use the Octreoscan as the nostic portion of the theranostic development.

So, this is just an example to show the performance with the Octreoscan. Clearly, if the sensitivity/specificity is only 50 percent/50 percent, then the positivity value is going to be just the same as prevalence. So, we would need to have an imaging that actually performed better than the population prevalence.

Next slide. So, I'm going to use the overall response rate difference, that 9.4 percent of the example, to talk about how a study can improve in design efficiency in terms of the sample size saving.

So, suppose 9.4 percent treatment effect on the overall tumor response rate difference is the truth. And if we, then, project that this 9.4 percent is true only with a 70 percent prevalence, this

difference will become 8.2 percent. To show an 8.2 percent improvement in overall response rate, we would need to screen 230 patients because prevalence is only 70 percent.

Now, if we, then, have good imaging nostics, suppose one imaging nostics has a performance, PPV, of .8. There, we would not need to screen 230 patients, but, rather, we would just need to screen 186 patients. That resulted in about 20 percent improvement or saving in the sample size.

So, if another nostics come along, if it has an even better PPV, then we can see the sample size saving is increasing when the performance on PPV is getting better and better.

Next slide. So, the essence of leveraging here is to answer a practical question, how much improvement will the nostics imaging offer to more accurately identify targeted patients who have the receptor for the therapeutic development?

With common sense, we know that, if we can have a higher degree of accuracy in identifying patients, we clearly improve the selection of patients. That also results in increased enrichment of patients who are likely to respond to the therapy in a therapeutic trial. Namely, we are decreasing

the chance of including patients who do not have an SSTR to positivity.

So, essentially, you then have a much more homogeneous patient population with STTR to positivity known, and that effect size that you're going to get estimated is going to be much more accurate if you really enrich the right patient population for study.

Next slide. So, I'm going to use the NETTER-1 design parameters. So, in NETTER-1, it assumed 40 months progression-free survival in the control arm and 30 months improvement in progression-free survival in the Lutathera arm. So, in order to detect a hazardous ratio of .47, the one with the red circle, if we are going to achieve an effect size of hazard ratio of .47, the study would need to have 74 events as progression-free events to achieve 90 percent power and to a 35 percent level.

So, we can, then, use this design parameter, not that the NETTER-1 is done this way, but to show you how the design efficiency can be gained with this newer approach. On the first column where the hazard ratio of .47 was assumed to the hazard ratio in the accurately targeted patient, meaning all the patients you studied, they are all

not just test positive, but also confirmed to be true positive, SSTR positive. So, essentially, you have 100 percent of patients you know exactly they have the receptor.

Then, study the treatment effect. If, indeed, you have a perfect performance of your nostic imaging, then you would just need 74 events. However, this design will be too optimistic, in that it did not incorporate the uncertainty of the nostic imaging performance. So, naturally, you are likely to need to increase your number of events after the interim time when the nostic imaging performance becomes available.

For example, people who were screened positive, they go into the therapeutic trial and they also had been tested with a biopsy, getting their histopathology results. So that, by some interim time, we will be able to know what the true PPV estimate is likely to be.

So, suppose the PPV is actually .8 rather than 100 percent. Then, in truth, the hazard ratio would need to be about .576. In other words, we would need to have about 138 events. This means at the interim time one would need to jack up the sample size. In terms of event number, it's almost twofold.

So, if we are too optimistic in the beginning, we would need to adjust that along the way if we incorporate a study design that is an adaptive design that allows you to have such modification on the event number.

On the righthand side, if someone has this hazard ratio of .47, but when that assumption was made it was assumed that the hazard ratio is in all the randomized patients who are screened positive, then you incorporate uncertainty from the get-go. And at an interim time, if this is a group sequential design, one would be able to do an interim analysis and find that, when the PPV is .8, the hazard ratio is actually much smaller. This means there's an even larger reduction in hazard. So, you do not need the 74 events. You actually just need about 58 events.

Therefore, if a group sequential design is employed, one would have a possibility to early terminate a study for efficacy. However, they could have some safety component that needs to be addressed as well. So, the slide here is under the premise of assuming that we are only dealing with the efficacy of the drug.

So, the principle here of this newer

design efficiency relates to, if one prespecifies an interim analysis, plans for that, the timing when you can assess the PPV performance of your nostics, that will be an ideal time for you to adjust possible event number, either to increase or to decrease, depending on whether you are too optimistic or you are realistic.

Next slide. So, had this approach been applied, the early studies that were mentioned in the morning talks and around noon talk, they would all need to be in place, so that the preliminary clinical finding of the therapeutic trial shows the proof of concept.

Next slide. So, the goal with this approach is that we use imaging agent in the therapeutic trial during the development of both. And so, the imaging component would include using the imaging to select the patient with a positive scan, use the imaging where you can specify important imaging factors if they are relevant, such as baseline tumor burden. We can use imaging to do post-treatment tumor response and post-treatment disease progression. And then, the imaging can also be used at a pre-specified time point for possible disease restaging or incorporating the multiple time points

where clinical outcome data were collected in a therapeutic trial for some clinical further followup on the imaging possible truth standard.

Oftentimes, there's interest to evaluate agreement between conventional imaging and the investigation of imaging taken.

Next slide. So, the utility of this leveraging is you want to be smart in doing this leveraging. While the therapeutic trial is under planning, try to add to it a pre-specified analysis using the available data to support a diagnostic imaging/drug efficacy evaluation, such as a PPV assessment in an interim analysis. You can add a design element for imaging claims, such as baseline tumor burden, for possible prognostic imaging utility. You could also add onto the existing protocol, not a new protocol, but just to leverage that existing protocol and address the clinical utility of imaging drug performance and analytical characterization. So here, there are many things that you can build in if you are interested in possible future labeling of an imaging drug.

We want to emphasize that the potential approval of this diagnostic imaging drug, it does not have to be directly linked to the effectiveness of

the therapy.

Next slide. So, these are the tangible imaging indications possible, depending on how you add those additional analyses, additional design element, or additional add-on protocol.

Next slide. So, to sum up, I consider this interim remarks. As we are beginning to see this kind of approach coming to the agency, we see the benefit of this leveraging approach present the potential of a favorable design efficiency that would allow the combined development time being shorter than the sequential approach.

And we do emphasize the establishment of the nostics analytical characterization for patient selection is required.

If this nostics component is an unapproved drug, we see that NDA, as a new NDA, will be needed for marketing this nostics as investigational imaging with thera as a theranostics pair.

To conclude, the potential imaging standalone indication, you can think of it as: if the therapy demonstrates efficacy, the benefit of the imaging as nostics have, at a minimum, patient selection. On the other hand, if the imaging -- I

mean, in a therapeutic drug -- failed to show the effectiveness, that's not the end of the world. There's still the possibility of adding some more components to your imaging drug development, so that you may get a diagnostic imaging claim.

In the event that the therapeutics is actually already approved, that is not in this in-parallel-with-leveraging setting. In this different setting, however, the nostics developer will be much more motivated to develop nostics that have a good performance because it means that there were some other nostic that has already been approved under a theranostics pair approach. So, the new one would need to be at least as good as the originally approved theranostics pair or be better than that. So, there is a good interest and desire of wanting to have a higher nostic performance.

And we hope that, as time goes by, we receive more of this kind of submission, and what are either the benefit we see or maybe they will have some lesson learned that we will be able to share in the future.

Next slide. I would like to acknowledge many of my colleagues throughout the constant discussion whenever we have a submission that comes

in.

Thank you, and thank you for your time.

DR. HSIAO: Thank you very much, Dr. Wang.

So, we'll move on to our next session. Please note that all the questions will be answered at the end on the panel.

The next speaker will be Dr. Ana Kiess, who is an Assistant Professor and a Residency Program Director in the Department of Radiation Oncology at Johns Hopkins University. And her trial is about Clinical Trial Considerations from Academic Perspective.

Please, Dr. Kiess.

DR. KIESS: Thank you very much for having me.

Next slide. These are my clinical research disclosures.

Next slide. From an academic perspective, there are very significant opportunities when we do pharmaceutical therapy trials for patients and investigators in collaboration with industry and the NCI, and there are also significant challenges. And I'd like to provide a general overview of these in the next 15 minutes, and potentially some ways

that we can catch up with our European and international colleagues in U.S. radiopharmaceutical trials.

Next slide. Most importantly, radiopharmaceutical therapies have the potential to significantly benefit patients with unmet need, as we have seen with the overall survival benefit in phase 3 trials of radium-223 for patients with metastatic castrate-resistant prostate cancer bone metastases and with lutetium dotatate with patients with metastatic midgut neuroendocrine tumors.

Next slide. As highlighted by Dr. Casey, there are many new agents in development in phase 1, 2, 3 trials.

Next slide. Dr. Jadvar is going to go into more detail on the many targeted agents and many of the other exciting new agents.

This is another figure from Dr. Sgouros' recent excellent review showing the targets in the published radiopharmaceutical literature are now addressing many different disease sites, including breast, prostate, hepatic, colorectal, thyroid, and hematologic malignancies. And there's now been the development of platforms such as the thorium-targeted conjugate platform that could potentially use ligands

such as antibodies for multiple disease sites.

Next slide. As these agents are developed and gain FDA approval, there has been, and will be, an explosion in early phase radiopharmaceutical trial opportunities. And I just want to highlight some of the different categories of trials in this investigator-initiated and sponsored trial category.

So, there are many studies of new disease indications. For example lutetium dotatate is being investigated in other neuroendocrine tumors, meningiomas, pheochromocytoma, and paraganglioma. Radium-223 is being investigated in other cancers with bone metastases such as non-small cell lung cancer, renal and breast cancer.

There's many exciting combination therapy trials that are exploring the synergy potentially between radiopharmaceuticals and immune checkpoint inhibitors. Radiation can cause antigen release and immunogenic cell death that increases tumor-specific T cell priming. And there's studies of lutetium dotatate and radium-223 in combination with these inhibitors. PARP inhibitors can potentially inhibit DNA repair and act as radiosensitizers, so are being investigated in combination with

radiopharmaceuticals, and many other systemic therapies are also being investigated.

I do want to highlight that these studies also will bring potential toxicities of combination therapy such as the study ERA 223 of abiraterone in combination with radium-223 showing increase of bone fractures and need for bone protection agents.

Next slide. There are also studies looking at earlier line or earlier stage indications for radiopharmaceuticals. My colleague, Phuoc Tran, at Johns Hopkins is the PI for a trial we have of combination stereotactic body radiation for macrometastases with radium-223 for micrometastases in Al-ACR metastatic prostate cancer. There's a study of radium in biochemically recurrent prostate cancer and of lutetium dotatate in new adjuvant therapy for gastroenteropancreatic neuorendocrine tumors.

There are interesting studies of personalized dosimetry of lutetium dotatate in adults for potential dose escalation, as well as for safe administration to children, and investigations incorporating biomarkers and looking at germline or somatic DNA repair pathway alterations and their potential impact on radiosensitivity.

Next slide. The NCI and CTEP have an important development initiative that is focusing on certain radiopharmaceuticals in combination with other agents and, also, really paying attention to incorporating dosimetry, radiobiology, imaging, and cancer biology into the trials. These include the listed open trials that investigate radium-223 with PARP inhibitors, chemotherapy, and TKIs.

Next slide. And the unique properties of radiopharmaceuticals present opportunities for interesting trials around imaging, developing criteria for patient selection, and criteria for response assessment using PET, CT, or other functional imaging, and using quantitative imaging or lesion analysis potentially even as a surrogate for dosimetry,

There are trials, as we mentioned, for individualized dosimetry where you can use absorbed doses for potential dose escalation and for high-risk patient populations.

There's also potential to answer scientific questions using dosimetry about fractionation and optimum cycle length, about relative biologic effectiveness, and tissue dose distribution, particularly for alpha emitters.

Next slide. I want to highlight one excellent study that recently came out using clinical dosimetry for lutetium PSMA-617. In this study, they performed serial lutetium PSMA-617 SPECT/CT scans to do 3D dosimetry of regions of interest, including normal organs, such as the salivary glands and kidneys, as well as tumor,

Next slide. And they were able to demonstrate the radiation -- next slide, please -- radiation dose effect that we see in radiation oncology with increased dose being predictive of more likelihood of PSA response. And I think this also corresponds with what Dr. Anscher was describing with the doses studied for Yttrium 90. We would expect this increase in dose to also correspond with response rate and other oncologic outcomes.

Next slide. And there is the possibility for treatment planning. Whereas, current prescriptions are based on fixed activity or weight-based activity, with certain dose adjustments, there is the potential for individual treatment planning and prescription, especially with specific indications.

Next slide. Along with all of these

opportunities comes a lot of challenges with radiopharmaceutical trials, especially in phase 1 and 2. And in the U.S., many centers are still developing the infrastructure to make this more efficient.

Next slide. In addition to requiring a radioactive materials license for the appropriate agents and having facilities for treatment and radioactive waste with the appropriate safety precautions, there's also the usual complex workflow and orders and scheduling of early phase clinical trials and the incorporation of frequent scans and blood sampling for dosimetry and pharmacokinetics, as well as all of the documentation that is required for safe administration of radiopharmaceuticals.

Next slide. This varies a lot, depending on which agent and radioisotope you are using. So, clinical trials with radium-223 are relatively simple. Because the drug comes as a preloaded syringe injection, there's minimal precautions for radiation safety and it can be performed in an unshielded, outpatient treatment room and requires only 30 minutes of dedicated time per treatment per patient. And the patients are eligible for discharge immediately.

Another step up is lutetium PSMA or

lutetium dotatate, which requires more significant effort for radiation protection and contamination prevention, particularly with a separate bathroom, given the urinary clearance. The treatment can require three to five hours of reserved time before the patient is eligible for a discharge, and various infusion and injection techniques are used, and for the lutetium dotatate, long peptide pre-infusions incorporated.

Next slide. And the most complex, in my opinion, is iodine-131 MIBG for pediatric patients. We do not have this type of treatment program open at Hopkins, but having seen in detail the operation at CHOP, I am really impressed with their ability to perform such high-level research and with such significant effort for radiation protection and contamination. Pretty much every surface is covered in plastic and the patients require three or more inpatient days for treatment, urinary catheter, and sedation or intubation during infusion.

Next slide. In addition to the logistics around the actual infusion, there's also logistics around accessing the research infrastructure. The Authorized Users are in nuclear medicine or, like me, radiation oncology. And the research pharmacies at

the cancer centers do not accept radiopharmaceuticals. So, the radiopharmacies are gaining a lot of research experience in IP accountability, quality assurance, different procedures, and therapeutic doses.

And due to radiation safety precautions, we have not been able to use the beautiful inpatient infusion suites, as pictures there at our outpatient cancer center. Our infusion suites or areas are in Radiation Oncology and Nuclear Medicine. There are three areas that we have with separated bathrooms and shielding, and there's also two inpatient shielded rooms.

So, there's not any medical oncology nursing. Our research nurses in Radiation Oncology and Nuclear Medicine have also become quite adept at the details of research nursing and oncology.

Next slide. Furthermore, with the radioactive biosamples, there's limited availability and access to research phlebotomy in core labs. And when we have been able to use these core facilities, we've had to incorporate specific procedures around spills and contamination and waste management incorporation with radiation safety, as well as regulated shipping.

Next slide. Finally, there can also be some delays related to radiopharmaceuticals, in particular, in addition to typical IRB and contract delays from any early phase clinical study. But the Radiation Review Committee process occurs along with IRB review. During phase 1, especially, there can be delays in between cycles due to the long-advanced ordering of the drugs and international shipping. And the ability to have studies open at multiple sites is limited, both by the radioactive materials license and all the complex use.

Next slide. These trials involve intense multidisciplinary coordination. And we have a team of multiple physicians, and our head physicist and research nurses and coordinators and our radiation safety officers are all heavily involved in our trials.

Next slide. For each patient, there's close communication with their primary medical oncologist prior to each cycle of treatment with review of labs and treatment response.

Next slide. And there's specific challenges according to which imaging tracer is being used and how to interpret the imaging and incorporate it into management, especially in follow-up scans.

Dr. Goeckeler and Dr. Anscher did a great job of going over the different variables with dosimetry, the opportunities, and the challenges of incorporating dosimetry into radiopharmaceutical therapies.

Next slide. And Dr. Casey highlighted some of the post-marketing requirements that have been put into place to try gain further understanding of late radiation effects in agents. As a radiation oncologist, we are very wary of the progressive and often irreversible late effects seen with cumulative radiation dose. And as we move to earlier line and earlier stage indications, I think this is going to br even more important.

Next slide. So, in conclusion, there's many exciting opportunities for radiopharmaceutical clinical trials, especially early phase trials, and multidisciplinary collaboration and preparation is key for the success of these trials. And I encourage those who expect them to consider further integration with the research infrastructure to make the process more efficient and to incorporate dosimetry for specific indications.

Thank you very much.

DR. HSIAO: Thank you, Dr. Kiess.

So, our next talk on the topic of Advancements in Therapeutics and Looking Backwards to Move Forward.

The first part of the talk will be delivered by Mr. Josh Mailman. So, Mr. Mailman is a nationally recognized for neuroendocrine tumor patients as well as an advocate for integrative oncology with nuclear medicine and molecular imaging. He is an inaugural Chairman of the Society of Nuclear Medicine and Molecular Imaging's Patient Advocacy Advisory Board. And he is also a member of the Education and Research Foundation for Nuclear Medicine and Molecular Imaging, Treasurer of the Neuroendocrine Tumor Research Foundation, and President of a Norcal CarciNET Community.

Please, Mr. Mailman.

MR. MAILMAN: Thank you very much.

If you can't hear me, well, we'll work forward with that.

Next slide. Since you've done a great job of introducing me, I won't really go through this slide very long, other than to say I was also a member of the Gallium-68 Working Group for the Society of Nuclear Medicine. Obviously, I'm not a doctor, and a lot of these are my own opinion.

Next slide, please. So, we've talked a lot about the looking forward on how we're going to do clinical trials in the future or how we're going to work on approvals. But I think it's also important to look backwards to see where we've come.

And from a patient perspective, we start hearing about the first PRRT in humans back in 1996. And it isn't until 2017 and '18 that we see our first approvals in Europe and the U.S.

Next slide, please. So, right, it's been 20 years since the first PRRT with Y90. We've had thousands of patients treated. This was adopted in treatment guidelines long before it was actually available as an approved in any geography, but it was selectively available in other geographies, which actually went to confuse patients because it was available pretty easily in Europe and in other parts, whether it was Australia or India, but it did take 21-plus years to get an approval in the EU and the U.S.

Next slide, please. So, this could cause a lot of confusion. This is actually something I did for the Fourth Theranostics World Congress that was held in Melbourne, Australia, in 2016, where I did a survey that actually looked at past patients in the

U.S. Actually, it was an around-the-world survey of what they felt when the approval of PRRT had come or was coming. And most everyone already thought in 2016 that it was approved in Europe or approved in the rest of the world. So, there was a lot of misconception, actually. I just reran this in the last two weeks in conjunction with NANETs and some other patient forums, and 80 percent of those that responded felt that it was approved, or Lutathera was approved in the EU more than three years prior to its approval in the U.S.

Next slide, please. So often when I do this, you know, I am a patient and an n of 1, but I do talk to other patients to kind of get an idea of what they feel about some of the topics that I'm discussing in a public forum. And what I really found was that there's a lot of confusion on the FDA's role in drug development and even less confusion about the NRC, because they're not necessarily aware of the NRC.

But some of the interesting things that came out of a Facebook discussion on the FDA's role in drug development for radiopharmaceuticals was really a sense of frustration that it was the FDA, it's up to the FDA to approve multiple rounds of

therapies, but it's done everywhere else, which, again, this is something where patients in the U.S. believe that there's a different approval somewhere else than what's currently going on in the U.S., and that the FDA approves the use for or the off-label use of a drug, which we've already heard earlier today is not something that the FDA does. But this is particularly of interest for those who have Lung NETs and who the label does not include Lung NETS. And so, there's some insurance coverage issues.

And there's a sense that the FDA -- and certainly when I was a patient first looking for PRRT -- there's a sense from patients back in 2010, and up until approval, that the FDA can just approve drugs without an application. There was a sense, a strong sense, that the FDA was holding or limiting, even back in 2010 and through '15, the approval of PRRT in the U.S., even though there was no application and no phase 3 trial, and no one to bring that through.

Next slide, please. So, we treated many. And I brought this up in different contexts. But the 20 years of PRRT, we did really great. I mean, it wasn't available in many places. We treated tens of thousands of patients worldwide and extended

countless numbers of lives, including my own, but this made it not universal, not universally available. We had lots of INDs that were individualized, even in the U.S., and then, the use of compassionate care in Europe, using non-standardized protocols and data collection that really hindered the ability for the oncology community to even accept that this data was for real.

Next slide, please. I'd often go to nuclear medicine conferences and see the famous nature valley of the death. Between bench and bedside, and the nuclear medicine docs who were at these nuclear medicine conferences were often saying that, by doing this compassionate care in INDs, or using these singular INDs for treatment, we were bridging that gap. But, in fact, what we were doing was delaying the ability to actually get to an approved and licensed product that could treat so many more. While we treated some, lots were left behind.

Next slide, please. As I said in my opening, I was a member of the Gallium-68 Working Group that started meeting in 2010 and '11. And what we had, even for a small set of INDs, the first two INDs that were for gallium-68, dota-something, had

different peptides, different data collection, different questions that were being answered.

And so, one of the things that we did inside of the Gallium-68 Working Group was we spent a lot of time harmonizing data, which is something that should have been -- you know, we've talked about this throughout the day, working on data collection and answering somewhat of the same questions.

Next slide, please. We've had the last talk, of course, talking over some of the challenges of randomized controlled trials and where they come over on INDs, or potentially over, also, on compassionate use, is they really do confirm research and they really do get the oncologists and those at the point of treatment to buy in. And they do matter for reimbursement.

But they are harder to do in some senses. They're expensive. We have many people who are untreated during the time of the RCTs, and Dr. Wang certainly went over some of the ideas of how we could do theranostics in therapy pairs, which I think is really hugely important as we go.

Next slide, please. And Dr. Jadvar is going to talk a lot about this in the next thing, but -- back up one slide, please -- but, obviously,

we're in a period of rapid expansion. And one of the reasons this entire event has been held, we have new peptides coming; we have new isotopes coming; we have, this May, fibroblasts that are going to be looked at.

And patients will really want access to these things, even before and faster than what has traditionally been available. And my big point is, we took 21-years-plus to get an approval, and we need to make sure that we aren't doing 21 years to get the next set of approvals out.

Next slide, please. Clearly, one of the things we need to do is move faster and smarter, which is why, as a patient, I'm really glad to see that the FDA and the NRC are getting together and with support of industry here and, also, the academic research centers.

Next slide, please. So, let's not repeat our past. We need to be able to do these small, more focused trials that help us bring new therapies forward faster. I think Dr. Wang's presentation was excellent in describing how we can do this. We must, especially in the early INDs, we must figure out how to harmonize our data collection, so we're actually making sure that any patient that is enrolled in any IND, the data is actually valuable in working forward

and being meaningful.

We must work towards registration. I certainly understand the value of the compassionate use that is done more routinely in Europe, but we need to be able to treat the majority and not leave so many waiting for therapy for so long.

And we've had certain conversations about personalized dose planning, and we need to come to agreement on the values and the methods to do that, and whether there is true value for that.

Next slide, please. And this is my last slide. It's really which way should we go from here. It depends on where we go.

With that, I'll turn this over to Dr. Jadvar, who can tell us a little bit of where some of the roads we're going to travel in the future.

But I will do the next slide and show you that this is the group of people that I represent in Northern California. We're a group of several hundred patients in the Bay Area who work together to make living with neuroendocrine tumors a much easier job for both patients and caregivers and researchers and clinicians.

And with that, I'll turn that over to Dr. Jadvar.

DR. HSIAO: Thank you, Mr. Mailman.

So, we've heard the patient's perspective. And now, we're going to hear the physician's perspective on advancements in therapeutics.

Our speaker will be Dr. Hossein Jadvar, who is an Associate Professor of Radiology in the Keck School of Medicine at University of Southern California in Los Angeles, California.

Please, Dr. Jadvar.

DR. JADVAR: Thank you very much. I hope that you hear me.

First of all, I'm very delighted to be participating in this forum and I want to thank the organizers for their invitation. And it's, obviously, great also to be in the same session with my friend, Josh Mailman.

So, as was mentioned, what I'm going to do is to review some of the radiopharmaceuticals in the domain of theranostics that we hope to see in the future and what the outlook looks like.

Can I have the next slide, please? Next. Okay.

So, this is a disclosure. I'm going to talk about agents in this presentation which are

obviously investigational and not currently approved for clinical use.

Next slide, please. So, before I do that, I want to mention that we had actually a relatively good past decade with a number of major radiopharmaceuticals that were approved. It started back in 2012 in the neuropsychiatric domain when we had three amyloid pep agents approved, one after another, to look at the amyloid content in patients with cognitive impairment and the possibility of Alzheimer's disease.

Then, more recently, again in this neuropsychiatric domain, we had the approval of the fluorine-18 fluorodopa in 2019 for imaging evaluation of patients with Parkinsonian syndrome.

And just this year, just a few months ago, very recently, we had the approval of the fluorine-18 flortaucipir, which is marketed as Tauvid. And that pep agent is basically an imaging-based bioassay for the tau protein that is deposited in the brain and looking at the tau pathologies, including Alzheimer's disease.

In the domain of oncology, back in 2012, there was approval of the C-11 choline for imaging evaluation of men with biochemical recurrent of

prostate cancer after definitive treatment. Because C-11 has only a half-life of 20 minutes, although it was used at some centers, it was not widely used around the country.

As was many times mentioned before, a first-in-class alpha particle therapy was approved in 2013 after the success of the Xofigo phrase 3 trial with radium-223 dichloride targeted to patients with metastatic castrate-resident prostate cancer and bone-dominant metastases.

In 2016, we had the very first pep agent, fluorine-18 fluciclovine, marketed as Axumin for leukemia at patients with biochemical recurrence of prostate cancer after definitive treatment.

And soon after that, we had approval of the gallium-68 dotatate, marketed as Netspot, which was also mentioned previously in this series of talks, looking gastroentropancreatic neuroendocrine tumors with the target being the somatostatin receptors.

In 2018, we had the theranostic pair approved for the gallium68 dotatate, which was the Lutathera. This is a beta particle theranostic pair for treatment of the same patients who undergo gallium-68 dotatate and demonstrate that they have a robust somatostatin receptor expression in patients

with neuroendocrine tumors.

And the iobenguane, marketed as Azedra, was also mentioned before. This is for patients 12 years or older who have metastatic pheochromocytoma or paraganglioma. Again, the target here, the agent here is an analog of norepinephrine.

And in 2019, we saw the approval of gallium-68 dotatoc, which is very similar to dotatate.

And very recently, again, in 2020, we had the approval of the copper 64 with a 12-hour half-life of the dotatate, which makes it more versatile in some cases for looking at neuroendocrine tumors and somatostatin receptor expression.

And finally, the most recent approval was the fluoroestradiol which is marketed as Cerianna. The target here is the estrogen receptor in patients with recurrent or metastatic breast cancer.

May I have the next slide, please?

So, from here on, what I'm going to talk about are agents that are not approved for clinical use, and we hope so, that at some point they get approved, but just to show you kind of a list of things to expect perhaps in the future as we move on.

The first one is zirconium-89

trastuzumab. Zirconium-89 has a 3.3-day half-life. This is an antibody which is targeting the human epidermal growth factor receptor 2, or HER2, which is a very important target in patients with, for example, breast cancer. And this very nice study published by one of our former trainees, Dr. Ulaner, who was at Memorial Sloan Kettering at the time, shows very nicely that, even though the primary tumor, breast tumor in this case, was not expressing HER2 receptor, as you can see on the left side, top panel A, but the metastatic sites in this patient did express HER2 receptors. And we can see the pep image on the righthand side, panel B, and you can see that the Immunohistochemistry shows that this metastatic lesion in the bone, in this case in the left femur, actually was expressing HER2 receptors.

Therefore, this brings up two points in here. First, that TRANCEs are extremely heterogeneous. And if we sample, tissue sample, one side of the disease where there is a primary tumor of metastatic site, that doesn't mean that the rest of the tumor sites are going to be the same. And therefore, information like this on a PET image is extremely important to decide what needs to be done next. And in this case, for example, this patient

would be eligible to receive anti-HER2 treatments, for example, Herceptin, or others. And that decision should not be made just based on the primary tumor which was negative for this receptor.

May I have the next slide, please?

This is another agent, again, labeled with zirconium-89, which is an anti-CD8 minibody. This is also out of the Memorial Sloan Kettering Cancer Center. Basically, this agent is looking at the abundance of the infiltration of CD-8 T-cells within the tumors. And that is an important feature for immunotherapy with checkpoint inhibitors to be successful. So, the hope is that, with this type of pep agent, we can, first of all, assess if those tumor sites are actually what we call tumor-inflamed; in other words, do possess the CD-8 T-cells that can facilitate treatment and also can be used for treatment response evaluation in patients who have tumor sites that are what they call immune-excluded or immune deserts. In other words, when there is no T-cells, those patients probably would not be candidates for this type of immunotherapy.

So, this is a clinical trial that is going on. It's recruiting, as you can see on this slide. And patients would receive a PET scan before and after

treatment. And, of course, they would be examined for treatment response. And these are some sample images performed at different days from day one to day seven. And the arrow is pointing toward a liver lesion that is hot or shows that there is a good infiltration of CD-8 T-cells in this case.

May I have the next slide, please?

Another very exciting development has been in the fibroblast activation protein inhibitor agent which was mentioned by Josh earlier. This is called FAPI. This is a gallium-68 FAPI that was developed at Heidelberg in Germany. And you can, basically, this is an enzyme that is presented or expressed in the microenvironment of the tumor. So, here, with this agent, we are not looking at the tumor directly, but we are looking at the microenvironment where the tumor resides and this desmoplastic reaction that is caused by the tumor. But it is not cancer-specific, of course. You can see it, also, in wound healing, inflammation, and other conditions.

This very nice paper was published by our German colleagues in JNM in 2019, and they basically showed that FAPI, gallium-68 FAPI, can kind of be a multi-cancer tracer. They showed images from 28 different cancers. And this slide, this is one of

their images showing the comparison between FDG-PET and FAPI, FDG-PET being on the top panel and the FAPI PET being on the bottom panel. And you can see in some cases actually FAPI is better for recognizing where the tumor or the distribution of the tumor is.

For example, if you look at the most left image panel, which it says for pancreatic cancer, the uptake level in the FAPI is more obvious or more conspicuous than the one on FDG, but the exact opposite can also occur. If you look at the most right panel for thyroid cancer, you can see that the FDG-PET was truly positive with some lesions in the mediastinum, but the FAPI was negative.

So, this suggests that there could be a complementary role between looking at the tumor directly and, also, looking at not the tumor, but the microenvironment of the tumor. And perhaps, of course, the hope is that it not only can be used for imaging, but, also, for theranostics based on FAP targeting and perhaps a combination therapy attacking both the tumor and attacking the microenvironment, the tumor that supports the tumor.

May I have the next slide, please?

So, I'm going to now talk about, the next few slides are going to be about PSMA. There's a lot

of excitement in here. PSMA is, basically, again, another enzyme which is transmembrane enzyme or protein.

You can see the schematics on the righthand side. It is not cancer-specific and it's not prostate-specific. So, it's actually a misnomer as a PSMA. And as was I think mentioned earlier, it does get expressed to a very relatively low level in some other tissues. The most level of expression is actually in the salivary glands, which I will show you later on.

But it turns out that, in prostate cancer and a number of other cancers actually, PSMA is overexpressed dramatically. In prostate cancer, you have almost a thousand times expression, higher than normal of the non-prostate tissue, and there's a good density of this PSMA, about 2 million of these transmembrane enzyme expressions per cell, per tumor cell, prostate tumor cell.

Also, you have to notice that there may not be expression, sufficient expression, in somewhere around 5 to 10 percent of prostate cancers. These are usually related to very aggressive prostate tumors, could have neuroendocrine differentiation or other types of histologies, but that can also happen

as kind of a false-negative reason.

Can I have the next slide, please?

So, there have been a good number of radiotracers, PET radiotracers, that have been looked at or designed. The very first one, the granddaddy of them all is the gallium-68 PSMA-11 that was developed in Heidelberg, Germany and Harvard.

There has also been a lot of interest in F-18-labeled type PSMA PET radiotracers. You can see the one in the middle which is DCFPyL or simply called PyL, with a lot of work that was originally done at Johns Hopkins University.

And then, the F-18 PSMA-1007, which is also from Heidelberg, Germany, with the difference being that the 1007 agent has very low renal excretory activity, and therefore, a prostate that does not have much urine activity, and the target or tumor or target-to-background ratio is better in this case. And also, structurally, it is similar to the PSMA-617, which is used for flortaucipir, for the treatment.

May I have the next slide, please?

So, let's just review quickly some of the data on the gallium-68 PSMA-11. This was a study that was led by Dr. Calais from UCLA, but a number of people from other institutions also contributed,

including ours at USC. This was published last year in Lancet Oncology.

That was a head-to-head comparison between fluciclovine PET-CT, which, as I mentioned before, is an approved agent and this gallium-68 PSMA-11 in 50 patients with a PSA in the low range, between 0.2 to as high as 2. None of these patients had started therapy, and all patients, obviously, received both imaging studies, and there was 15 days between the scans without any treatment between those scans.

And as you can see, the detection rate or the positivity rate for PSMA was substantially higher in this case, especially in the domain of metastases, as you can see in the graph that is shown on the left-hand side. This may be partially due to the target-to-background ratio, as PSMA usually has a very high target-to-background ratio.

Can I have the next slide, please?

This is another study that was also multi-center and led by USC colleagues, Tom Hope (phonetic), and was published in 2019 in JAMA Oncology. They looked at the same tracers, that gallium-68 PSMA-11 with regard to positivity and accuracy in localizing recurrent prostate cancer.

And we can see again that, as was shown with many other studies, that in this rather large group of patients -- they had 635 patients involved in this study -- as the PSA went up, the positivity rate also went up. And in fact, you can see in the graph that at a very, very low PSA level, less than 0.5, the positivity rate was approaching about 40 percent.

Can I have the next slide, please?

This is also another study from UCLA. They looked at PSMA and, again, gallium-68 PSMA-11, in 270 patients in a very low PSA range, less than 1 nanogram per milliliter. And they wanted to know what the impact on salvage radiotherapy planning is. And in this case, about 50 percent of the patients had positive PSMA studies. And it turned out that 20 percent of the patients had at least one lesion that would have not been covered by the RTOG guidelines for the treatment field.

So, if you look at the picture on the righthand side of this slide, this is a composite picture, and the yellow dots are basically all the lesions that were PSMA-positive from all patients, not just one patient. It's kind of put on this skeleton, generic skeleton. And the green are you

can see is the area that would have been considered for radiation treatment, salvage radiation treatment, but there are many, many, many yellow dots that are outside of that region. And therefore, this just proves that PSMA can be helpful for treatment planning and, hopefully, reducing your failure rate.

Can I have the next slide, please?

So, because of those studies and the one on the last slide that I just showed, the UCLA group is participating in a clinical trial. It's called PSMA-SRT trial. This is going to be a randomized trial. They are going to look at patients who are post-radical-prostatectomy by chemical recurrence. PSMA should be greater than 0.1. And the primary outcome here is greater than 20 percent declining SRT failure at five years. And I'm not going to go through all the details, but, anyway, if you are interested, you can look up the details of the PSMA-SRT.

Can I have the next slide, please?

So now, let's move on with the theranostic pair for PSMA. This is some of the earlier images showing that in some patients who have been previously heavily treated with everything that we know of with regard to treatment of these patients

in metastatic castrate-resistant prostate cancer, they can have remarkable responses that can be obtained with this data particle, lutetium-177 PSMA-617.

This is a patient who had a very diffused disease in the bone. You can see the gallium-68 PSMA-11 scans in here at baseline, and then, received a number of cycles of lutetium theranostic pair, and he did really well, not only from an imaging point of view. After four cycles, you can see the PSMA PET study there, with basically disappearing, all those diffused bony disease, but also the PSA going dramatically to almost zero, less than 1 in this case, starting from 1,000.

Can I have the next slide, please?

And so, this is another landmark study that was published in Lancet Oncology in 2018. This was a phase 2 study out of Peter Mac in Melbourne, Australia, from our colleagues there. They looked at 30 men with metastatic castrate-resistant prostate cancer. Most of them had prior treatments, including chemotherapy and ADT.

They selected patients who were PSMA-positive on PET scan, on a PSMA PET scan, but had no discordant disease; in other words, no disease that

was FDG-positive. So, they just kind of made sure that they primed treatment for PSMA positivity; had no sites that were not PSMA-positive and FDG-positive.

Anyway, so these patients received radioligand therapy, four cycles. And we can see about half of the patients received all the four cycles. The response was quite good. In about 60 percent of patients, there was PSA decline more than 50 percent. In other studies, it's been shown about 50 percent. So, the number to remember is the PSA decline of more than 50 percent can be seen in 50 percent of patients.

But there could be some delayed response. If you give the first treatment and there's really not major response, it doesn't mean that it's not going to happen. It turns out that up to 20 to 30 percent of patients may need to have another treatment or a second cycle before you see some response.

And on the left panel, the paper also showed the streamers plot and the waterfall plots of the response in these cases. As you can see, pretty impressive.

The next slide, please. And because of all these interesting results, there are a number of

trials that are going on. One of them is a therapy TheraP trial, which is a randomized trial comparing lutetium-177 PSMA-617 versus cabazitaxel. Again, these are patients with metastatic cancer disease and prostate cancer. They should have a PSMA-positive lesions with measurable size sites; should have a SGD max greater than 10. There should be no discordant FDG-positive disease. Again, they are primed in this case through imaging and selected.

And you can see what the arms of the studies are. There are 200 patients that would be participating, and it's a one-to-one randomization. Endpoints, you see the list there, including PSA response, overall survival, quality of life, progression-free survival, and such.

Can I have the next slide, please?

This is the VISION trial. Everybody is waiting for the publication or the results of this study, this trial. It's very much patterned after a simple trial for radium-223. It's lutetium-177 PSMA versus best supportive care. This was a two-to-one randomization. And again, these are metastatic castrate-resistant prostate cancer PSMA-positive patients. And this is an international study; 750 patients participated, and the minimal follow-up is

up to 15 months. And we are, again, awaiting the results of this phase 3 trial.

Can I have the next slide, please?

So, we talked about lutetium-177, but you can also have the alpha particle. In this case, there have been some studies in patients that have been published mostly from Europe and in this case for the

actinium-225, and on the left-hand side, from Mike Sathekge from South Africa, using bismuth-213, another alpha emitter.

And you can see that in both cases at least, these are small case reports or case series reports showing dramatic responses. In, for example, the one with actinium, in this case you can see -- and this image has been shown many, many times by many people around the world -- that the patient did not respond very well the lutetium-177 PSMA. In fact, his got worse. But, after receiving, basically, three cycles of actinium-225 PSMA, the PSA went down dramatically and, also, the scan looked much, much better. So, this is also an active area of interest and research.

Next slide. So, this also was mentioned earlier. There are these PSMA targeted thorium-227

conjugates. I am showing you in this slide some of the pre-clinical studies showing that the efficacy, potential efficacy of this particular approach using the thorium-227 for therapy in this form. You can see that there was a good inhibition of tumor growth, and based upon these encouraging results in these animal studies, pre-clinical studies, a phase 1 trial is being prepared to be done. I think it's led by Bayer. Again, this is in patients with metastatic castrate-resistant prostate cancer. And I have the clinical trial number there, if you are interested.

Next slide, please. And I think this is basically my last slide. So, there are other targets that we can look at this. This is the chemokine receptor 4. It has a role in progression of metastases in many, many cancers. I listed some of those cancers there. However, in this panel, I show you pictures of a patient who had multiple myeloma with very diffused marrow involvement. You have FDG-PET-CT on one side and, also, on the very left-hand side, this is a gallium-68 Pentixafor, which is targeting the chemokine receptor. And you can see that there is a concordance in the marrow involvement, and the patient can also be treated with the theranostic pair, in this case lutetium-177

Pentixather, which opens up a completely new domain for theranostics using this particular target.

Can I have the next slide, please?

So, in summary, I hope that I showed you, at least gave you a taste of what may be going on in the future. Theranostics is a very, very exciting field. As we understand cancer better, the cancer biology, and find new targets and ways that we can image those targets, and also deliver localized therapy to those targets, I think theranostics is definitely in the domain of precision and personalized cancer care.

And again, I thank you very much for your time and for the invitation.

DR. HSIAO: Thank you, Dr. Jadvar.

Now we're in panel time. So, there are a couple of questions that came through the chat earlier. So, I'll read out loud. First of all, there are two questions for Dr. Casey.

The first question is about, which receptors or transporters are considered key leading to PRRT absorption and renal toxicity? Dr. Casey, could you help answer this question?

DR. CASEY: I'm sorry, I didn't unmute myself in both places. Sorry.

Hi. Thanks for this question. So, my reading of the article that I presented about the renal toxicity, it's specific to PRRT, and it's the megalin and tubule receptors. They're endocytic receptors at the proximal tubule membrane. I'm not sure if that answers the question that was asked.

In terms of the transporters, one is more intracellular, and my understanding from one of my colleagues is that it is MATE1 and MATE2 transporters after the endocytosis happened.

DR. HSIAO: Thank you. And there's another question for Dr. Casey as well. For Azedra, which is often delivered as two injections, is the toxicity in the package insert related to all patients including those with two treatments or only after one treatment? Is Azedra toxicity greater after the second therapeutic dose compared to the first?

DR. CASEY: So, did you say hematologic toxicity or all toxicities?

DR. HSIAO: It was not specified.

DR. CASEY: Okay.

DR. HSIAO: So, if you can comment on both?

DR. CASEY: The package insert for the I-131 iobenguane, or the Azedra, the registration

study only included 88 patients. It was single-arm. And the safety data is a pooled population. Fifty of the 88 patients had more than one dose of the Azedra. So, in Section 5 of the label, where we discuss the specific warnings and the specific toxicities, under mylesuppression, you can see the breakdown in terms of how the blood counts nadir after one or after two doses. And certainly, there was longer times to nadir and recovery for the thrombocytopenia and neutropenia in patients, in the 50 patients who received two doses.

In terms of the other toxicities, I probably can't comment without going back into the review because the safety population was pooled, for example, for Section 6 of the label, for all of the other common adverse events. So, that's just specific to the hematologic, and there was, I guess you could call it, increased toxicity if you used the surrogate as having prolonged neutropenia and thrombocytopenia after dose two.

DR. HSIAO: All right. That's great. Thank you, Dr. Casey.

And I have another question for Dr. Kiess. So, the question is, "Are the simpler logistics with radium-223 for administration related

to the fact that it is an alpha isotope? Would the ability to infuse alpha without need for shielding also apply to AC-225-based treatment?"

DR. KIESS: Thank you. That's a good question. The radiation safety and the logistics that go along with it are related mostly to the gamma emissions, so the energy and fraction of gamma emission in the decay spectra. So, for radium-223, it's a particularly safe agent because only 1 percent of the energy is emitted as gamma; whereas, 95 percent is emitted as alpha and 4 percent as beta. And those gamma emissions are particularly low energy as well as low fraction of the total emission. So, radium-223 is like your best-case example.

For actinium-225, there are some higher-energy gamma emissions that are imageable up to 440 kiloelectron volts. The precautions around that are very regional and national. So, I know in the initial studies in Germany of the PSMA-targeted actinium-225, the patients, they have very conservative regulations and the patients were hospitalized, inpatient, until 48 hours after injection. But I don't know what the current radiation precautions are at other sites or with other studies.

DR. HSIAO: Thank you, Dr. Kiess.

We have another question that I'm not sure it's specified specifically for any panelists, but I'll read it out. The question is, "For most RPT agents, the MTD is being determined like chemotherapy for the average patient instead of the individual, meaning most patients are underdosed. What can be done to change that in early phase trials?" It sounds like it might be for Dr. Kiess or Dr. Jadvar.

DR. JADVAR: I'm not sure how to answer that. I think there was an earlier talk on clinical trial design, and this is a rather general question that is being asked. So, I don't want to say something that is all-encompassing and changes the norm. So, I'm not sure exactly how to answer that question.

But it is correct, what is being stated here is true, that there could be -- you know, we are looking at the average patient rather than the individual in this case.

And maybe the other panelists or whoever is on the phone can also chime in.

DR. KIESS: I think this is an area of active discussion whether or not we can in the future consider moving towards absorbed dose prescription instead of administered activity prescription.

There's a lot of complex factors that go into prescribing by absorbed dose. I think most of the trials that are incorporating individualized dosimetry are looking at it for specific indications, like dose escalation on an individual patient basis or retreatment or treatment of children or higher-risk patients. In that setting, when it's not a phase 1 dose escalation or dose-finding trial, but specifically looking at indications, I think it's sort of simpler to incorporate, and it's a good initial step towards incorporating dosimetry as standard of care.

DR. MARIANI: If I can contribute? This is Maurizio Mariani speaking.

I think everything goes back to the choice of the dose and the dose regimen. Because if the dose is sufficiently high, then maybe they define an acceptable level of toxicity. That means that, if you push the dose sufficiently high, then, for a single patient, you would be able to lower the dose rather than increasing the dose, based on dosimetry, which is not the best plan, actually. So, everything goes back to the selection of the best dose for a given population.

I believe that a different indication, a

different population, deserves different doses because the risk that you take is, of course, higher for those patients that have a shorter life expectancy, for example.

But, if you do dosimetry, then if you have a patient with multiple metastases, you would really be in a difficult position to choose which one, which metastasis you would take into consideration because of the variable uptake in the metastasis. So, you would have a metastasis with very high uptake; the other with low uptake. So, then, dosimetry becomes very tricky if it's not based on overall safety match.

DR. HSIAO: Thank you very much.

I think it's actually about time we come to the close of Session V. So, I actually will pass this along to our overall workshop organizer to see how they want to handle the time afterward. So, either Lisa or any organizer team? Maybe would Dr. Marzella want to now --

MS. DIMMICK: Yes. So, thank you, Session V and Dr. Hsiao, for moderating Session V. This has been a great workshop.

So, actually, I'm going to turn it over to Dr. Marzella to kind of close out the meeting

today, and then, we'll go from there.

DR. MARZELLA: Can you all hear me?

MS. DIMMICK: Yes, your audio and video are on.

DR. MARZELLA: Great. Thank you.

So, Dear Colleagues, this has been a very productive and informative workshop. Thank you for all the work that you have done today.

The main takeaway message from the workshop is that collaboration between manufacturers and regulatory agencies is essential for development of new technologies and products for use in radiation medicine.

A parallel review process is important to anticipate hurdles and find solutions early on in product development, and we heard a number of examples during the workshop.

For instance, consistency in development of specifications and instructions for use is enhanced by consultations between FDA and NRC hearing application reviews. And I would like to encourage manufacturers to seek the joint participation by the two agencies.

We also appreciate today the input that we received from the radiopharmaceutical and device

manufacturers and the clinical investigators about your experience in product development with the FDA and the NRC. We will consider your advice.

We heard at today's workshop about new policy initiatives to streamline regulatory requirements. And I think it's clear that we have now acquired a considerable amount of expertise, particularly with radiopharmaceuticals, and that the science and experience has reached a point where we need to reassess our regulatory requirements for pre-clinical and clinical studies. And so, stay tuned for those developments.

We also want to acknowledge the urgent voices of patients who need access to new technologies for their serious, unmet medical needs. And we, as a whole collaborative enterprise -- regulators and scientists and manufacturers -- pledge to do our best to speed up the development of these new, promising technologies that we've heard about.

At this point, also, I want to thank our expert speakers for your informative presentations. We will make recordings, transcripts, and slides from the workshop available. And so, you can benefit from relooking at the information presented today.

I also want to express my deep

appreciation to the workshop's Steering Committee and for the work that you have done to develop today's successful program.

In particular, I want to congratulate Lisa Dimmick for leading today's virtual meeting. Well done, Lisa. Congratulations. Excellent.

MS. DIMMICK: Thank you.

DR. MARZELLA: Kudos are also due to Frank Ludderodt and Lisa for your leadership role in developing this very successful workshop program.

A special acknowledgment also goes to Danae Christodoulou for the role that you and your FDA team play in the development of radiopharmaceuticals focused on product quality.

A final nod to our distinguished attendees. We appreciate your interest and your participation, and we look forward to continuing to work with you to advance the field and the availability of new products.

With that, I would like to bring the second FDA-NRC Workshop to a close. Thank you all. We are now adjourned.

(Whereupon, at 4:50 p.m., the workshop was adjourned.)