FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

MEDICAL IMAGING DRUGS ADVISORY COMMITTEE MEETING

(MIDAC)

Virtual Meeting

Tuesday, August 1, 2023

12:00 p.m. to 4:10 p.m.

Meeting Roster

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P R O C E E D I N G S

(12:00 p.m.)

Call to Order

DR. ROYAL: Good afternoon, and welcome. I would first like to remind everyone to please mute your line when you are not speaking. For media and press, the FDA press contact is Audra Harrison. Her email is currently displayed.

My name is Henry Royal, and I will be chairing this meeting. I will now call the August 1, 2023 Medical Imaging Drugs Advisory Committee to order. Rhea Bhatt is the acting designated federal officer for this meeting and will begin with introductions.

Introduction of Committee

Introduction of Committee

MS. BHATT: Good morning. My name is Rhea Bhatt, and I'm the acting designated federal officer for this meeting. When I call your name, please unmute yourself and turn on your camera. Please introduce yourself by stating your name and affiliation for the record.

We'll begin with MIDAC members, starting with Dr. Bolch.

DR. BOLCH: Wesley Bolch, University of Florida.

MS. BHATT: Thank you, Dr. Bolch.

Next, we have Dr. Hackney.

DR. HACKNEY: David Hackney from Harvard University, Beth Israel Deaconess Medical Center.

MS. BHATT: Thank you.

Next, we have Dr. Herscovitch.

DR. HERSCOVITCH: Peter Herscovitch, National Institutes of Health Clinical Center, Bethesda, Maryland.

MS. BHATT: Thank you, Dr. Herscovitch.

Next, we have Dr. Jacobs.

DR. JACOBS: Paula Jacobs, National Cancer Institute, Bethesda, Maryland.

MS. BHATT: Thank you.

Next, we have Dr. Oates.

DR. OATES: Hi. Liz Oates, University of Kentucky.

MS. BHATT: Thank you, Dr. Oates.

Next, Dr. Sanghani.

DR. SANGHANI: Hi. I'm Rupa Sanghani. I'm a nuclear cardiologist at Rush University in Chicago.

MS. BHATT: Thank you.

Next, we have our industry representative, Dr. Mintun.

DR. MINTUN: Mark Mintun from Eli Lilly and Company and Avid Radiopharmaceuticals.

MS. BHATT: Thank you, Dr. Mintun.

Next, we'll move on to our temporary voting members starting with Dr. Applegate.

DR. APPLEGATE: Good morning. I'm Kimberly Applegate, a pediatric radiologist retired from the University of Kentucky in Lexington.

MS. BHATT: Thank you, Dr. Applegate.

Next, we have Dr. Dewaraja.

DR. DEWARAJA: Hi. I'm Yuni Dewaraja, Department of Radiology at University of Michigan.

MS. BHATT: Thank you.

Next, we have our patient representative, Ms. Gillespie.

MS. GILLESPIE: Hi. Terry Gillespie, patient advocate, Chicago, Illinois.

MS. BHATT: Thank you.

Next, we have Dr. Larson.

DR. LARSON: Steven Larson, Memorial Sloan Kettering Cancer Center.

MS. BHATT: Thank you, Dr. Larson.

Next, we have Dr. Nedrow.

DR. NEDROW: Hi. Jessie Nedrow, University of Pittsburgh, the Hillman Cancer Center.

MS. BHATT: Thank you, Dr. Nedrow.

Next, we have our chairperson, Dr. Royal.

DR. ROYAL: I'm at Washington University in St. Louis.

MS. BHATT: Thank you, Dr. Royal.

And Dr. Xiong?

DR. XIONG: Chengjie Xiong, Washington University School of Medicine, St. Louis, Missouri.

MS. BHATT: Thank you, Dr. Xiong.

Next, we'll move on to introductions of our FDA participants.

First, we have Dr. Ganley.

(No response.)

MS. BHATT: Are the FDA participants able to introduce themselves?

First, we have Dr. Ganley.

DR. KREFTING: Ira Krefting, director for safety, Medical Imaging and Radiation Medicine Division.

MS. BHATT: Thank you.

DR. COTTER: Samantha Cotter, safety evaluator from the Division of Pharmacovigilance in the Office of Surveillance and Epidemiology at FDA.

DR. COHEN: Jonathan Cohen, supervisory pharmacologist supporting Imaging and Radiation Medicine.

DR. PLYKU: Donika Plyku, physicist at the Division of Imaging and Radiation Medicine at CDER.

DR. FOTENOS: Anthony Fotenos, clinical team leader in the Division of Imaging and Radiation Medicine.

DR. HOFLING: Alex Hofling, deputy director, Division of Imaging and Radiation Medicine.

DR. MARZELLA: Lou Marzella, and I'm the

director of the Division of Imaging and Radiation Medicine.

MS. BHATT: Thank you.

That concludes our panel and FDA introductions, and back to you, Dr. Royal.

DR. ROYAL: For the topics such as those being discussed at this meeting, there are often a variety of opinions, some of which are strongly held. Our goal is that this meeting will be a fair and open forum for discussion of these issues and that individuals can express their views without interruption. Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the chairperson. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the advisory committee members take care that their conversations about the topic at hand take place in the open forum of this meeting.

We are aware that members of the media are

anxious to speak with the FDA about these proceedings; however, the FDA will refrain from discussing the details of this meeting until its conclusion. Also, the committee is reminded to please refrain from discussing the meeting topics during breaks. Thank you.

Rhea Bhatt will read the Conflict of Interest Statement for the meeting.

Conflict of Interest Statement

MS. BHATT: Thank you, Dr. Royal.

The Food and Drug Administration is convening today's meeting of the Medical Imaging Drugs Advisory Committee under the authority of the Federal Advisory Committee Act, or FACA, of 1972. With the exception of the industry representative, all members and temporary voting members of the committee are special government employees or regular federal employees from other agencies, and are subject to federal conflict of interest laws and regulations.

The following information on the status of this committee's compliance with federal ethics and

conflict of interest laws, covered by but not limited to those found at 18 U.S.C. Section 208, is being provided to participants in today's meeting and to the public.

FDA has determined that members and temporary voting members of this committee are in compliance with federal ethics and conflict of interest laws. Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that that agency's need for a special government employee's services outweighs their potential financial conflict of interest, or when the interest of a regular federal employee is not so substantial as to be deemed likely to affect the integrity of the services which the government may expect from the employee.

Related to the discussions of today's meeting, members and temporary voting members of this committee have been screened for potential financial conflicts of interests of their own as

well as those imputed to them, including those of their spouses or minor children and, for purposes of 18 U.S.C. Section 208, their employers. These interests may include investments; consulting; expert witness testimony; contracts, grants, CRADAs; teaching, speaking, writing; patents and royalties; and primary employment.

Today's agenda involves the discussion of dosimetry data needed to support the initial clinical study in an original IND application for certain new positron emission tomography or PET drugs. FDA would like to obtain the committee's input on the following: 1) the sufficiency of available data from animal or human studies involving certain positron emitting radionuclides -- for example, carbon-11 and fluorine-18 -- to allow a reasonable calculation of radiation-absorbed dose to the whole body and critical organs upon administration of a new PET drug containing certain radionuclides to a human subject in first-in-human studies; and 2) the reasonableness of a proposed list of numerical

radioactivity thresholds for new PET drugs containing these radionuclides, such that phase 1 studies will both a) administer subthreshold activities, and b) obtain sufficient human data so dosimetry calculations may be found safe to proceed in the absence of dosimetry data, based on prior animal administration of the new PET drug under investigation.

This is a particular matters meeting during which general issues will be discussed. Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, no conflict of interest waivers have been issued in connection with this meeting.

To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements that they have made concerning the topic at issue. With respect to FDA's invited industry representative, we would like to disclose that Dr. Mark Mintun is participating in this meeting as a non-voting

industry representative, acting on behalf of a regulated industry. Dr. Mintun's role at this meeting is to represent industry in general and not any particular company. Dr. Mintun is employed by Eli Lilly and Company.

With regard to FDA's guest speaker, the agency has determined that the information to be provided by the speaker is essential. Dr. William Hallett has acknowledged that he is employed by Invicro as head of Imaging Physics. As a guest speaker, Dr. Hallett will not participate in committee deliberations, nor will he vote.

We would like to remind members and temporary voting members that if the discussions involve any other topics not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record. FDA encourages all other participants to advise the committee of any financial relationships that they may have regarding the topic that could be affected

by the committee's discussions.

Thank you, and back to you, Dr. Royal.

DR. ROYAL: We will now proceed with the FDA introductory comments from Dr. Anthony Fotenos.

FDA Introductory Comments - Anthony Fotenos

DR. FOTENOS: Good afternoon. I'm Anthony Fotenos, nuclear medicine physician and clinical team leader in the Division of Imaging and Radiation Medicine. Welcome to the Medical Imaging Drugs Advisory Committee. The last time this committee met, our division was known as the Division of Medical Imaging Products, or DMIP, but in 2017, our name changed, so now we go by D-I-R-M or DIRM.

FDA convened this advisory committee meeting to discuss issues involving pre-IND and phase 1 radiation dosimetry data for certain groups of new positron emission tomography or PET drugs. First, a comment regarding scope.

Today's meeting is classified as a general matter type meeting. This means that product, sponsor, and/or application specific issues and

questions will not be discussed, nor are any thumbs up or down votes planned; rather, the general matter issue we will be discussing reflect stakeholder concern regarding burden of animal dosimetry data collection for certain groups of new PET imaging drugs. The rationale for the meeting is stakeholder and FDA's preliminary position that data already available often allows reasonable calculation of radiation risk for human subjects prior to collection of phase 1 dosimetry data.

Where we need your advice is regarding sponsors of new INDs for certain groups of PET drugs, specifically when sponsors would prefer not to submit drug-specific animal dosimetry data. We will be asking you to discuss the sufficiency of reviewed dosimetry data and the reasonableness of the approach under consideration for investigational administration prior to the availability of phase 1 dosimetry data such that for administration less than or equal to X, FDA may generally find administered activity safe to proceed from a radiation safety perspective,

whereas for administration greater than X, the status quo will be maintained of case-by-case IND review regarding the reasonableness of available animal or human dosimetry data.

As you will learn in greater detail later, the approach under consideration is essentially a leveraging approach where X is derived from dosing and administration FDA has already found to be safe and effective in corresponding prescribing information.

You should have a copy of the complete agenda. Here's a brief outline. Dr. Hallett, medical physicist at Invicro, will provide a scientific overview and share his perspective from industry. Then Dr. Zanotti-Fregnoara, staff scientist from the section on PET Neuroimaging Science and Branch of Molecular Imaging at the National Institute of Mental Health NIH, will share his perspective from an active translational laboratory.

FDA will speak next. Dr. Plyku, our division's medical physicist, will provide a

summary of FDA's systematic review of publicly available dosimetry data and discuss the approach under consideration. Finally, Dr. Cohen, from the Office of Rare Diseases, Pediatrics, Urology, and Reproductive Medicine, and Dr. Cotter, from the Office of Pharmacovigilance and Epidemiology, will provide brief perspectives on PET drug radiation safety from their pharmacology/toxicology and pharmacovigilance disciplines, respectively. Finally, there will be an open public hearing, and then the discussion questions will be posed to the panel.

But first, I'd briefly like to introduce PET drugs within a broader regulatory and historical context. This table spans the next two slides and encapsulates some regulatory milestones at the intersection of nuclear medicine and FDA's Center for Drug Evaluation and Research. Highlighted in yellow for each year is the introduction of a formal definition within federal act, regulation, or guidance of terms specifically relevant to the field of nuclear medicine. Since these terms may

often be used more loosely elsewhere, I hope this regulatory introduction also helps to keep us all on the same page in terms of nomenclature.

The table starts in 1975. That's when new drug regulation defined the term "radioactive drug" as a drug or biological product exhibiting spontaneous disintegration of unstable nuclei with the emission of nuclear particles or photons. These 1975 regulations also ended an exception agreed to in 1963 with the Nuclear Regulatory Commission, then called the Atomic Energy Commission, for oversight of investigational use, and provided certain new authority for oversight of basic research to FDA-authorized radioactive drug research committees, or RDRCs, a program that remains in place to this day.

The year 1987 saw a rewrite of FDA's IND regulations, including two sentences on radioactive drugs and data on radiation-absorbed dose. We'll come back to these two sentences shortly because they provide an essential framework for today's discussion.

Fast forward 10 years to 1997. That's the year Congress passed the FDA Modernization Act or FDAMA. FDAMA defined a new subset of radioactive drugs using the term "PET drugs." FDAMA defined PET drugs as articles exhibiting spontaneous disintegration of unstable nuclei by the emission of positron particles.

Emitted positron particles annihilate locally with electrons to release dual 511 keV photons from where they are capable of leaving the body for diagnostic imaging with a PET camera. FDAMA also defined an encompassing group of radioactive drugs using the term "radiopharmaceutical," including single photon emitters and defined by a common intended use of diagnosing or monitoring rather than treating disease.

In 1999, Part 315 was added to the Code of Federal Regulations directly after Part 314, the part describing new drug applications. 21 CFR 315 further applied the statutory requirements outlined two years earlier under FDAMA for diagnostic

radiopharmaceuticals, as did CDER's three-part guidance published in 2004, entitled Developing Medical Imaging Drugs and Biological Products.

Most recently in 2017, the FDA Reauthorization Act, or FDARA, introduced a new 520(p) pathway for approving certain new uses of approved drugs under 510(k), de novo, or PMA device marketing applications. Notably, under Section 706, FDARA expanded the definition of contrast agents. Under this expanded definition, contrast agents include both diagnostic radiopharmaceuticals and non-radioactive drugs, with both essentially defined by their shared characteristic of serving to increase relative signal intensity for diagnostic or monitoring purposes.

Finally, less than a year ago in the Food and Drug Omnibus Reform Act of 2022, Congress again leveraged an expansive definition of "contrast agent" to clarify that all radioactive drugs and all medical imaging agents remain legally defined as drugs.

For those who might prefer to see information visually, this slide provides a Venn-like depiction of the terms just highlighted. Again, from a regulatory perspective, this meeting provides an opportunity to discuss pre-IND and phase 1 dosimetry data at the intersection of PET drugs -- the box at slide center -- and 21 CFR 312.23, the IND dosimetry regulation introduced above and excerpted in full on the slide that follows.

Under the heading "Additional Information," FDA's IND regulations state that in certain applications, as described below, information on special topics may be needed. Such information shall be submitted as follows. If the drug is a radioactive drug, sufficient data from animal or human studies to allow a reasonable calculation of radioactive-absorbed dose to the whole body and critical organs upon administration to a human subject. Phase 1 studies of radioactive drugs must include studies which will obtain sufficient data for dosimetry calculations. With this basic

regulatory foundation introduced, I'll conclude by previewing FDA's discussion points to the advisory committee.

These will be displayed again after the guest speaker, FDA presentations, and open public hearing at the end of the afternoon. First, we will ask the committee to discuss the sufficiency of reviewed data from animal or human studies involving fluorine-18; carbon-11; gallium-68; copper-64; rubidium-82; and ammonia-13 to allow a reasonable calculation of radiation-absorbed dose to the whole body and critical organs upon first-in-human administration of a new PET drug containing one of radionuclides.

Second, we will ask the committee to discuss the reasonableness of the approach under consideration involving administered activities for new PET drugs containing one of these radionuclides such that phase 1 studies that will both initially administer one or more activity levels less than or equal to the value specified, and collect sufficient human data for dosimetry calculations,

may generally be found safe to proceed from a radiation safety perspective in the absence of dosimetry data based on prior animal administration of the new PET drug under investigation.

I will now turn the podium over to our first guest speaker, Dr. Hallett. Thank you.

Guest Speaker Presentation - William Hallett

DR. HALLETT: Hello, and thank you for the introduction. I'm going to give you a perspective somewhat from the UK because the imaging center that I work in is based in the UK. This is our facility in London. It was originally built by GlaxoSmithKline to support drug development, and to cut a long story short, it's now part of Invicro. We have imaging centers both in the U.S. and the UK. The UK one is essentially a PET facility, and we mostly work with carbon-11 and fluorine-18 and not some of the longer-lived isotopes that you mentioned there; so I can only really give you a perspective on that aspect.

I'm going to set the scene for the discussion today. I realize this is a panel of

experts, and much of this will be familiar, but hopefully it's useful for other people dialing in and listening into this.

Why do we need radiation dosimetry? The driver for this is that the basic principles of radiation protection that apply to medical exposures are that we should justify and optimize dose exposures. From the European perspective, in the EU, there is the basic safety standards directive. The UK of course has left the EU, but we're still going to follow the same abiding principles, and the relevant legislation in the UK that followed on from the basic safety standards is the Ionising Radiation Medical Exposure Regulations, and that's unlikely to significantly change.

So in terms of the radiation dose to clinical subjects, in terms of imaging, we're really considering stochastic risks at relatively low dose, and those risks are, to some extent, a little bit uncertain. We would be working below the threshold for tissue effects, for example, in

nearly all cases in PET.

For patients, that's implemented using diagnostic reference levels, which are generally agreed guidance levels for particular procedures, and there's no dose limit as such. For research subjects, we need to obtain ethical approval, and we have to provide some estimate of risk from the radiation exposure. We need to put that in some context that can be understood by the subjects and appreciated in terms of other risks; for example, equivalent background exposures, the increased potential risk of cancer induction later in life. The formal framework for that is to use what we call dose constraints, and there are guidelines surrounding those constraints.

So just going back to basics and reviewing the framework that we use for radiation dose, we start with the absorbed dose, which is the energy transferred by radiation to the subject per unit mass, and for imaging procedures, we are in the milligray domain, which is millijoules per kilogram of tissue.

Radiation risk also depends not only on the administered radiopharmaceutical or drug, but also on where it goes in the body: the tissues, the organs that are exposed. The radiation sensitivity of those tissues is known to differ from one organ to the next, and that's encoded in these tissue-weighting factors. We also have radiation-weighting factors, but in the context of PET or PET/CT, even those factors are all one, so we can more or less ignore that.

Then the effective dose is to sum those contributions over all the organs as a weighted sum, and the unit there is the sievert. And just to set that in context, for the UK, the average background radiation dose is something like 2.3 millisieverts per year. For employees, there is a dose limit, which is 20 millisieverts a year, but very few radiation workers would get anywhere near those kinds of occupational exposures. And in terms of translating that into a risk, the ICRP recommended risk factor is 1 in 20,000, although, as I've already mentioned, it's somewhat uncertain

at low dose.

So overall then, we can say that factors affecting PET doses are the PET drug, the radioisotope that's being delivered, and then how the body processes that in terms of biodistribution and excretion. So you can generalize those factors in terms of the subject's age, sex, weight, health, and their current condition. The classic example of that is with FDG, where you get a different uptake pattern if the subject has recently eaten to being fasted, and obviously you want to standardize against that.

The standard approach to PET dosimetry is to use a mathematical model that contains a simplified human phantom. We know that a uniform body distribution is simply too inaccurate if we assume that, and in order to obtain the distribution in the body, we need to get some information either from preclinical experiment in, say, rodents, where we can take tissue samples or an imaging study. The results of such a calculation enable us to compare medical exposures of different PET drugs

and estimate radiation risk, but they are not accurate enough to individually plan doses. We're not actually measuring the doses to organs. At the bottom there, you can see the difference between a simple uniform estimation and a more sophisticated one taking account by distribution.

So the inputs into that model that we need to obtain are the measurements of radioactivity concentration at different time points. We then integrate that over time, and then multiply by standardized organ mass to obtain these time integration activity coefficients. You can think of it as a mean residence time in the organ because it has the units of time.

This is the OLINDA code, which is now the widely used code to do these calculations. The beauty of this is that all the complicated physics calculations in terms of absorbed dose within an organ and between organs has already been done. You just need to input the actual activities in each organ. If you just click on, you can see the output of that. You get the organ absorbed in

equivalent doses and also the summed effective doses, depending on which weighting factor scheme you want to use.

For a preclinical PET dosimetry experiment -- and I'm talking about rodents here in particular -- you give the tracer to multiple subjects, one subject per time point. You then harvest the organs at that time point. You weigh samples and count the radioactivity in a gamma counter. Multiple counters are really ideal here because you have quite a lot of samples to count when you have a short half-life to contend with.

Then you have to scale that information to in some way adjust it to the human situation, so what you're doing there, really, is adjusting for the relative organ weight and also the total body weight. You can't possibly adjust for differences in metabolism. Then these resulting coefficients are entered into the code, OLINDA in this case.

For a clinical study, we give the tracer to multiple human subjects for carbon-11 or fluorine-18. The scans will take anywhere between

90 minutes to 4 hours. We do multiple time points, perhaps six or so, increasing the spacing between them post-injection, and then we can generate the same curve. If you press on, you'll see a little movie there. There we go. Then you have to generate your data in terms of drawing regions of interest over the organs, and then that's what's input into OLINDA. And that's our drawing, the regions of interest over the CT that we get as a convenience, an extra bit of data. We need the CT anyway for attenuation correction purposes, and that's just the curves that you generate.

Just to summarize the data that we've collected over the years, we've done 24 dosimetry studies since 2012, mostly in the rat but some in human. You can see that the carbon-11 cluster quite tightly around 5, 5 and a half microsieverts per megabecquerel. The fluorine-18 is a bit more of a spread, but again it's clustering around 24-25 microsieverts per megabecquerel. So on average, we get a fairly consistent answer.

If you look at where we've done both

preclinical and human dosimetry, well, clearly there's a difference there in those two cases. Where we've repeated the preclinical study, which is not something we would normally have to do, but where we've done it, even years apart, we get a very similar result. So this suggests that the methodology is repeatable, at least within center, but there is some difference between preclinical and human estimation.

In terms of study timelines, for a preclinical study, we've sometimes been asked to do it as quickly as possible, and as long as you have the staff available and equipment is available, the fastest turnaround we've been able to do is about a month. If you click on for comparison for a clinical study, it's a much longer process. You have to make sure that you can produce the radiopharmaceutical to GMP standard; and because it's going into man, you have to get all your regulatory approval done, including ethics, as well as expert opinion on the use of a particular radiopharmaceutical.

You have to recruit your subjects; that can take months. It can be harder to get a patient group if that's what you're interested in. Then you've got to do a more complicated analysis involving region drawing over the images and so on. All of this adds time, so we're talking about something like a year, and it's also, at least in order of magnitude, more expensive.

So looking at this a slightly different way, in terms of our in-house dosimetry, we've done 17 clinical ligands, carbon-11 and fluorine-18 only, and another 55 ligands used clinically, where we've got the dosimetry from other sources. You can see from the literature and those other sources that there's variable quality in the data differences in the methodology used.

Some of the data has been around for a while, as the scanners have improved considerably since then and a different species used. There are details that are, to some extent, unknown or just aren't mentioned in the source that you're looking at, for example, what's the assumptions made about

emptying of the bladder; are they all healthy or some are patients; and so on.

Nonetheless, on average, this is consistent between clinical and preclinical. Carbon-11 is coming out around 5, within 2 microsieverts per megabecquerel and F-18 around 25, a bigger range. I guess you don't really know whether it's due to methodology or metabolism, and almost certainly there's contributions from both in there.

In terms of translation, I've already mentioned that you can have discordancy between the preclinical and clinical estimate. It can be higher or lower, in fact; so there are examples of both there. But again, within center, within our center, the methodology seems to be repeatable; it's just the translation that's less so.

To summarize what those limitations of preclinical dosimetry are, there are differences in metabolism, which you can't really correct for and are expected to be more rapid in smaller species. There are differences in anatomy. Famously, the rat lacks a gallbladder, so that affects the dose

that you see in the small intestine. You have to extrapolate renal excretion from your preclinical experiment to a human voiding model. So for a particular tracer, it's fair to say it's not reliable, really, for the human dosimetry estimate; and that's even true for non-human primates, which we don't do in the UK, but just looking at the literature, there are still differences.

In terms of arguments for and against preclinical dosimetry, while there's always an intention to reduce the number of animals used in research wherever possible, on the other hand, it does give forewarning in the early stage of development of any unusual kinetics or uptake. But it's fair to say that it's not really a reliable predictor for human dosimetry in an individual case.

I've been asked to comment on the differences in the radiation protection frameworks between Europe and the U.S. In Europe, including the UK, it's the effective dose that we look at, and the guidance is to keep that below

10 millisieverts a year for healthy subjects. You can exceed that in certain situations, for example, with a subject group with reduced life expectancy or more elderly subjects because of the reduction in radiation risk with age. You need more justification for younger healthy subjects. We never scan below 18, for example. Preclinical data is considered acceptable if no human data is available and, in fact, we've even done dosimetry studies where we had no preclinical data at all. That would have to be justified on an individual basis.

That limit -- I shouldn't say limit; it's very much a guidance -- is also applicable to dosimetry studies. So if you're doing a dosimetry study in healthy volunteers, you've still got to keep within your 10 millisieverts a year, and that includes the CT component, which can be as much as half of the dose for a dosimetry study in man. In the U.S., my understanding is that you're looking at both the effective dose and the critical organ doses, and usually staying within 50 millisieverts

a year or 30 millisieverts for more radiosensitive organs, but this leads to typically higher doses in the U.S. than in Europe.

This is the guidance from our regulator in the UK, and you can see that for an application to use a novel PET tracer, they would like an estimate of the effective dose, which is based on the best available information at the time. But there is a lot of flexibility in that. They're a panel of experts, and they will take into account other factors such as tracers expected in a very similar profile, for example.

In terms of the European guidance for radiodiagnostics, which are radiotracers which may have widespread clinical application, the requirements are in terms of pharmacology, pharmacokinetics, and toxicology, and the pharmacokinetics would include a dosimetry component. The toxicology for these tracers, where there is expected to be no pharmacological effect and it's given a very low dose, can be a reduced tox package.

In terms of what the impact is on study design within our center, we mostly do brain, although we mostly do whole-body studies as well. You can see that if you're trying to work within a 10 millisievert per annum dose constraint, you're talking about something like only up to 4 carbon-11 scans. That's usually more than we need. Not many studies need four, and you may have an extended time in which to do those, so that would be relaxed a bit. But for fluorine-18, that really limits you to about 2 scans within a year. But if you're looking at disease progression, you're probably looking over a longer time scale anyway.

So thinking a little bit ahead about what might be alternative approaches to performing these dosimetry studies either in preclinical/clinical situations for short-lived tracers, well, one approach would be to consider a conservative default effective dose. I don't wish to propose a particular figure, but most tracers would fall below the figures that I've given there.

If you then need to characterize that a bit

more in man because you're not sure about that, you could consider a single whole-body human scan to characterize uptake. I know that approach is used in some centers in Europe. The question would be whether that was sufficiently representative of the population you want to study. Then moving on, if that tracer is going to be used more widely -- for example, if it's going to be used as a clinical radiodiagnostic -- at that point, you might want to consider actually performing a proper human dosimetry study, but that wouldn't really apply to most carbon-11 labeled PET drugs.

Thank you. I think we're at the end. Thank you.

DR. ROYAL: Thank you very much, Dr. Hallett. We will now proceed with a speaker presentation from Dr. Paolo Zanotti-Fregonara.

Speaker Presentation - Paolo Zanotti-Fregonara

DR. ZANOTTI-FREGONARA: Hi. Good morning, and thanks for inviting me to this meeting. My name is Paolo Zanotti-Fregonara, and I work in the lab in the National Institute of Mental Health

called the Molecular Imaging Branch. This is a lab whose goal is to create new PET research, so essentially for brain diseases. So therefore, we are often in the situation where we inject new radioligands in humans under INDs. Of course, along the usual safety assessment, we need to have an estimation of the dosimetry. I'm talking only about carbon-11 and F-18 here because these are the isotopes that we use.

In the past years, we have tried to simplify and streamline the dosimetry part of the validation of new ligands, and we summarized our approach and proposal in three opinion papers that were published in the journals of our field, and the scope of this talk is to give you an overview of these three papers and explain the rationale behind them.

To summarize the main points, animal dosimetry is resource-intensive and poorly predicts human values. Human dosimetry is even more expensive, exposes multiple subjects to radiation, and you may find out at the end that the tracer

doesn't work because creating new radioligands is a type of research with a high risk of failure, and it's only when you really explore the organ, like the brain, that you will discover whether the tracer works or not.

Finally, the dose for specifically carbon-11 tracers we think is very predictable and primarily based on the isotope, so the proper solution would be to abandon animal dosimetry for both F-18 and carbon-11 to postpone dosimetry until the tracer is proven to work, and specifically abandon human carbon-11 dosimetry, even in humans, and use an average dose.

Until, let's say, 10 years ago, this was the traditional pathway we used at NIH for new radioligands. We would first perform human dosimetry in monkeys. I am aware that the FDA does not mandate the use of monkeys, but we used monkeys as a model because we have easy access to monkeys, and they are, of course, the best model. Once the dosimetry in monkeys was done, we would do dosimetry in humans, which means acquiring 5 to 10

whole-body scans and calculating the dosimetry. Once the dosimetry is known, then we would test the validity of the new tracer, for example, by doing brain studies. The problem with this pathway is immediately evident. By the time you discover that the tracer does not work, you have already done all the animals and human dosimetry, so you have spent a lot of money, you have irradiated subjects, and used the resources for nothing.

We first published these two papers about 10 years ago in which we argued that, first, animal dosimetry should be abandoned because it poorly predicts the human dose. Then we proposed to validate the new tracers directly in humans by injecting first a single human subject with low activity and do a whole-body scan.

The reason was to check whether the biodistribution of the tracer was not unusual. In particular, we wanted to avoid that there was an abnormal disproportionate accumulation in one organ that would give a high organ dose. If that is not the case, then we would proceed with brain scans to

determine whether the radioligand is worth pursuing. If it is, then we would go back to the dosimetry part and complete the dosimetry studies.

This is the approach that we have been using for the past 10 years because it was submitted to our radiation safety committee, and it was approved. Then more recently, a couple of years ago, we published this other paper in which we argued that carbon-11 dosimetry should be abandoned altogether, even for humans, and instead we would use an average effective dose of 5 microsieverts per megabecquerel. This was the contents of the letter, and now I'm going to give you the data these recommendations are based on.

First, for animal studies, monkeys poorly predict human dosimetry. In the literature, there are 16 carbon-11 tracers and 21 F-18 tracers for which the dosimetry of humans and monkeys is available. In terms of effective dose, the monkey scans unpredictably under- or over-estimated the human effective dose with a mean difference of about 30 percent. The organ dose is not

surprisingly even less well estimated.

In particular, in only one-third of the tracers, the target organ was the same between the two species. So the target organ is the organ that receives the highest dose and is more likely the limiting factor for the amount of dose activity you can give to humans. In terms of the cases, monkeys were not even able to predict which was the target organ, let alone calculate the dose.

As I was saying, in the lecture, we spoke only about the monkeys because this is the best model for humans with the understanding that if even monkeys cannot estimate what is the dose to humans, there isn't a chance that mice can, and indeed, I came in contact recently with a German team from Leipzig. They don't have access to monkeys, so they routinely use mice and piglets for human dosimetry, and they have results that are very different from the actual human dosimetry, so they are trying to convince the German FDA to let them abandon human dosimetry as well. So we're not the only ones with this line of thinking, and I

suspect that there are more.

This graph shows you the doses in humans. These are not extrapolated from monkeys. These are human doses of all tracers published in the literature that I could find. There are 77 carbon-11 tracers and 144 F-18 tracers. The average dose for carbon-11 is 5 microsieverts per megabecquerel. The average dose for F-18 is 20 microsieverts per megabecquerel, 4 times larger.

Even without me giving you the value of these kind of deviations, you can visually see how the carbon-11 doses are most tightly clustered around the mean of 5, so we propose to use an average carbon-11 dose for humans. One may object that if we use an average dose, we may miss some outlying value. So if you click once again, you see there is this very high outlying point for carbon-11, which has a dose of about 15 microsieverts per megabecquerel. We are talking something like 7 standard deviations above the mean.

There are two things to be said. First,

even for such a high value, we are practically still one standard deviation below the mean for F-18. That is because the dose of carbon-11 is so low, that we are always within a safe range. But second, I will say that when you find the value that is so outlying and so unique compared to everything else that you published, you cannot exclude the hypothesis that there were some issues with the data analysis.

This is a standard carbon-11 tracer for the brain receptor. There are many, and they all share similar biophysical characteristics, molecular weight, lipophilicity, so you do not expect a dose that is 7 standard deviations away. For these tracers in particular, we have animal dosimetry, which shows a standard of 5 microsieverts per megabecquerel dose. So either animal dosimetry is so bad that it cannot catch something that is 7 standard deviations away or the study needs a replication.

We have a similar case for F-18. The second arrow, that is this very high data point of about

50 microsieverts per megabecquerel. And this 50 actually is the average between men and women, and the average between men and women is almost a factor of 2. There can be sex differences also because you use two different anthropomorphic phantoms, but it's never a factor of almost 2. Then for this tracer, we do have a replication study in humans which found a more standard dose of about 30 microsieverts per megabecquerel and no sex differences.

Even if we can question these outlying values only on methodological grounds, there is still some variability around the mean of 5 microsieverts per megabecquerel, so how important is this variability? I will say not very much because knowing whether the dose is slightly above or slightly below 5 really has no significant biological meaning.

It should not be forgotten that the variability is also explained by methodological choices. Whenever you do dosimetry analysis, you determine which are the choices that affect the

numbers that you find reported in the paper; for example, how you draw the region of interest around the organs; which organs you use as source organs; and, for example, the settings of the bladder. When you simulate the dose with an anthropomorphic phantom, you can decide whether the bladder voids at 1 hour after injection, or 4 hours, or 1 and 4 hours, or never voids. This can change a lot of the dose to the bladder, but also it can change the effective dose because there is more or less radioactivity inside of the body.

There are some papers in the literature which report two sets of values with different body types, and the results can be significant or they can be in the double digits, which means that these could be the values of a completely different tracer if you chose a different voiding schedule, for example.

I said before that animal dosimetry is poorly predictive of human dosimetry, but also human dosimetry is poorly predictive of human dosimetry because in the literature, there are

18 tracers for which the effective dose was reported by two different teams mainly because there were two different teams working on the same tracers; and often unbeknownst to each other, they were working on the dosimetry paper, and then they published the results. This is a very nice natural experiment to see how reproducible is human dosimetry, and the answer is not very much. The difference can be important, and in only 3 of these 18 tracers the dose difference was more than 10 percent.

If we go to the next slide, this is to remind you that we are not the only ones questioning the utility of the scans because carbon-11 is already being abandoned somewhere. Specifically, at the University Hospital of Amsterdam, they abandoned both animal and human carbon-11 dosimetry for all tracers, except those that are expected to enter routine clinical practice. For F-18 tracers, in Amsterdam they use the protocol we adopted here at the NIH, so directly in humans but with one first whole-body

scan, and then validation of the tracer.

This is the last slide. Our opinions are that we should abandon animal dosimetry for both F-18 and carbon-11 because the doses are low for these isotopes, and the animals are not a good model. We don't think it's a justifiable use of animal research in this case. For F-18, we can go directly into humans with a single whole-body scan and then do dosimetry after the tracer has been proven valid, and for human carbon-11 dosimetry, we may simply replace with an average dose.

Thank you very much, and I would be happy to take questions.

Clarifying Questions to Speakers

DR. ROYAL: Thank you, Dr. Zanotti-Fregonara.

We will now take clarifying questions for Dr. Hallett and Dr. Zanotti-Fregonara. Please use the raise-hand icon to indicate if you have a question, and you'll find that under the reactions tab at the very bottom. Remember to lower your hand by clicking the raise-hand icon again after

you've asked your question. When acknowledged, please remember to state your name for the record before you speak and direct your question to a specific presenter, if you can. If you wish for a specific slide to be displayed, please let us know the slide number, if possible.

Finally, it would be helpful to acknowledge the end of your question with a thank you or the end of your follow-up question with, "That is all for my questions," so we can move to the next panel member.

Okay. I see we have a question from Terry Gillespie.

MS. GILLESPIE: Hi. Thank you. One of my questions is I noticed that they kept saying "healthy patients," and I'm a patient advocate. I don't know. I see that most people that need these types of scans or isotopes are not healthy, so I was wondering what they qualify as a healthy patient. Thank you.

DR. ROYAL: Dr. Hallett or Dr. Zanotti-Fregonara, would you like to answer that question?

DR. ZANOTTI-FREGONARA: Well, yes. Indeed, dosimetry analyses are usually performed on healthy patients, and then we assume dose is estimated in healthy patients, and active controls can be translatable to patients. I will say, in most cases, this is a reasonable assumption, especially when you study diseases like the brain.

Of course, there can be differences if there are significant organ failures with the kidneys or other organs that are supposed to clear the waste away from the body, but generally speaking, yes, this is the standard procedure. We do dosimetry estimated in healthy controls.

DR. HALLETT: Yes, it's a very good question. In a few of our dosimetry studies, because the biodistribution and the excretion is likely to be affected by the disease, for example, we have also been asked to do the dosimetry in patients, as well as healthy volunteers. But in any case, the dosimetry number that you get is really only valid as an average over a population. So you don't expect it to be predictive for an

individual person, but it's just to give you an average value that you can use to compare different tracers and which tracer you should use if you have a choice.

MS. GILLESPIE: My question then is, should the average be adjusted? Because 90 percent of the people using this stuff is not healthy anymore. So that means that the uptake to an organ or something else would be more likely, I would think.

DR. HALLETT: Yes, potentially, but it's only one of the variables. I mean, a particularly important factor, for example, is if a tracer is excreted by the kidneys, then patients are encouraged to go to the bathroom to void, get rid of the tracer that's excreted that way; so that can have a really big effect on the dose, actually. A lot of tracers are used only in healthy subjects. If we're using a tracer to investigate a particular pathway in the body -- a PET tracer which is really only being used for basic fundamental research -- then it may not be used in patients.

MS. GILLESPIE: Okay. That is all. Thank

you very much.

DR. ROYAL: Okay. That question was from Terry. I'm looking for her last name.

MS. GILLESPIE: Gillespie.

DR. ROYAL: Gillespie. Okay.

Dr. Xiong had his hand raised, although you may have put it down.

Do you have a question or comment, Dr. Xiong?

DR. XIONG: Yes. Thanks. Chengjie Xiong again. My question is to the last speaker. I think maybe your next-to-last slide, when you talk about human dosimetry data are also poorly reproducible, you give the example of, I believe, 18 studies of the same tracer, and they came up with different numbers.

Can you try to explain what are the reasons behind this, when people are using the same tracer and perhaps the same subject population as well? I don't know; that could be a major reason. Can you interpret or maybe explain what are the possible reasons people are using different protocols,

different populations, different statistical approaches? What are the major reasons behind that?

DR. ZANOTTI-FREGONARA: Well, I think there are multiple reasons at the same time. First, these are different subjects, which can give different time-activity curves. The way you are drawing the region of interest might be different. The organs that you choose can be different. The bladder, voiding time, and how they are set up, that can be different. The software that you use can be different.

There is not one major reason, but these dosimetry studies are not well harmonized, in my opinion. You can find the different approaches in the literature. There are people who collect the urines and measure the urines, and there are people who will just simply draw a time-activity curve around the bladder, and this can give some variation.

DR. XIONG: Right. Maybe I'll follow up there. How large are those studies in terms of

some percent?

DR. ZANOTTI-FREGONARA: Right. They can be quite small. I would say that the vast majority of the studies are less than 10 subjects. Sometimes you have more for tracers like FDG, which are common, but it's not unusual to find dosimetry studies with 2 subjects or 3 subjects, and then also can increase the noise of the numbers.

DR. XIONG: Great. Thank you for your answer.

DR. ROYAL: Okay. Dr. Mintun has his hand raised.

DR. MINTUN: Yes. Mark Mintun, Lilly and Avid Radiopharmaceuticals. My question is to Dr. Zanotti. I found the presentation really compelling and think that it could lead to acceleration of innovation and finding new tracers. But I noticed that -- well, could you comment on whether the types of data and your arguments for how to simplify doing first-in-man studies with F-18 and carbon-11, could that be used and extended to the questions that we've been given with gallium

and copper?

I see gallium is also an incredibly important agent for being able to test radiopharmaceuticals. Would there be an obstacle? Is it a matter of not enough data to conclude this, or is there something intrinsic about not being able to extend the arguments you're making for carbon-11 and F-18 to gallium and copper agents on our question? Thank you very much.

DR. ZANOTTI-FREGONARA: In principle, the protocol can be applied to other isotopes. I did not consider isotopes other than carbon-11 or F-18 because we work only with carbon-11 and F-18. So that is the only reason why I limited my presentation to these two isotopes.

DR. MINTUN: Thank you.

DR. ZANOTTI-FREGONARA: Yes.

DR. ROYAL: Dr. Dewaraja has her hand raised.

DR. DEWARAJA: Yuni Dewaraja, University of Michigan. My question is kind of related to the first question about the large variability in the

data for effective dose coefficients. My question is, I see in the plot that was shown in one of the slides, there was some extreme outliers. The F-18 values seem to be going from 5 to 50 microsieverts per megabecquerel.

DR. ZANOTTI-FREGONARA: Yes.

DR. DEWARAJA: Was there any attempt to identify, at least for those extreme outliers? I would think it would be relatively easy to try to identify whether there was anything specific in their protocol that would have led to values like 50 microsieverts per megabecquerel. I'm assuming many of these studies used OLINDA, and there are things like, as you mentioned, the bladder model, but also things like mass scaling for the different organ masses; so whether there was anything specific that you could identify.

DR. ZANOTTI-FREGONARA: Yes, correct. I read carefully the study, but I was not able to find any obvious reason for this dose. I also tried to obtain the original data, but they were not available anymore because this study is a bit

older, and I contacted the authors. Yes, so can't explain, but I believe that if we were trying to replicate the study, we may probably find a different dose.

DR. DEWARAJA: Thank you. So you think it's reasonable to include those outliers in the discussions?

DR. ZANOTTI-FREGONARA: I think that outlier I don't think is reasonable to include.

DR. DEWARAJA: Thank you.

DR. ROYAL: Okay. If there are no further questions, we will now proceed with the FDA presentations, starting with Dr. Donika Plyku, followed by Dr. Cohen and Dr. Cotter.

FDA Presentation - Donika Plyku

DR. PLYKU: Good afternoon. My name is Donika Plyku, and I'm a medical physicist at the Division of Imaging and Radiation Medicine at CDER. I will start my talk by highlighting interest in developing PET imaging drugs and discussing a few radiation dosimetry and regulatory aspects.

The main part of my talk is on a dedicated

literature review on radiation dosimetry data for PET drugs, and this includes both investigational and approved ones that were analyzed in order to assess the value of nonclinical dosimetry studies for PET drug development and to evaluate what could be considered as safe administered activity levels for first-in-human studies with certain new PET drugs in the absence of animal-derived human-absorbed dose estimates. I will end by discussing a few radiation dosimetry aspects that may help to put the approach under consideration into perspective.

Positron emitting radionuclides share some unique characteristics such as a relatively short physical half-life for measurement of fast biological processes and also relying on the 511 keV annihilation photons to produce detectable signals for imaging. Advancements in cancer imaging and diagnosis and therapy, as well as management of other diseases, highlight the utility of PET drugs. In addition, the innovations in PET/CT imaging and technology provide continuing

and increased research and applications of PET drugs.

The table shows various PET radionuclides. These are listed here in increasing physical half-life order, and I have highlighted six radionuclides that are in focus for today and for which FDA-approved PET drugs exist. The graph shows FDA-approved PET drugs over the course of 50 years, and please note there's an increased number of approvals in the recent 10 years. Currently, there are 19 FDA approved and also about 85 total abbreviated NDAs for PET drugs in the U.S.

Earlier today, Dr. Fotenos talked about the Code of Federal Regulations pertinent to radioactive drugs, and this is shown here. This regulation has direct implication on the design of phase 1 studies, which must obtain data for dosimetry calculations, and therefore IND submissions for new products include dose estimates for human organs that are often extrapolated from animal biodistribution data.

The extrapolation methods make assumptions

about the differences in metabolism, anatomy, and biodistribution between animals and humans, and these assumptions contribute to uncertainties in predicting radiation dose to human organs. Animal dosimetry studies are important, but there is a tendency to underestimate human organ-absorbed dose when extrapolated from animal data, and the differences and associated uncertainties between extrapolated absorbed dose values and those calculated from direct measurements in humans are important to consider.

The measured percent injected dose per gram in animal tissue is extrapolated to percent injected dose in human organ often using the relative organ mass extrapolation method, and this assumes that the metabolism is similar between animals and humans and varies only as a function of organ mass. Nonclinical studies may provide an estimate for human organ-absorbed dose and could also be useful to identify unexpected high uptake in a particular organ before administering the drug to the patient or to a human subject. The

time-activity curve can be fit and integrated to obtain what we call a reference organ residence time.

Once we obtain the residence time in source organs, one can obtain or calculate the absorbed dose to target organs, and following MIRD methodology, this requires employing the reference human phantom. Earlier, Dr. Hallett talked about how this calculation is done. The pictures show a reference human phantom's evolution throughout time that are used for this calculation. This methodology is appropriate in diagnostic nuclear medicine, where we do calculations based on reference representative of a general population and not for a single patient.

This slide highlights current FDA recommendations on nonclinical dosimetry studies for new PET drug development. Investigators are encouraged to contact FDA early, and recommendations are generally provided upon review of pre-IND submissions and IND opening protocols when plans to conduct or results of animal

biodistribution and dosimetry studies are reviewed.

The submissions may also include human organ dose estimates, and I want to highlight here that currently, the review of dosimetry provided in the pre-IND and IND submissions of new PET drugs is performed on a case-by-case basis, as Dr. Fotenos also explained, and review issues generally include limitations on animal-to-human extrapolation and recommendations on planning and design of animal biodistribution studies and on the design of clinical dosimetry studies.

Future accommodations will involve an approach to compare planned administered activity for first-in-human studies with new PET drugs or the maximum protocol-specific administered activity covering the pre-phase 1 dosimetry cohort; so basically comparing the planned administered activity in the submission of the IND opening protocol with mean administered activity values that have been derived from approved drugs for each of the six PET radionuclides shown on the slide. This is in the absence of animal-derived radiation

dose estimates. In other words, the approach under consideration involves administered activity values for first-in-human studies that may allow foregoing animal biodistribution studies, and I will describe this approach in more detail after I talk about how these values were determined.

One of the early and few studies that looked at the value of nonclinical dosimetry studies is the study published by the Oak Ridge symposium by Sparks and Aydogan. In this study, the authors looked at the various extrapolation techniques to predict residence time in humans using both nonclinical and clinical data for several extrapolation methods such as relative organ-mass and physiological time, or a combination of the two. The residence times, or what we actually call time-integrated activity coefficients for source organs, were calculated using animal and human data, and ratios of animal-derived versus human measures were plotted for each extrapolation method.

In these histograms, you see distribution of

these ratios for each extrapolation method, and one can look at the geometric mean of these distributions being less than 1, basically indicating the tendency to underestimate the residence time in human organs when calculating from animal biodistribution studies or dosimetry studies. Also, in this study, the physiological time extrapolation had an improvement on this ratio; however, the data reviewed in this study were limited, so there is a need to repeat such studies with all available clinical experience with PET drugs that we have now.

Studies conducted by colleagues at NIH -- Dr. Zanotti-Fregonara talked about this -- that were shown earlier in the previous talk, they performed the review of dosimetry data of carbon-11 and F-18 drugs and the relative radiation profile between them. Dr. Zanotti talked in detail about the observed variability in those estimates and explained what the variabilities could be attributed to.

Other studies that we found in literature

wrote about strengths and weaknesses of various extrapolation methods for these calculations and factors affecting animal-to-human extrapolation. Specifically for murine species, several factors have been reported to cause discrepancies between mouse- and human-derived, organ-absorbed doses, and there is a need for standardization in dosimetry methodology and reporting in order to ensure reproducibility of results. A more recent study looked at the gallium-68 radiolabeled macromolecules and compared five extrapolation methods, and suggested that the best approximation of the actual human dosimetry was provided by the method which applied a metabolic scaling to the murine data.

These considerations prompted FDA to re-evaluate the utility of animal dosimetry studies and come up with recommendations to streamline the assessment of the radiation safety of PET drugs. In order to determine administered activity levels for first-in-human studies that may allow foregoing animal dosimetry studies, we followed this

approach.

First, we decided to leverage findings for the safety of approved PET drugs when administered at the AA levels specified on the drug label. In the table, you can see all FDA-approved PET drugs, along with indications for adult patients and recommended administered activity on the prescribing information. Secondly, a systematic review of human dosimetry estimates of PET drugs derived from both nonclinical and clinical dosimetry studies was also conducted, and collected dosimetry data were analyzed.

In this literature review, articles were selected with reported human organ radiation dose estimates from both animal and human studies, and these were calculated according to MIRD or related methodology. Specifically, we looked at the organ-absorbed dose values and whole-body effective dose coefficients for the radionuclides or drugs radiolabeled with these PET radionuclides. In addition, we looked at the proportion of published studies with administered activity above the mean

administered activity from drug labels or prescribing information of approved drugs, and we did this in order to evaluate the range of administered activity values in the available clinical data.

Dosimetry data from a total of 322 PET drugs were analyzed, and this includes both investigational and approved ones. The left and right figures show the whole-body effective dose coefficients and organ-absorbed dose coefficients, and actually the maximum organ-absorbed dose coefficients for both animal-derived and human-measured data in these studies, and you can see the gray and black data points, respectively.

Overall, we observed that animal studies provided close estimates to values derived from human studies, and also the variability in dose estimates derived from clinical studies was lower for the majority of the studies shown. The organs exhibiting maximum organ absorbed dose coefficients were generally identified as the organs of excretion, such as the kidneys, urinary bladder,

and not the more radiosensitive organs such as the blood-forming lens of the eye or the reproductive organs.

We calculated the whole-body effective dose and maximum organ-absorbed dose values by using the dose coefficients and the average study AA, so administered activity over all subjects in the study, and this is what is shown on these two figures. You can see that the whole-body effective dose values were less than 20 millisieverts for F-18, gallium-68, and copper-64, and less than 10 millisieverts for the short-lived radionuclides such as carbon-11 and the rest. This is well below the generally accepted whole-body dose limit of 30 millisieverts.

Figure 4 shows the maximum organ-absorbed dose values in milligray, and one can look at the proportion of the studies with maximum organ-absorbed dose above 50 milligray or millisievert, as this is generally accepted as the organ-absorbed dose threshold for the less radiosensitive organs, and this proportion ranges

from 1 to 26 percent for the majority of the cases and about 50 percent for copper-64. Overall, drugs labeled with this PET radionuclide have a relatively safe radiation profile.

The lower radiation profile of the six radionuclides that are in focus today is clear if we compare effective dose estimates to those reported in zirconium-89 or I-124 studies, and radionuclides are listed in this figure in increasing physical half-life order, starting with rubidium-82, and up to copper-64 are separated here, zirconium-89 and I-124. And you can see that the effective dose estimates are about 10 to 15 times higher for the longer-lived radionuclides, and there is less variability in those estimates for the shorter lived ones.

I would like to note that FDA does not have defined thresholds that limit the organ-absorbed dose or whole-body effective dose for diagnostic radiopharmaceuticals studied under an IND application; however, the CFR Code Title 21 Part 361 outlines upper radiation dose limits to

individual organs and the whole body for the radioactive drugs studied under an institutional RDRC protocol for adult subjects, and these organ-absorbed dose limits are shown in this slide for both single-dose administration and annual total dose commitments.

In this table, I wanted to compare the mean administered activity values, or actually the statistics of administered activity values, in the available clinical studies published in literature with the mean of the recommended administered activity from the approved drug labels. You can see that this is shown here in the red column, combining the clinical dosimetry experience for both investigational and approved drugs.

The approach under consideration for today's meeting is to use the calculated mean AA, or administered activity, of approved drugs for each radionuclide -- so basically the mean of the recommended AA -- for first-in-human studies with new investigational PET drugs to generally allow the investigator to forego animal radiation

dosimetry studies. I wanted to compare the proportion of studies with reported administered activity that exceed the values in the red column, and this ranges from 30 to 75 percent, with the highest being the copper-64 studies. Here, I excluded nitrogen-13 because there is only one approved drug.

Also, what is relevant is to compare, actually, the dose estimates for the approved drugs and the clinical studies, especially the studies with AA that are an administered activity higher than the mean administered activity from the drug labels. You can see that there is a slight difference in effective dose estimates between the two. In the left, this is the mean effective dose for approved drugs, and on the right you have the mean effective dose for other available clinical studies. There is a slight difference between published and approved drugs.

A similar comparison can be done in terms of organ-absorbed dose estimate and actually in terms of the maximum organ-absorbed dose values, as this

organ is generally the critical organ. The maximum organ-absorbed dose of the approved drugs are lower than the absorbed dose estimates of published studies, with administered activity higher than the mean AA from the approved drug labels. The largest difference here, more than a factor of 2, is for copper-64.

So generally, comparing radiation dose estimates for studies with administered activity higher than this mean AA value shows that reducing administered activity at the mean drug label AA level generally serves to reduce radiation dose and may allow for reasonable calculation to ensure the safety of first-in-human subjects, pending availability of required clinical dosimetry data.

To put this approach under consideration into perspective, it helps to look at conservative approaches to determine upper administered activity limits for human dosimetry studies. So going back to the biological endpoint of performing radiation dosimetry in diagnostic nuclear medicine, we are talking about risk of cancer induction later in

life, which is a stochastic effect. The input data come from measured time-activity in reference source organs. The calculation involves MIRD methodology and reference human phantoms and models that relate dose to risk. In addition, one should consider the added dose from CT scanning when evaluating the radiation safety or the total effective dose.

CT dose value is shown here for a typical diagnostic F-18 FDG PET/CT imaging. So the optimal administered activity in diagnostic imaging is the lowest activity to achieve the imaging objective, which is a reliable diagnosis. We try to balance image quality with risk due to radiation exposure.

The context of this biological effect is the radiation induced risk, and in order to simulate the worst case radiation dose scenario, we calculate a risk associated with the high absorbed dose delivered to a single organ, and clearance of the activity by physical decay only upon administration of a PET drug. So the target organ cancer risk -- in this case, the kidneys -- is

calculated or estimated for an 18-year-old female subject using absorbed dose calculated for this hypothetical scenario for each radionuclide, and the calculation used the NCI RadRAT tool for radiation risk.

The relative risk is expressed in risk index. This is the ratio of radiation induced risk versus the natural incidence of cancer. The plot in the bottom shows risk index calculated for 4 radionuclides listed in increasing physical half-life order. I'm sorry, it's not, because carbon-11 is not after F-18, but 4 radionuclides shown here. The risk index for F-18, gallium-68, and copper-64 were 1.3, 2, and 4 times higher than the risk index for F-18 FDG typical scan, respectively. For carbon-11, this risk index is about 3 times smaller than the risk from F-18 FDG, risk associated with typical administration for an F-18 FDG scan.

Other studies in literature performed simulations for carbon-11 labeled compounds to estimate the administered activity level that would

not exceed 50 millisieverts to an individual organ. The purpose is to rule out the possibility of radioactivity accumulation in a single organ when the biodistribution is unknown.

In this study, Gatley calculated an upper limit of 130 megabecquerels, or 3.5 millicuries, and suggested to be used in performing a preliminary study in humans without risking this organ absorbed dose limit. This approach allows also the assessment of a worst-case scenario, so activity accumulation in a single radiosensitive organ in order to conservatively plan initial human PET studies.

Other ways to conservatively determine the maximum AA for human studies with new PET drugs would be to use the maximum reported absorbed dose in the clinical studies and RDRC absorbed dose thresholds, and such calculations are also available in the studies published by Zanotti-Fregonara. It must be noted that in FDA's experience with clinical dosimetry data of PET drugs, such case scenarios have not been observed.

This flowchart helps to understand the current recommendations for nonclinical and clinical dosimetry studies and what would change the future state if the approach under consideration is implemented in the pre-IND and IND submission review for new PET drugs. In the current state, the available dosimetry in the submitted protocols are reviewed on a case-by-case basis to decide that the study is safe to proceed from a radiation safety perspective or to recommend collection of phase 1 clinical dosimetry data.

In the future, or going forward, if the approach under consideration of the mean administered activity values from approved drugs are utilized, then in the absence of drug-specific animal dosimetry data, if the maximum protocol-specified administered activity covering the pre-phase 1 dosimetry cohort is less than or equal to the corresponding mean AA values for PET drugs approved as of today, and will involve a study population with a similar risk profile, then the clinical data can be considered to allow a

reasonable calculation of absorbed dose and may generally be sufficient to find the corresponding portions of the protocols safe to proceed from a radiation safety perspective.

Conversely, sufficiency of the drug-specific animal dosimetry should continue to be reviewed on a case-by-case basis if the maximum protocol-specified administered activity covering the pre-phase 1 dosimetry cohort exceeds the corresponding AA for PET drugs approved as of today, or if the study population is notably dissimilar in terms of radiation risk.

To illustrate this, I included some simple examples for this implementation. If the planned AA for a first-in-human study with a new PET drug -- for example, a new F-18 drug -- if the planned AA is about 185 megabecquerels or 5 millicuries, which is less than the mean administered activity from all approved F-18 PET drugs, 8 millicuries, then the study may be found generally safe to proceed from a radiation safety perspective without conducting animal

biodistribution studies. If no; if the planned AA is higher than the mean AA value from approved PET drugs, then the case-by-case IND review will continue, and there may be a potential need to collect animal dosimetry data.

Further recommendations for collection of clinical dosimetry data will be to start with an administered activity, which is less than this mean recommended AA; so basically lower administered activities can start by administration in a single human subject, and then activity escalation rules can be considered depending on the imaging and clinical dosimetry results.

If the radioligand is worth pursuing, then collection of phase 1 clinical dosimetry data can proceed in a similar way depending on the starting administered activity in the protocol. Activity de-escalation rules can also be considered depending on the imaging and initial clinical dosimetry results.

So to summarize, our literature review provided a previously unavailable collection of

radiation dosimetry data for PET drugs derived from both nonclinical and clinical studies, which supplements previous reviews for carbon-11 and F-18 drugs and provides all published data for other PET radionuclides. The approach under consideration is to use the mean administered activity from prescribing information or drug labels containing the six radionuclides, and in addition, safety review of first-in-human studies. This was developed after analyzing all available clinical dosimetry data from both FDA approved and investigational PET drugs.

The issues for discussion are to discuss sufficiency of reviewed dosimetry data and discuss the reasonableness of this approach under consideration. Thank you for your attention, and I would like to take this opportunity to thank my FDA colleagues for the hard work and the invaluable discussions.

DR. ROYAL: Thank you, Dr. Plyku.

We will now proceed with the presentation from Dr. Cohen.

FDA Presentation - Jonathan Cohen

DR. COHEN: Good afternoon. My name is Jonathan Cohen, and as part of the FDA's presentation to this AC, I would like to speak about nonclinical perspective on animal dosimetry studies that support diagnostic radiopharmaceuticals or PET drugs for regulatory submissions. The focus of this presentation is to provide a pharmacology and toxicology assessment on the utility of nonclinical biodistribution and dosimetry studies in animals that support diagnostic radiopharmaceuticals or PET drug IND submissions. So when I refer to PET drugs, my intent is to both include small molecules, as well as biologics. The following points that I'm going to make are not intended to apply to therapeutic radiopharmaceuticals.

This assessment is based upon current federal regulations, as well as FDA guidance documents that apply to PET drugs and the principles to reduce, refine, and replace animal use in research. Specifically, there are three

questions. What nonclinical and clinical data can be relied upon to support development of PET drugs? Can sponsors optimize their nonclinical studies to ensure the efficiency of clinical development without jeopardizing safety for first-in-human studies? And last, can PET drug safety be predicted by the radionuclide properties?

The current regulations allow for a risk-benefit assessment on the nonclinical study requirements. As an example, PET drugs encompass a very diverse set of target patient populations, as well as indications, and our recommendations are based upon the totality of this information. There are several guidance documents that support the development of PET drugs. This includes ICH M3R2, exploratory IND guidance, as well as the more recent microdose guidance. They describe general studies that are recommended to support the safety of first-in-human INDs for these PET drugs.

While I mentioned that the guidance documents are recommendations and they're based upon the agency's current thinking, there are

federal regulatory requirements that specify that for radiopharmaceuticals, there must be sufficient data from animal or human studies to allow a reasonable calculation of the radiation-absorbed dose. For NDAs and BLAs, it must be an evaluation of the safety for the drugs and biologics, and that's included in the labeling and prescribing information.

I want to briefly comment on two nonclinical guidances, ICH M3R2 and the microdose guidance, and how they apply to nonclinical biodistribution and dosimetry studies. The vast majority of these PET drugs are administered at microdose levels, so not more than 100 micrograms for small molecules or 30 nanomoles for protein products or biologics. There are a number of recommended studies to support the pharmacology, which generally include in vivo and in vitro characterization, binding studies, off-target profiling, as well as studies to determine the PK properties, and dosimetry studies. The main thrust of these studies is that they demonstrate evidence that the radiolabeling

doesn't significantly alter the pharmacology of the ligand.

As I mentioned, I want to draw a distinction between current regulatory standards for products that are indicated as diagnostics and radiotherapeutics. Both products, the primary pharmacology studies that mention in vitro and in vivo characterization, recommended to demonstrate evidence that the radiolabeling doesn't alter their pharmacodynamic properties; however, for diagnostics, biodistribution and dosimetry studies are recommended to inform on their target organ uptake. Safety pharmacology studies are generally not needed. For therapeutics, the biodistribution studies are needed to inform human dose selection of the radiotherapeutic, and the safety pharmacology endpoints can generally be included either in the biodistribution, dosimetry, or toxicity studies.

Pharmacokinetic information in the test species is important in providing information about the systemic exposure and the half-life of the

drug, as well as other information that's relevant to potential drug-drug interactions. Toxicity studies, the requirements of those are based upon the cold mass dose, as well as the frequency of dosing.

I want to make a few additional points regarding nonclinical biodistribution studies, particularly the significance of them. These studies demonstrate target organ uptake, for example, uptake into the central nervous system. They can include animal disease models to support the mechanism of action of the PET drug. And more importantly, they also provide information of the PET drug's stability, it's metabolism, as well as it's route of elimination. They can provide information that supports the clinical PET imaging such as the imaging time window post-dose, as well as signal to background noise. The extent of these studies is also dependent upon the marketing intent, as well as the patient numbers.

The primary pharmacology and proof-of-concept studies support safety and

clinical efficacy of these first-in-human clinical studies. There's value for the pharmacodynamic and biodistribution studies that characterize new radioligands. We also acknowledge that there are differences between animal and human radiation-absorbed dose, and sponsors will frequently consider other data sources in the absence of animal dosimetry studies, and this is on a case-by-case basis.

We can consider a weight of evidence approach to evaluate PET drugs and the radiation-absorbed dose. For example, the radionuclide half-life and biological half-life for small molecules and peptides are generally less than 24 hours. This contrasts with monoclonal antibodies that have half-lives of several days and may be labeled with either zirconium-89 or iodine-124. The longer half-life will result in greater exposure and radiation risk. Another consideration is the range of administered activities for short-lived radioisotopes such as C-11, F-18, as well as the effective dose. There

should be justification provided for the organ and effective dose levels. And last, the proposed clinical dose should be as low as reasonably achievable.

To summarize, animal biodistribution studies are of value for the contribution to understand the PET drug mechanism of action, pharmacokinetics, as well as absorption, distribution, metabolism, and excretion. It's an ongoing evaluation on the need for these animal dosimetry studies to support first-in-human PET drugs, and the weight of evidence approach should be applied on a case-by-case basis and consider the totality of evidence. And last, we're considering this streamlined approach for first-in-human studies of PET drugs.

I have here, just for reference, guidance documents that I've referred to in this short presentation. Thank you.

DR. ROYAL: Thank you, Dr. Cohen.

We'll now proceed with a presentation from Dr. Cotter.

FDA Presentation - Samantha Cotter

DR. COTTER: Good afternoon. My name is Samantha Cotter, and I'm a safety evaluator in the Division of Pharmacovigilance within the Office of Surveillance and Epidemiology. Today, I'm going to provide a brief overview of postmarketing drug safety and surveillance activities conducted by our division for all marketed products, including, but not limited to, drugs used for PET imaging procedures.

To better understand the safety profile of marketed products as used in the real world, FDA relies upon clinicians and the public to report safety concerns. During this presentation, we will review how to report adverse events to FDA; discuss how the agency uses adverse event reporting information to monitor the safety of marketed products; discuss the FDA Adverse Event Reporting System, also known as FAERS; discuss FAERS reporting trends for PET drugs; and provide examples of PET drug safety labeling, changes, and communications.

Safety is evaluated throughout the lifecycle of approved products. Prior to drug approval, as noted on the left-hand side of the figure, safety is evaluated during the phase 1 to phase 3 clinical trials in conjunction with dosage and efficacy evaluation. Following drug approval, on the right-hand side of the figure, safety surveillance continues in the postmarketing setting, incorporating a variety of data sources. A critical part of the overall safety evaluation, whether prior to or following product approval, is the implementation of strategies and actions to minimize the risk identified regarding safety concerns.

Following completion of the phase 1 through phase 3 trials, if FDA concludes that the risk-benefit balance is positive, as noted in the yellow diamond on the figure, a determination may be made to approve the drug product. Although premarketing clinical trials are the gold standard to determine safety and efficacy at the time of drug approval, all trials have limitations. One

important limitation of premarketing clinical trials is the size of the population that is studied. These trials are generally smaller than the size of the population that would be exposed to the product under real-world conditions.

These phase 1 through 3 trials are adequate to characterize events that happen frequently; however, rare events may not be observed. Accordingly, FDA continues pharmacovigilance monitoring of drug products through case level review, and in some cases larger post-approval epidemiologic studies.

FDA uses several data sources to identify and evaluate safety concerns, one of which is the FDA Adverse Event Reporting System. Other key data sources include but are not limited to the following: periodic adverse drug experience reports from drug manufacturers; case reports and studies in the published medical literature; and outside inquiries such as citizens' petitions or interaction with foreign regulatory agencies. When we identify new safety concerns, FDA works with the

applicants to update prescribing information or to communicate directly to healthcare professionals or consumers to share new safety information.

Two pathways exist for patients, consumers, and healthcare professionals to report a suspected adverse event to FDA. First, on the left-hand side of the figure, these postmarketing reports can be submitted directly through FDA's MedWatch program. Alternatively, on the right-hand side of the figure, reports can be submitted to the product manufacturer who is then required to submit all such reports to FDA. It is through this route that the vast majority of reports are received and entered into the FAERS database.

To directly submit a report to MedWatch, the FDA's Medical Product Safety Reporting program, health professionals, patients and consumers can utilize the FDA MedWatch website and directly submit reports via the internet, or the form can be downloaded, completed, and sent back to the agency by mail, email, or fax.

So how does FDA use these FAERS reports?

Pharmacovigilance staff review reports in addition to other data sources like the medical literature to identify new safety concerns with a product. Screening of cumulative adverse event reports from multiple sources and of both serious and non-serious outcomes is an approach to better understand the postmarketing safety profile of products. We consult the prescribing information of the product to determine if an event reported is already known or contains new safety information. If a new signal is identified, we work with the appropriate division -- in this case the Division of Imaging and Radiation Medicine -- to open a newly identified safety signal, also referred to as NISS. If we determine that a new safety concern should be labeled or communicated to the public, then we work to make that happen.

This chart is adapted from the FAERS public dashboard, displaying all report types -- direct, expedited, and periodic -- received by FDA for drugs and therapeutic biologic products. Here, we present the adverse event reports in FAERS for all

products on the left Y-axis, as noted by the red trend line, and for approved PET drugs on the right Y-axis, as noted by the green trend line. Please note, that the left axis is in millions and the right axis is in hundreds.

Data presented in this figure cover the years of 2002, when the first PET drug adverse event report was received by FDA, through the end of 2022. It is important to note that FDA initially began receiving adverse event reports in 1968, and although the years 1968 through 2002 are not presented in this chart, the reports from these years are represented in the total number for all products reports in FAERS, tallying approximately 26 million through 2022, as noted in the footnote.

In contrast to the number for all products reports in the FAERS database, there are only 562 reports through the end 2022 for PET drugs. As these products are not being used to induce a clinical effect but rather for diagnostic purposes, it is not surprising that the safety issues might be infrequently reported for these drugs. The

first PET drug to be approved by FDA was in the 1970s. Additional drugs have been approved over the years, with the most recent being approved earlier this year in 2023.

You can see in the chart a rise in the number of reports for PET drugs in 2018 on the green trend line, which, based on a separate analysis of this data, correlates with the time following the 2016 approval of gallium dotatate Ga-68 and fluciclovine F-18. We again see a rise in the number of reports between 2021 and 2022, which also correlates with the 2020 and 2021 approvals of five PET drugs. On this slide, we give an overview of some of the more recent safety-related labeling changes, also referred to as SrLCs, that have been communicated to the public by FDA. Of these, the Division of Pharmacovigilance contributed to the hypersensitivity reactions, SrLC, identified with the radiolabeled dotatate PET drugs in 2021.

FDA has many pathways to communicate safety information to the public, and this slide only

provides a few that may be utilized. First, on the left-hand side, we have an image of the FAERS public dashboard. The dashboard is a highly interactive web table that allows the public to query FAERS data. While the FAERS public dashboard offers opportunity to search adverse event reports received by FDA, there remain limitations to the data. These include duplicate and incomplete reports existing in the system; the fact that the existence of a report does not establish causation; information in reports has not been verified; and an incident rate cannot be established with the reports.

In the center of the slide, we see a snapshot of the web posting potential signals of serious risks and new safety information identified by FAERS. Other forms of communication include updates to prescribing information or product labeling, as shown in the upper right-hand side, and also drug safety communication to the public and healthcare professionals, as pictured in the lower right-hand corner of the screen.

In summary, FDA continues to monitor all products, including, but not limited to, PET drugs throughout the life cycle, utilizing various pharmacovigilance and epidemiologic data sources in an attempt to ensure that the benefit-risk balance of a product continues to remain favorable during the postmarketing phase of its life cycle. Voluntary reporting of adverse event data associated with drug products by healthcare professionals and patients is an important activity to support the safe use of FDA-approved drug products. We encourage continued reporting of drug-related adverse events, including adverse events from PET drugs through the MedWatch program. Thank you.

Clarifying Questions to Presenters

DR. ROYAL: Thank you very much, Dr. Cotter.

We will now take clarifying questions for the FDA presenters. Please use the raise-hand icon to indicate you have a question, and remember to lower your hand by clicking the raise-hand icon again after you have asked your question. When

acknowledged, please remember to state your name for the record before you speak and direct your question to a specific presenter, if you can. If you wish for a specific slide to be displayed, please let us know the slide number, if possible.

Finally, it would be helpful to acknowledge the end of your question with a thank you and the end of your follow-up question with, "That is all for my questions," so we can move on to the next presenter.

I see that Dr. Bolch has his hand up.

Dr. Bolch?

DR. BOLCH: Yes. Wes Bolch, University of Florida. I have a question for the first speaker, Dr. Plyku. My question is simply, on your tables for absorbed dose, were those any source organ with highest activity or was there some factoring in of radiosensitivity? Could it have been any organ in the body or was there a subset of radiosensitive organs that were a part of that table?

DR. PLYKU: Yes. Thank you for that question, Dr. Bolch. The organ-absorbed dose

estimates on the table are the estimates that are reported in the studies. So as calculated, these are dosimetry calculations, and what I showed were the maximum organ-absorbed dose in those studies, in the collective studies. So the radiosensitivity is included in the effective dose estimates.

I mentioned that the organs that are exhibiting maximum organ dose values in the majority of the studies that we collected were usually the organs of excretion for most of the studies that we analyzed, not the more radiosensitive organs, and these were as reported in the published data.

DR. BOLCH: Okay. Thank you very much, and thank you also for introducing the risk index. I just wanted to alert the individuals of some work between the University of Florida and Memorial Sloan Kettering. We have a pending paper that has been accepted in Medical Physics that is going to address the concept of risk index, and part of that article is a comprehensive annex that goes through all different radionuclide reference phantoms and

looks at effective dose; detriment; weighted dose; risk index; and lifetime attributable risk. It should be informative in this regard. Thank you very much.

DR. PLYKU: Thank you for letting us know.

DR. ROYAL: Okay. Dr. Jacobs had her hand up.

DR. JACOBS: Yes. It seems to me, listening to the first presentation, that several different approaches to what could be a cutoff were evaluated from approved agents using the package insert, from published data, from using the RDRC 50 millisieverts limit. It was unclear to me how those compared with each other and what were the trade-off discussions between using one type or another?

I'm not sure if this question is clear, but it seems there are several different ways that this could be looked at, and I didn't get a sense of the pros and cons of each method.

DR. PLYKU: Thank you, Dr. Jacobs, for the question. You're correct. I described the

approach we followed to come up with cutoff mean AA values, and the approach is to look at the approved drug label and recommended administered activity levels. In addition to that, we looked at all the available clinical studies with all the PET radionuclides and drugs in order to evaluate the variability in dose estimates and reported dosimetry data, and put these mean AA values in perspective.

The additional approaches that were included in my later slides were not part of that determination in particular but were considered as bad or worst-case scenarios so we can have a perspective of recommendations for the mean AA values and also calculations of relative radiation risks in available clinical studies. But I also wanted to mention that FDA has not had an experience and has not observed such scenarios in the IND submission review of PET drugs, so those additional approaches were to supplement my discussion, so to say, and to put things in perspective, but not used to calculate the cutoff.

DR. JACOBS: So the cutoff was primarily based on the approved PET drugs, perhaps with the consideration that those have had much more general exposure in diverse patient populations as a kind of a worst case?

DR. PLYKU: Mainly on the findings of the safety of the approved PET drugs.

DR. JACOBS: Thank you.

DR. ROYAL: Dr. Larson has his hand raised.

DR. LARSON: Yes. Thank you very much. This is a question for Dr. Cotter. Thank you very much for that very illuminating presentation about FAERS. I wanted to ask about the follow-up on these interesting findings a bit more. I know you were careful to point out the mechanism of action and other things were not intrinsically in the data, or even the incidence, but is there a way that FDA will follow up on this data? For example, with FDG, I didn't notice very many remarks on adverse reactions and, of course, millions of scans are done every year with FDG, whereas with the gallium dotatate, there was a rather significant

signal.

So can you comment on how you follow up on this and whether there's any sort of denominator to these findings? Once again, thank you very much for your comments.

DR. COTTER: Thank you very much for your question. So first of note, with FDG, since it's been on the market longer, we have a tendency to see a drop in the number of reports that are submitted to the agency, and that's probably why we saw the recent spike in the gallium dotatate and the fluciclovine product. If we do receive reports, we definitely have the ability to reach out to the individual that submitted the report, but we realize that that number of 562 compared to the 26 million appears as a lower number. That's why we're continuously going through the medical literature, looking at information that's coming in from the manufacturers.

We try to cast a wide net of looking at different data sources because we do acknowledge that the numbers are on the smaller side, but I

also think part of the reason for us giving the presentation is to make individuals in the community and healthcare providers aware that we really take those reports seriously. But in regard to following up, we definitely have the ability to reach out to the individual that submitted the report.

Does that answer your question?

DR. LARSON: Yes. Thanks very much.

DR. COTTER: Thank you.

DR. ROYAL: Okay. Dr. Jacobs had a question. Oh, maybe not. I don't see any more hands raised.

Anyone else have a question?

MALE VOICE: Yes --

DR. ROYAL: I see a bunch of hands raised now.

Dr. Nedrow?

DR. NEDROW: Hi. I have a question for Drs. Plyku and Cohen, particularly about the microdosing and the mean administered activity for copper-64. As copper-64 is an FDA-approved agent

and dotatate is a peptide-based agent and has a lower molecular weight, will that mean activity will also be recommended for agents that are not maybe an antibody but of a higher molecular weight, ranging from 20 to 80, or up to an antibody per kilodalton, or is that going to be relying only on a microdosing of less than 30 nanomoles for protein-based agents? Thank you.

DR. PLYKU: Dr. Nedrow, thank you for the question. If you can clarify, the question is about microdosing, in particular copper-64, radiopharmaceuticals?

DR. NEDROW: On your talk, which was very nice, the mean administered activity of the current FDA-approved agents would be an adjusted level to start, but for copper-64, the agent is dotatate, which has a low molecular weight, and the pharmacokinetics, the peptides vary drastically different than something of a higher molecular weight. And Copper-64's longer half-life would allow agents that might be a little bit heavier or have a higher molecular weight, maybe not as high

as an antibody. But for the recommended administered activity, the mean value, would that be applied to all copper-64-based agents, or would there be a molecular weight cutoff, and that there would need to be a more individual evaluation by the FDA?

DR. COHEN: Hi. That's a really good question because copper-64, with a half-life of around 12 hours, it's suitable for labeling both peptides and antibodies. As far as the differences in the PK, certainly small peptides will be, presumably, eliminated a lot faster than larger, whether they be modified antibodies or antibodies themselves, and that could definitely affect the the radiation exposure.

My understanding is that we have not actually delved in to look in that detail, but it's likely that that would actually tip the balance in terms of what we would say would go with an approach under a certain limit versus over a certain limit because the characteristics would be different. There's only one currently FDA-approved

product, and that's copper-64, which is Detectnet.

DR. NEDROW: Thank you.

DR. PLYKU: I also want to mention that the approach under consideration is the same for the six radionuclides, and even though we did a small group analysis, radiolabeled molecular type that would be in the literature review, which we aim to publish later, the approach under consideration doesn't include those aspects for the radionuclides. So it's uniform for the six radionuclides.

DR. ROYAL: Okay I have five other panel members who have their hands raised, so I'm going to try to move along a little bit more quickly.

Dr. Dewaraja?

DR. DEWARAJA: Yes. This question is for Dr. Plyku, the first speaker. Thank you for your presentation. My question is regarding whether the bone marrow was considered in any of these studies when reporting the organ-absorbed doses.

DR. PLYKU: Thank you, Dr. Dewaraja, for the question. In the studies, we identified the organ

with maximum absorbed dose, and that was not the bone marrow. It was generally the organs of excretion. The absorbed dose estimates for all organs were considered in the collective dosimetry data, but this was not the organ with maximum absorbed dose.

DR. DEWARAJA: However, some of the studies did include the dose to bone marrow. Is that what you're saying?

DR. PLYKU: Yes, because we collected all the reported dosimetry estimates.

DR. DEWARAJA: Okay. Thank you.

Actually, I have one other quick question. You also mentioned that there was much higher variability in the animal data compared with human data. Do you think that is because of the variability -- because you mentioned there were multiple different methods for extrapolation from animals to human studies. Would that have been a reason for the higher variability that you saw with the animal data compared with the human data?

DR. PLYKU: I think it may be one of the

reasons, and probably there is more systematic uncertainties performing animal distribution studies. I would think that variability in animal data could be attributed to more uncertainties associated with performing such studies..

DR. DEWARAJA: Thank you.

DR. ROYAL: Dr. Xiong has a question.

DR. XIONG: Chengjie Xiong, biostatistician from Washington University. I've got a question for Dr. Plyku, and then maybe another one for Dr. Cotter. The first one, I want to [indiscernible] again to the cutoff you're using. My understanding is there a total of 19 approved drugs, and your cutoff is entirely based on the 19 numbers in the prescription information. Is that correct?

DR. PLYKU: Yes.

DR. XIONG: If the prescription information gave a window, gave an interval, what do you use then?

DR. PLYKU: I'm sorry. Can you repeat the question?

DR. XIONG: I don't know if this is actually real. Sometimes the prescription gives you a window from one number to the other number, some interval; and then you use the smaller one or the bigger one?

DR. PLYKU: Yes. Thank you for asking the question. We used the mean administered activity in that range. Sometimes prescribing information is per weight, patient weight, and for that case, we used an average human adult of 70 kilograms to calculate that mean administered activity.

DR. XIONG: Right. I think you mentioned in your literature review there are some studies, clinical studies, that are also approved drugs. So my question is, are any of those used in your derivation of the cutoff?

DR. PLYKU: Yes, because those were reviewed when the drug was approved, so the derivation of the cutoff, those are included.

DR. XIONG: Okay.

DR. PLYKU: In the data of the label, the clinical data is included in that determination.

DR. XIONG: Alright.

DR. PLYKU: That's the recommended dosing.

DR. XIONG: Okay. That's great. You also gave a percentage of the clinical studies in your literature review that are exceeding the cutoffs, and the percentage ranged from 30 to some higher percentages. What is the message you are trying to convey there? Do those studies have a worst safety profile in some sense, in addition to what you showed as them having a higher effective dose, typically?

DR. PLYKU: Yes. Thank you for that. The reason I showed that was to look at the clinical experience with investigational drugs, compare that with the approved drugs and the relative radiation dose between the two. The effective dose was slightly different, and in the investigational drug, higher administered activities could have been administered, higher activities, higher than the mean AA of the approved drug.

The largest difference is in the organ-absorbed dose estimate because that could be

even higher than the effective dose, whole-body effective dose. The message is to present collective clinical experience with all available PET drugs, and put these mean AA values in perspective if we were to use them as recommendations later.

DR. XIONG: Great. That's very helpful.

My last question maybe involves Dr. Cotter's presentation as well. In your presentation, Dr. Plyku, you gave a hypothetical stochastic risk index, and in Dr. Cotter's presentation, there is a really nice table of the adverse events related to those drugs. So I wonder whether the FAERS database also follow things like the development of cancer or some other conditions in the long term, and whether that type of information will eventually be available to those approved drugs so that the risk index may not have to be based on a hypothetical situation.

DR. COTTER: Thank you very much for your question. In regards to events like cancer with drugs, we see that FAERS is much better for adverse

events that are rare and also have a temporal relationship with the drug. Events of cancer, if it occurred 20 years after the patient received the PET drug, the individual reporting would have to submit that they think that the PET drug had a link to the cancer, or at least have the PET drug as part of the past medical history for the patient.

So cancers are difficult to identify in FAERS; however, we do also within our office have the Division of Epidemiology, and they are often looking at epidemiologic data, and I believe that that might be a better source for that. But there are multiple attempts to look at postmarketing data, whether it's the adverse events or epidemiologic studies.

DR. XIONG: Great. Thanks. I have no more questions.

DR. ROYAL: Okay.

Dr. Sanghani?

DR. SANGHANI: Hi. This is Rupa Sanghani. Thank you for the presentations. I have questions specifically about F-18 because it has the widest

range of mean values, but yet we also have the most data. We have the most number of animal and human trials and the most number of already FDA-approved agents.

With the literature search you've done, is there anything to point towards either looking at a specific ligand or a specific target organ that might help further refine the F-18 target so it's not quite so broad, and could that be used in the cutoffs?

DR. PLYKU: Thank you for the question. You're correct. F-18, there are more F-18 clinical studies and the variability is larger. In the cutoff, we didn't consider the specific targeting mechanism and target organ when determining the cutoff; however, we did look at the published studies and the type of targeting molecule in this different radiopharmaceuticals.

I didn't show that in my presentation. That is part of our literature review. We didn't consider that because our approach, initial approach, was to base our determination of this

cutoff based on the findings of the safety of approved drugs up to now. But that was part of the literature review, and it will be part of the published article.

DR. SANGHANI: Thank you. I have no further questions.

DR. ROYAL: Dr. Herscovitch?

DR. HERSCOVITCH: Thank you. This is Peter Herscovitch with a question for the first FDA speaker. You plan on using the administered activity as per package inserts as the basis for your thresholds, although informed by RDRC limits and the published literature for investigational drugs. For F-18, there are many approved drugs, as well as a large investigational literature for C-11, and gallium-68, fewer approved drugs, but a very large published literature. In contrast, though, for copper-64, there is just one approved drug and relatively few human studies. Perhaps I'm wrong, but I saw eight in one table.

So do you think, given the relative paucity of data from copper-64 in relation to the other

radionuclides, that copper-64 should be included in your approach of using package insert administered activity, and should be included or lumped in with, say, C-11 and F-18, where there is a very large amount of data?

DR. PLYKU: Thank you, Dr. Herscovitch for that very relevant question. We decided to include copper-64, given the relatively lower radiation profile. But you're right; there is only one approved drug for copper-64 and less clinical studies. We included this in the shorter-lived, half-life radionuclides when compared to other longer-lived ones; therefore, we included it in this group.

DR. HERSCOVITCH: Yes. Thank you. Thank you for that answer.

DR. ROYAL: Dr. Applegate?

DR. APPLEGATE: Thank you. I also had a question for Dr. Plyku, and I really appreciate all of her responses and depth of knowledge. This is regarding the review and the analyses. I haven't heard anything, and may have missed it, or any

comment on the use of these agents in children or potentially pregnant women. If she would comment on anything that she came across and potential FDA review in those two populations, and also if -- well, go ahead. Thank you.

DR. PLYKU: Thank you, Dr. Applegate, for the question. I think that patient population falls under the population with higher radiation risk, and these recommendations apply to adult patients, not pediatric patients or this approach under consideration that we are discussing. In my scheme, I think that would fall in the population with higher risk, or higher expected risk.

DR. APPLEGATE: Okay. That answers my question. Thank you.

DR. ROYAL: Okay. We will now take a break. We'll reconvene at 3:10 Eastern Time. Panel members, please remember there will be no chatting or discussion of the meeting topics with other panel members during the break. Additionally, you should plan to reconvene around 3 p.m. to ensure that you're connected before we reconvene at

3:10 p.m. Thank you.

(Whereupon, at 2:42 p.m., a recess was taken, and meeting resumed at 3:10 p.m.)

Clarifying Questions (continued)

DR. ROYAL: We will now reconvene the meeting. As there are no registered open public hearing speakers, we will take the remaining time to answer any clarifying questions. Please use the raise-hand icon to indicate that you have a question, and remember to put your hand down after you have asked your question. Please remember to state your name for the record before you speak and direct your question to a specific presenter, if you can.

If you wish for specific slide to be displayed, please let us know the slide number, if possible. As a gentle reminder, it would be helpful to acknowledge the end of your question with a thank you, and the end of your follow-up question with, "That is all for my questions," so we can move on to the next panel member.

We have an FDA hand raiser. I don't know

the name.

DR. FOTENOS: Hi. This is Anthony Fotenos, clinical team leader, again, in the Division of Imaging and Radiation Medicine. I just wanted to take this opportunity to follow up on a couple of the questions for the FDA presenters with respect to the scope of the approach under consideration.

Some on the panel may be under the impression that the activity values under consideration apply to all patients during the development of a new PET drug, or potentially even to the entire premarket and postmarket population. Another way of saying this, for example, is for the copper-64 approved agent, that all future copper agents would be expected to have that administered activity, or at least that would be a path of least resistance. And I want to make very clear that that's not the scope of consideration under the proposed approach.

What we're talking about is, essentially, the first human subject, or subjects, though probably most formally referred to as the

pre-phase 1 dosimetry cohort. And it's specifically that population of phase 1 study subjects limited to sponsors who do not want to perform animal dosimetry studies.

So another way of saying this is that phase 1 clinical dosimetry is required for any new PET drug, and all those questions about an antibody having a special biodistribution and exploring for the lowest adequate dose, et cetera, that would still be our standard recommendation for dose optimization, and we would expect that there would be escalation and de-escalation rules in IND opening protocols, conditional again on the clinical dosimetry that would be drug specific and is still required.

So I'm trying to make an overall scope chop if any on the committee are under the impression that we're talking about administered activities for the entire population for a given drug. Thank you.

DR. ROYAL: Dr. Jacobs?

DR. JACOBS: My question actually was

related to what just came up here, what was just clarified. My view of what is being proposed here is that for a brand new PET drug, preferably C-11 or F-18, the sponsor would go to the FDA and say, "We don't think we need to do animal preclinical studies for the following reasons." And the FDA would either agree or disagree at that point, and they would say, "Yeah, but you're planning on studying very young people with very high doses, so we don't think that's a good idea," or something like that.

So it is more a guidance approach than anything else. And my question is, have I got this right? And that's to the last speaker.

DR. FOTENOS: Yes, precisely. The approach under consideration is essentially a clarifying and streamlining approach on this division's part to say that, in general, the administered activity that you're proposing for this first-human cohort is less than that for corresponding approved products, and you want to skip animal dosimetry study, and you still plan to do phase 1 clinical

dosimetry, and de-escalate, and find the right dose, et cetera. It's just clarifying a pathway forward in a public open way instead of doing it on a per IND basis.

DR. JACOBS: So it's not an open get-out-of-jail free. The assumption is that in many cases you are clearly able to justify it, and in other cases, you wouldn't.

DR. FOTENOS: Yes.

DR. JACOBS: Okay. Thank you; very helpful.

Questions to the Committee and Discussion

DR. ROYAL: Are there any other clarifying questions?

(No response.)

DR. ROYAL: If not, the committee will now turn its attention to address the task at hand, the careful consideration of the data before the committee, as well as the public comments. We will now proceed with questions to the committee and panel discussions. I would like to remind public observers that while this meeting is open for public observation, public attendees may not

participate, except at the specific request of the panel.

After I read each question, we will pause for any questions or comments concerning its wording. If we can display the first question. Discuss the sufficiency of reviewed data from animal or human studies involving F-18, C-11, gallium-68, copper-64, rubidium-82, and nitrogen-13 to allow a reasonable calculation of radiation-absorbed dose to the whole body in critical organs upon first-in-human administration of a new PET drug containing one or more of these radionuclides.

One thing we would like to discuss is whether or not this wording is clear. If you have any comments about the wording, please raise your hand.

DR. ROYAL: Mark? Dr. Mintun?

DR. MINTUN: Well, actually, given the lack of comments, I was going to say that I thought it was clear. So I could stop there because I think the next question is going to say discuss what we

think about the question. So I will pause and let you continue, Dr. Royal.

DR. ROYAL: Okay.

DR. MINTUN: But yes, I thought it was clear.

DR. ROYAL: Well, it's because you anticipated the next thing.

So now that there have been no questions or comments considering the question, we will now open the question for discussion, and I guess I'll take the chairman's prerogative and just make a comment here.

One of the things I'm struck by, as we spent an awful lot of time talking about issues related to measuring effective dose and some limitations of measuring effective dose, I would just point out that the connection between effective dose and risk is also tenuous. For example, if you did a study with an effective dose of X in someone who had a life expectancy of less than 10 years, the risk in that person approaches zero.

On the other hand, if you do that same dose,

no variability, and knowing what the dose is in an 18 year old, it's going to be several times greater than that same dose in a 60-year-old person. So although risk is related to dose, it's also related to age of exposure and life expectancy.

Dr. Jacobs?

DR. JACOBS: Yes. I think that from the data there -- first of all, I agree with you a hundred percent that the risk is not high in somebody in my age group for sure, but for children, it certainly is relevant. But the other thing is the amount of data available for F-18 and C-11 seems to me is clearly sufficient.

I'm not convinced that we have enough data for the gallium or the copper to really make a reasonable calculation, and for that, I'm willing to have an argument with whoever would like to have one.

DR. ROYAL: Okay. Would someone like to argue in favor of this proposal for other radionuclides besides F-18 and copper-11?

Dr. Larson?

DR. LARSON: Well, I wouldn't call it an argument, but remember that the scope, as was nicely defined by the last speaker, is for a very specific and limited indication. That's really to move more rapidly to a first-in-human dosing, and that, to me, is important here because it will greatly accelerate certainly the development of radiopharmaceuticals with gallium or copper, I think, because it will eliminate the need for costly preliminary studies.

We are talking about very low doses here. I mean, the issue of safety, for example, comes up, and certainly all of us want to use the doses as low as reasonably acceptable, but these are not doses for which there is really firm data that there is a lot of potential risk. So in that sense, I would say that this is a reasonable starting point. Now, you could argue a little more about copper, I suppose, because it does have a 12-hour half-life, which is not insignificant, but rubidium, and nitrogen, and gallium all are really pretty low.

So I would say that it's true that we would feel a lot more comfortable if there was the same numbers with gallium and copper in terms of the sufficiency of reviewed data. But nonetheless, I think that incorporating that with a concept that we're really talking about very safe doses, which have been previously used extensively in patients, even in the case of copper, I would argue that we could go ahead with this list.

DR. ROYAL: One of the things that I was really struck by in Dr. Plyku's presentation is she showed the slide of what the effective dose was per megabecquerel for all tracers, and then I-124 and zirconium. And it did seem like these tracers would give significantly lower doses than the other two tracers. So it kind of made sense to me anyways that you might group all of these together.

Oh, a lot of raised hands.

Dr. Mintun?

DR. MINTUN: Yes. Thank you. Mark Mintun. I feel similarly that while there's more data in two of these, I felt the way the question is worded

is that there is actually data that can allow a reasonable calculation. I would argue that for the tracers that have the longer half-life and the least amount of data -- for instance, the copper-64 would be in that category -- I would expect that when the FDA actually calculates what they would consider a threshold dose, you could conceivably say, due to less data, we would be more conservative and be on the lower side of that.

But I think that there is actually demonstration with multiple different ways that we've calculated the effective dose for all of these tracers. And as you just pointed out, Henry, and I was going to point out, the half-life of these means that you can collect images, within those half-lives, reasonably high-quality images without having high amounts of dosimetry, which is not quite as true when you have the much longer half-life agents, where they end up having a lot more dose to the patient for the amount of imaging you can get out of them in a reasonable time.

So I would say that all of these have enough

data that one can make a reasonable risk assessment and calculate a level of dose that is safe. I'm not saying they should all be exactly the same formula for doing it. Like I said, it could be that ones with a little longer half-life, you'd want to be a little more conservative in your calculation, but I think all of them could be used to generate a first-in-human administrative sort of threshold. Thank you.

DR. ROYAL: Terry Gillespie.

MS. GILLESPIE: Hi, everyone. I just want to put a patient view into this. I've been having PET scans once a year, sometimes twice a year, for 20 years, and this kind of bothers me that you're willing to do a calculation and not prove a human being that was using these drugs really need these scans; they need the PET scan and they need to find out what's going on, and not to make it worse for them. If they're doing a first-time PET drug, and they're already sick, I don't know; the calculation doesn't seem like a risk I'd want to take, but would have to take.

Does that make sense? I'd have to take it because I need the PET scan to see what's going on. Would I want to? No, because you guys have no idea. You're guessing. It's something to think about if your loved one was in the same situation as I am, a 20-year lung cancer survivor, and have to have that PET scan, or CT scan; have to, every year. Some people are going every 3 months. Some people are going once a month. It's a lot to think about when you're guessing at the dosage. That's all I have.

DR. ROYAL: Thank you.

MS. GILLESPIE: Thank you.

Dr. Herscovitch?

DR. HERSCOVITCH: Hi. Thank you. This is Peter Herscovitch with comments. First, I do want to say that I want to congratulate FDA staff for doing an outstanding literature review and analysis, and I hope they can publish their results at some point. And the question is, did they provide a reference standard? They received extensive review with respect to dosimetry and

safety, and I think provide reasonable reference data, along with all the extensive reports of investigational drugs, especially for C-11, F-18, and gallium.

Also, it's interesting to note and compare their results to the paper of 2012 by van der Aart, where Dr. Hallett I believe was one of the co-authors, and they came up with the same average effective dose coefficient, roughly 6 microsieverts per megabecquerel for 37 C-11 drugs, which is basically the same as the FDA's more extensive recent analysis. So it's excellent. It's very nice to see this agreement.

As was previously noted, I was impressed by the fact that the ED values from human studies of investigational PET drugs were typically quite low, or less than 10 millisievert, or rem, for C-11, and 20 millisievert, for example, for F-18. But also importantly, one has to consider individual organs, and in those cases from their extensive review, in general, the organs with the highest administered dose coefficients were not the organs of concern,

for example, under the RDRC regulations, blood-forming lens and gonads, and I felt that was very encouraging as well.

However, I am still concerned that perhaps there's not enough data available for copper-64, both with its longer half-life than copper, fluorine, or gallium, and also, it could be used to label antibodies, which often have a rather different in vivo biodistribution. So I will perhaps come in somewhere in between Dr. Jacobs and some of the other comments, that I do think there are sufficient data from all the studies summarized for copper-11, F-18, and gallium-68, and of course for N-13 and rubidium, but I am still concerned about copper-64 with regard to sufficiency of data. Thank you.

DR. ROYAL: Dr. Nedrow?

DR. NEDROW: Yes. I think, overall, the data presented was well done, especially for F-18 and carbon-11. Based on the initial comment at the very beginning of this, I think it helped verify, but I'm just curious if maybe the FDA could further

elaborate on this to help streamline to get the initial in-human dosimetry studies done at these proposed doses or a variation of those.

That's not going to be every agent that comes through, but is there a criteria for a PET agent that could potentially qualify for this radiation dose? For example, if you're doing brain imaging and you have slight modifications to your small molecule, or a peptide with a different type chelators, more so for copper-64, but fluorine-18 if you wanted to try the aluminum fluoride type thing, or minor modifications, or a second generation of PET agents that have been tested thoroughly on a first generation; is that more in line with what the FDA is thinking, or is there just going to be some criteria of what agents would actually qualify to be considered for this?

Thank you. If someone could elaborate on that a bit more.

DR. FOTENOS: FDA is recognized, and I'm happy to respond. Thank you. I think the short answer to your question is our interpretation of

the applicable regulation is that there's very little flexibility regarding the need for human dosimetry if you want to go to phase 2. Phase 1 studies must perform human dosimetry for the drug under investigation. FDA's interpretation of what is a new drug, any variation in the structure will make it a new drug. I mean, even a new manufacturer makes it a new drug.

That's really not the question. To answer your question directly, the scope here is just the need to perform animal dosimetry data for a given product prior to, essentially, clinical dosimetry, and trying to create a flexible approach, given that the studies we see during phase 1, they have a huge variety of aims. Some are carefully dose escalating.

There are a lot of clinical pharmacology principles for dose optimization that are independent of our discussion here, and those don't go out the window whether or not you get animal dosimetry data, but it's a very narrowly tailored question about the need for animal dosimetry data,

recognizing, essentially, that as soon as the clinical dosimetry data is in hand, those prior animal dosimetry estimates really play no role. They don't go into labeling. They don't go into decisions about raising or lowering the dose or any activity for future cohorts. So we're sort of narrowly focused on this question of the need for animal dosimetry data, but the approach is for the isotopes still listed.

DR. ROYAL: Okay.

Dr. Dewaraja?

DR. DEWARAJA: Yes. My question -- I don't know if this is a separate discussion -- but is related to --

DR. ROYAL: Please state your name and your affiliation.

DR. DEWARAJA: Yuni Dewaraja from University of Michigan. I'm not sure if this is a separate discussion, but I would like to know what the status is regarding the chemical toxicity or mass dose requirements with animal studies because I know that it's been very hard to get data on that,

but we've been looking at some PSMA studies, where we're trying to get some mass dose information and how much animal data is available for that.

Is that a consideration here also?

DR. COHEN: Answering the question, this is Jonathan Cohen. Regarding the extent of nonclinical data that's recommended to support a first-in-human study, or phase 1 study, that's mainly a case-by-case basis depending upon what the target is, what available published literature there is, and what available nonclinical data. That's also kind of outside the scope of dosimetry. Typically, we recommend sponsors that are developing products that follow the microdose guidance and stay within those limits of less than 100 micrograms per small molecules, 30 nanomoles for proteins and biologics, and more details, generally, prior to submitting an IND with a meeting request.

I don't know if that clarifies for you.

DR. DEWARAJA: So that's not going to change. You're still going to require the animal

studies for chemical toxicity and --

DR. COHEN: Yes. We're still going to recommend that one does tox studies to support their development unless they can provide justification for not doing those studies.

DR. DEWARAJA: I see. I feel there's sufficient data for the animal dosimetry or clinical dosimetry, but generally it has been quite difficult to find information on chemical toxicity or mass dose information from any of these approved agents. Thank you.

DR. COHEN: You're welcome.

DR. ROYAL: Are there any other comments from the panel, comments or questions?

Dr. Xiong?

DR. XIONG: Thank you. Chengjie Xiong. I'm going to just comment from maybe a statistical point of view. Certainly, if you say there is only one drug within the radionuclide class, and all the statistics or the cutoffs are based on one drug, there is a lack of information, and that's just from a purely statistical point of view. Like C-11

or F-18, you just don't have many drugs to support your conclusion.

The other comment -- and I think I already made some related comment an hour or two ago -- is about the stochastic risk. I think your data shows a hypothetical 18 year old somewhere between 5-fold, if I recall correctly, to 20-fold increase of risk of cancer of kidney. I would love to see some kind of real data if available. I know that's not in the FAERS database, but perhaps some other that can make people realize what that really means as a function of many other factors, sex, age, and all those things we just talked about.

I don't know. I think Dr. Bolch -- I believe that's his name -- mentioned some of the studies they are doing. I do think if that's real-world data on the PET drugs, that could be really important to look at.

DR. ROYAL: I think the data that you were citing was a 5 percent increase in cancer risk as opposed to a 5-fold cancer risk.

DR. XIONG: Is that 5 percent or 20 percent?

DR. ROYAL: We'd have to see the slide again.

DR. XIONG: I think that's slide 25 from Dr. Plyku's presentation.

DR. PLYKU: It was a 4-fold increase for copper-64 as compared to F-18 FDG. That was the highest difference, 4-fold.

DR. ROYAL: So you're saying that the risk was 4 times greater than it would have been for F-18.

DR. PLYKU: Yes, for that unrealistic case.

DR. ROYAL: The lifetime risk for getting cancer is 25 percent, or dying of cancer, so 4 times that would mean there would be a 100 percent chance that you'd die of cancer. But, again, the 4-fold increase is that compared to F-18.

Dr. Bolch?

DR. BOLCH: Yes. Wes Bolch, University of Florida. Just a quick comment on this risk. We've been talking about risk index. Aside from the effective dose, the risk index does factor in, to

the best of our knowledge, age- and sex-specific variations in risk, and they're coming from studies of atomic bomb survivors supplemented by other studies. But there's huge confidence -- uncertainties on those risk estimates. So we should never presume that they apply to any particular patient. It's really just a measure of risk to be optimized to image quality benefit. It's really a tool for dose optimization, and we really need to be careful about whether it's a meaningful risk to any particular patient undergoing these very low activity administrations. Thank you.

DR. ROYAL: Dr. Applegate?

DR. APPLEGATE: Yes. Kimberly Applegate. I wanted to ask -- and I tried to put it in the chat -- for all of this discussion we've been having, the slide where the data were provided for humans and animals that Dr. Plyku had for what was available, and it had the relative data points, where there were many, and as Dr. Chengjie had mentioned, the statistics were quite adequate for

the main PET agents that we use today, so for F-18 and carbon-11, and maybe gallium, but not so much for the others.

So if we had that in front of us when we were having this discussion, I think it would help us, where we might come to a more consensus in our discussion; at least it would help me. So I'm asking if that can be done, if we can have that one slide put in front of us, because we don't have as much data on the less used radionuclides.

DR. ROYAL: So there was a slide that had all of the radionuclides, including I-124 and zirconium. That would be a nice slide to display.

DR. APPLEGATE: Thank you.

MALE VOICE: Henry, I think this corresponds to tables 3 and 4 in our printed packet.

DR. ROYAL: Can the FDA display the slide?

AV TECH: Hi. Which of Dr. Plyku's slides was it?

DR. ROYAL: It's the slide that has the effective dose for all the radionuclides, including zirconium and iodine.

MALE VOICE: Slide 19.

DR. ROYAL: Yes, that's the slide.

DR. APPLEGATE: Now, if you just focus on the right-hand side, there's a ton of data and low variability for -- well, it looks like for carbon.

DR. COHEN: You mean the left side, Kimberly, right?

DR. APPLEGATE: The left-hand side, yes; the left-hand side of the table, but not so much for the right-hand side.

DR. ROYAL: Yes. Someone commented about having only one data point for copper-64. There are at least a lot of data points displayed on this slide.

DR. APPLEGATE: Yes, and that's true. There was another --

MALE VOICE: The slide right before that, number 18, I think has got more detail that you can see. Yeah, that one. I was was concerned about the copper-64 because it was not very much of them.

DR. APPLEGATE: Yes.

DR. ROYAL: So I am supposed to summarize

what the panel thinks, and I'm not sure that I'm ready to do that yet. Maybe we should just quickly go through all of the panel members with this slide up, and you could tell us whether or not you would want any of these six radionuclides excluded from having sufficient data to avoid animal dosimetry prior to phase 1 studies.

DR. APPLEGATE: Could we also have the next slide? Because it had the animal and the human.

DR. ROYAL: Sure.

DR. APPLEGATE: I don't know if we could have both of them.

DR. ROYAL: I'm going to just go down the roster of members and ask you where you stand, and I'm going to start with Dr. Bolch.

DR. BOLCH: I'm a little confused in that the copper-64 data seemed disparate between this slide and the previous slide, but I guess I'll say I support the proposed list as presented to us by FDA.

DR. ROYAL: Okay.

Dr. Hackney?

DR. HACKNEY: I have the same concern as Dr. Bolch. I'm not sure what to do about the copper because it doesn't seem to match between those two data sets, and maybe we just need more time to look at it. But certainly accepting that, I'm happy with the suggestion from the FDA, and I echo Dr. Herscovitch's congratulations for the very well done presentation.

DR. ROYAL: Dr. Herscovitch?

DR. HERSCOVITCH: I think there's more than enough data to support copper-11, fluorine-18, and gallium-68. I do have some reservations about copper-64 with regard to the paucity of data and its longer half-life.

DR. ROYAL: Okay. Dr. Jacobs?

MALE VOICE: If I may, the FDA has a comment.

DR. ROYAL: I don't see a hand raised. Who has a comment?

There it is. Okay. FDA has their hand raised.

DR. FOTENOS: Just very briefly, with

respect to this question of the discrepancy between the two slides, one is, as was mentioned, contains both human and animal data, and the previous one is a subset of the human.

DR. ROYAL: Thank you for that clarification.

Dr. Jacobs?

DR. JACOBS: Yes. I'm with Dr. Herscovitch here. I think there's more than enough data, except I'm a little concerned about the copper because there's so few of them, and it's a longer half-life. On the other hand, a careful implementation of it might be acceptable as well because I think the FDA will be looking very closely at what's being proposed by someone. So I have no question about all of them but the copper.

DR. ROYAL: Okay. Thank you.

Dr. Oates?

DR. OATES: Yes. I'm fully supportive of all six of the radionuclides. I found this discussion to be fascinating, great presentations, great discussion, and great deliberation, but I'm

in favor of all six of them being put forward.

DR. ROYAL: Dr. Sanghani?

DR. SANGHANI: I share similar concerns about copper-64 as the others, given its longer half-life and a smaller amount of data, but I think the approach, as was mentioned at the beginning of this session, is really what's important, so I support all six.

DR. ROYAL: Okay.

Dr. Mintun?

DR. MINTUN: Yes. I also support all six. I understand the concerns about copper, but I don't think there's anything mysterious. It's going to behave, I think, in a pretty predictable way, and its longer half-life means it's at the far-right of that set of curves there. But I don't think anything unexpected will happen with it, so I'm happy with all six.

DR. ROYAL: Dr. Dewaraja? Sorry. I keep mispronouncing your name.

DR. DEWARAJA: I support the suggestions as it is for all six of them. I think that's plenty

of data.

DR. ROYAL: Terry Gillespie?

MS. GILLESPIE: In listening to the scientific part of this, I guess I could agree that all six don't have to do animal trials before human, hoping.

DR. ROYAL: Thank you. Dr. Larson?

DR. LARSON: Yes, I agree with all six, especially in the scope as been defined by our FDA colleagues.

DR. ROYAL: Dr. Nedrow?

DR. NEDROW: Hi. I agree also that all six should be fine within the scope as just stated by FDA. And I'm sure, as has been presented multiple times, that the consideration of the pharmacokinetics of the agents, especially for copper-64, will be a factor in determining if animal dosimetry is needed or not.

DR. ROYAL: Dr. Royal is in favor of all six. I would just say we're not eliminating the need for human dosimetry; it's just the order in which it would be obtained, and it would be

obtained in a very small number of people.

Dr. Xiong?

DR. XIONG: I share some of the concerns that are expressed already about some of the radionuclide drugs, but I think that the strength of this is the data are based on the approved data, drugs, which we know the safety profile pretty well. So I'll go with all six drugs, six classes, without the animal dosimetry study.

DR. ROYAL: Dr. Bolch has his hand raised.

DR. BOLCH: Yes. Wes Bolch, University of Florida. Well, my colleagues are saying they're fine with all six, but there are seven here. So I just want to clarify, when you say you're okay with all six, is that proper, or did people mean to say seven and they said six? So I just want to clarify that, Henry. Thank you.

DR. ROYAL: No, I'm counting them. One, two, three, four, five, six, seven. So you must be a mathematician. Yes, there are seven, and I believe that everyone was referring to the seven, not the six.

Okay. So my summary of the discussion of this first question is that probably three-quarters of the panel members agreed with including all six radionuclides, and a quarter thought that that --

DR. BOLCH: You mean seven.

DR. ROYAL: -- all seven radionuclides, and maybe 25 percent that that copper-64 should be treated differently.

Okay. If we could have the display of question number 2 --

DR. APPLEGATE: Hey. I just want to ask, Henry -- this is Kimberly Applegate -- if I'm a voting member. I believe I am.

DR. ROYAL: Yes, you are.

DR. APPLEGATE: Right. So I would also like to vote.

DR. ROYAL: Oh, I didn't call your name? I'm sorry.

DR. APPLEGATE: No, that's ok. I also agree with the FDA proposal that all seven of these radionuclides would be appropriate going forward, although there are less data for copper. Thank

you.

DR. ROYAL: And Dr. Sanghani has her hand raised.

DR. SANGHANI: Yes. It is six, correct? Because O-15 was on the previous slide, but I do not believe it is part of the six that we are actually looking at. So this slide has the actual six we are voting on.

DR. ROYAL: So Dr. Bolch was just trying to confuse us.

(Dr. Sanghani laughs.)

DR. BOLCH: Okay. The slide that we were looking at had seven.

DR. ROYAL: Yes, but what we're voting on is F-18, carbon-11, gallium-64 [sic - 68], copper-64, rubidium-81 [sic - 82], and nitrogen-13.

Okay. I think we can move on to question 2. Question 2 is discuss reasonableness of the --

MS. BHATT: Dr. Royal, if I can jump in, I just want to clarify that this is not a voting question, so a discussion question.

DR. ROYAL: Yes?

MS. BHATT: Before we move on to discussion question 2, I just wanted to clarify that question number 1 is a discussion question, so panel members shared their opinions and their remarks, but it was as a discussion, not as a voting question. Thank you.

DR. ROYAL: Right.

FEMALE VOICE: Thank you.

DR. ROYAL: Okay. Question 2 is discuss the reasonableness of the approach under consideration involving administered activity values for new PET tracers containing F-18, C-11, gallium-68, copper-64, rubidium-82, and nitrogen-13, such that phase 1 studies were both initially administered one or more activity levels less than the value, and collect sufficient human dosimetry calculations that may generally be found safe to proceed from a radiation safety perspective in the absence of dosimetry data based on prior animal administration of the new PET drug under investigation.

Any questions about the wording of this question?

(No response.)

DR. ROYAL: Okay. I don't see any hands raised, so I'm going to assume that the --

DR. DEWARAJA: I have a question. Sorry. This is Yuni Dewaraja. I'm a little confused. I thought we said that it was going to be we're to collect human data for the first patient only, but here it says -- I'm confused by the wording here. One of the previous presenters had mentioned something about doing the dosimetry only for the first patient.

DR. ROYAL: Can someone from the FDA clarify how many patients you would anticipate be studied for dosimetry in phase 1?

DR. FOTENOS: Sure. Again, the regulation under consideration is the phase 1 studies must include human dosimetry, so there's some flexibility in terms of when that occurs. The approach here is designed to accommodate both some of the specific considerations -- for example, mentioned was individual labs by our guest speakers -- but also not be limited to those

specifics.

So in short, our general recommendation, though, would be that the clinical dosimetry studies occur as soon as possible during phase 1 investigation, and, generally, dosimetry studies sort of follow clinical pharmacology logic in terms of the number of patients studied. So we're typically seeing in the range of 6 to 20. Those are common rules of thumb, but they're not statistically powered or anything like that. I hope that addresses the question.

DR. DEWARAJA: My question was mostly regarding that I thought there was a mention of doing one patient at a lower activity. Where does that come in, the first patient?

DR. FOTENOS: The approach under consideration could include that. Protocols that describe that sequence, exactly, would certainly qualify as generally safe to proceed from a radiation perspective, but the approach is designed to be more flexible and not to require anyone to follow a specific lab's recommendation or approach.

So the approach you mentioned would qualify, but it's not the only approach that would qualify.

DR. DEWARAJA: Thank you.

DR. ROYAL: Any additional clarifications regarding this question?

(No response.)

DR. ROYAL: Okay. I think we need to have the table of recommended administered activities for each of these radionuclides displayed.

AV TECH: May I have the slide number, please?

DR. BOLCH: I believe it was table 2 in Dr. Plyku's presentation, corresponding to table 5 in the printed document.

DR. PLYKU: Slide 21.

DR. BOLCH: And we're talking about the second-to-the-last column, correct?

DR. ROYAL: Yes.

So the way I understand this table is that one would be able to start doing an FDG dosimetry study and phase 1 study using 8 millicuries of activity for fluorine-18, 15 for carbon-11,

et cetera. So the question before us is whether or not we agree with this table, is the way I understand it. And the only thing I would comment on is some of the activities have been rounded off. Some of them are reported in three digits, suggesting more significant figures than are really warranted, and I would just round them off properly to military values. With gallium-68, I might put 4. I might put 40 for rubidium.

Any other comments about that column of suggested activities?

DR. JACOBS: Jacobs here.

DR. ROYAL: Dr. Jacobs?

DR. JACOBS: Yes. Paula Jacobs. It was my understanding that this would be the upper limit, and it would also be, in many cases, recommended that it would not be necessary to use the entire amount for your first patient; that you would start off with whatever would allow you to get a decent image to just verify that it didn't go someplace that you weren't expecting, and that then you would go on and do a regular dosimetry in the normal

fashion.

DR. ROYAL: Could someone from the FDA address that comment?

DR. FOTENOS: We agree, and from clinical pharmacology principles, definitely recommend that phase 1 investigation explore multiple administered activities. This is to be considered the upper bound prior to obtaining clinical dosimetry, certainly not a lower bound.

DR. ROYAL: Dr. Bolch?

DR. BOLCH: My camera turned off. A couple of comments. Can you hear me, Henry?

DR. ROYAL: Yes, definitely can.

DR. BOLCH: I would round off the values, the megabecquerels, to two significant figures instead of three. And it's my understanding that the proposal is that you could start the first-in-human trial if the administered activity is below this level without the need for preclinical animal data.

Am I saying that correctly?

DR. FOTENOS: Yes, exactly.

DR. BOLCH: Okay. Thank you.

DR. ROYAL: I'm kind of hearing two different things, because I thought Dr. Bolch just said you could start at this dose, and then I thought I heard the FDA say good pharmacologic practice would be to start from a lower dose.

DR. BOLCH: Well, these would be upper limits.

DR. FOTENOS: Both statements are true, essentially. We have our recommendations, and then we also have the principle of flexibility. And of course, what's not stated in the question, and probably should be -- it was certainly covered in the briefing document and on the slides -- is that the population under study needs to be similar to the approved population. And it's not explicitly in that one sentence to the question, so I want to make sure to highlight that there's always clinical judgment in terms of the investigational population.

DR. ROYAL: Okay. Dr. Nedrow?

DR. NEDROW: Yes. I like the mean

recommended administered activity. I'm just wondering if the FDA considered doing it based on megabecquerels per kilogram to have a more normalized dose to patients.

DR. FOTENOS: Most of the approved products, especially for adult use, are not weight-based. Even though studies that are proposing weight-based approaches are fair game, it would seem inconsistent with at least the bulk of the approved products today.

DR. ROYAL: Dr. Herscovitch?

DR. HERSCOVITCH: Hello. This is Peter Hercovitch from the NIH. I would just like to make the comment about those data in the second-to-the-last column on the right being the upper limit, but also that they're based on the package insert. And, in general, I think package insert doses are based on the ability of the radiopharmaceutical to be useful as a diagnostic to detect disease like a small metastases, whereas initial human dosimetry studies I think can often require lower doses because one is typically

measuring radioactivity from whole organs.

So I think there is a fair amount of judgment that could go into it, and I think the folks from the FDA did mention starting off with lower doses than in that table. But in terms of opinion, I think those are reasonable upper limits and thresholds, and even though I did express concerns for copper-64, I do have confidence that in interactions between the investigators and the FDA, this isn't going to be a blanket approval of, yes, you can use four; consideration will be built into what the FDA approves. So I feel somewhat more comfortable about copper-64, knowing how the FDA will apply these limits. Thank you.

DR. ROYAL: Thank you, Peter.

Okay. I don't see any more hands raised, so to summarize the comments, it seems like the panel is comfortable with the reasonableness of this approach and is comfortable with the activity levels that are in that table.

Before we adjourn, are there any last comments from the FDA?

DR. MARZELLLA: We greatly appreciate the discussion and the preparation that went into it. Thank you very much.

Adjournment

DR. ROYAL: Okay. We will now adjourn the meeting. Thank you to the FDA staff and to the panel members

(Whereupon, at 4:10 p.m., the meeting was adjourned.)