FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

MEDICAL IMAGING DRUGS ADVISORY COMMITTEE (MIDAC)

Friday, September 8, 2017

7:30 a.m. to 4:10 p.m.

FDA White Oak Campus

White Oak Conference Center

Building 31, The Great Room

Silver Spring, Maryland

Meeting Roster

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C O N T E N T S

C O N T E N T S (continued)

C O N T E N T S (continued)

C O N T E N T S (continued)

P R O C E E D I N G S

(7:30 a.m.)

Call to Order

Introduction of Committee

DR. HERSCOVITCH: Good morning, everyone. Just the first standard reminder for everyone to silence your cell phones and any other devices you might have. I would also like to identify FDA's press contact, Lauren Smith Dyer.

If you are here, Lauren, please stand. Thank you.

My name is Peter Herscovitch. I am serving as acting chair of the Medical Imaging Drugs Advisory Committee. I will be chairing the meeting today. I would like now to formally call the Medical Imaging Drugs Advisory Committee meeting to order.

We will start by going around the table and let folks introduce themselves, and let's start down on my right. If members of the committee could identify themselves and where they are from.

DR. FRANK: My name is Richard Frank. I am

the chief medical officer of Siemens Healthineers.

DR. HERNANDEZ-DIAZ: Sonia Hernandez-Diaz, Harvard T.H. Chan School of Public Health in Boston.

DR. HENNESSY: Good morning. My name is Sean Hennessy. I'm at the University of Pennsylvania.

DR. LATOUR: Larry Latour. I'm a senior scientist with National Institutes, Neurological Disorders and Stroke.

DR. FURIE: Karen Furie. I am a neurologist and chair of neurology at the Alpert Medical School of Brown University.

MS. BRYANT: Brenda Bryant, patient advocate, Supporting Our Sisters International, Hyattsville, Maryland.

DR. VAUGHAN: Bill Vaughan, a consumer rep from Falls Church, Virginia.

DR. SIEGELMAN: Evan Siegelman, radiologist, Hospital of the University of Pennsylvania.

DR. JACOBS: Paula Jacobs, National Cancer Institute.

DR. HERSCOVITCH: Peter Herscovitch, the NIH Clinical Center.

LCDR SHEPHERD: Jennifer Shepherd, designated federal officer.

DR. APPLEGATE: Kimberly Applegate, pediatric radiologist at the University of Kentucky in Lexington.

DR. TOLEDANO: Alicia Toledano, Biostatistics Consulting, LLC.

DR. BRENT: Good morning. I am Jeffrey Brent. I am medical toxicologist from the University of Colorado, contrary to what it says in the guide. I am not at the University of Pennsylvania. I am at the University of Colorado.

DR. JONES: Hi. My name is Christopher Jones. I am with FDA CDER's Division of Pharmacovigilance.

DR. BLEICH: Hi. I am Karen Bleich. I am with FDA Division of Medical Imaging Products.

DR. FOTENOS: Good morning. Anthony Fotenos, medical officer, Division of Medical Imaging Products.

DR. MARZELLA: Good morning. Lou Marzella, director of the Division of Medical Imaging Products at CDER at the FDA.

DR. HERSCOVITCH: I just have a few introductory comments before we begin the more formal statement. First, I would like to thank everyone for coming to the meeting: members of the public; patients; industry representatives; and also, the members and ad hoc members of this advisory committee. I would like to thank the FDA for planning this meeting.

There are a couple of folks who couldn't come here in person because of airport closures and weather situations, and we will have a couple of telephone participants. While we're on the topic of the telephone, I will give a reminder for everyone to speak to the microphone, press the button when you are talking, unpress the button when you are finished, so our proceedings can be recorded.

Because of the interest in this topic, we have a packed agenda with lots of speakers, so I'm

going to have to be rather strict about timing. I have a timer on my cell phone, and I'll use it to try to ensure that we all keep on time so we have the opportunity to hear from everyone who's here and conclude on time later this afternoon.

Also, I'd just like to draw your attention to the request from FDA staff concerning our discussions, and this is taken from their briefing materials. It is important we note the FDA's intention in convening this meeting is to solicit advice, limited in scope, to satisfy safety issues with regard to gadolinium retention in patients with normal renal function.

We do not plan on extending the discussion to overall risk-benefit considerations at this time. That would have to involve, for example, for each drug, an assessment of demonstrated benefit in relation to any relevant safety issues and not just retention.

Those topics would be beyond the scope of the meeting, and we need to remain focused today on the issue of gadolinium retention.

We do have a couple of people on the phone, and could you please introduce yourselves?

DR. BOLCH: This is Wes Bolch at the University of Florida Medical, medical physics.

DR. HERSCOVITCH: Thank you.

DR. WEISMAN: This is Michael Weisman, rheumatologist from Cedar Sinai Medical Center in Los Angeles.

DR. HERSCOVITCH: Thank you for phoning in so early. It's 4:30 in the morning.

I do have now a formal opening statement. For topics such as being discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal today is that the 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 chair, me. We look forward to a productive meeting today.

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 your 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 FDA about these proceedings. However, FDA will refrain from discussing the details of this meeting with the media until its conclusion. Also, the committee is reminded to please refrain from discussing the meeting topic during breaks or our lunch. Thank you.

Now, I'm delighted to pass the microphone to Lieutenant Commander Jennifer Shepherd, who will read the conflict of interest statement for us.

Conflict of Interest Statement

LCDR SHEPHERD: Good morning. 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 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 the agency's need for a special government employee's services outweighs his or her 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 interest 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 discussion of the potential risk of gadolinium retention in the brain and other body organs in patients receiving gadolinium-based contrast agent for magnetic resonance clinical imaging procedures. 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 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. Richard Frank is participating in this meeting as an nonvoting industry representative acting on behalf of regulated industry. Dr. Frank's role at this meeting is to represent industry in general and not any particular company. Dr. Frank is employed by Siemens Healthineers.

With regard to FDA's guest speaker, the agency has determined that the information to be provided by the speaker is essential. The following interests are being made public to allow the audience to objectively evaluate any presentation and/or comments made by the speaker.

Dr. Brent Wagner has acknowledged that he owns shares of JPMorgan stock. He is also the principal investigator of two studies, R01DK, 102085 study titled "Chemokine Receptors in MRI Contrast-induced Organ Fibrosis," and a VA merit award study titled "Fibrocyte Contribution to Systemic Fibrosis in Chronic Kidney Disease." As a guest speaker, Dr. Wagner 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 participants to advise the committee of any financial relationships that they may have regarding the topic that can be affected by the committee's discussion. Thank you.

DR. HERSCOVITCH: Thank you very much.

We will now proceed with the FDA's opening

remarks from Dr. Ira Krefting.

Dr. Krefting, please step up.

FDA Introductory Remarks - Ira Krefting

DR. KREFTING: Good morning, everybody. As you've heard, my name is Ira Krefting. I am deputy director for safety in the Division of Medical Imaging Products at the Office of Drug Evaluation IV in CDER, the Center for Drug Evaluation and Research.

Why are we here today? Well, we have asked you all to come on this Friday because we want to seek advice about gadolinium retention in the brain and in other organs of the body.

So what do we mean by retention? This is the fundamental definition for the rest of our talk today, and that's persistence of gadolinium for a longer time than would be predicted from the acute time course of gadolinium leaving the body in urine or feces.

Where do we need advice? Well, we're asking for advice about the safety of gadolinium retention in the brain and other organs, interpretation of

the rapidly accumulating scientific findings, advice about the possible clinical signals, recommendations for studies to fill the gaps in our knowledge, and recommendations on our regulatory path forward to ensure safe use of these products.

Not for today's discussion, as you have already heard from Dr. Herscovitch, we will not be discussing in any detail the comparative efficacy of the specific GBCAs. We'll use that term, "gadolinium-based contrast agents." We will not address other risks such as hypersensitivity reactions, which are already included in the label of these products.

A quick overview, I hope all of you have a detailed agenda. We have a full day planned for everybody. Dr. Fedowitz will follow my introduction. She'll give an overview of regulatory actions and a quick history about NSF, nephrogenic systemic fibrosis.

As you heard, we will have a guest speaker, Dr. Wagner. We are very happy he could make it here from Texas. He'll be talking about the

pathophysiology of the gadolinium agents and retention of gadolinium based on his research.

Later in the morning, we will have the industry presentations. Those presentations will be followed by FDA speakers. The first three speakers will be giving information about adverse event reporting. We call that FAERS data, FDA Adverse Event Reports, information about epidemiologic studies and the sales profile of the gadoliniums.

Later, we will hear more about the scientific findings with gadolinium retention and about endpoints in the evaluation of safety of these agents.

Following an early lunch, we will have the open public hearing, and I want to follow Dr. Herscovitch's introductory statements. We're very happy that so many people could make it here. We understand travel is very difficult. We also want to extend our wishes and prayers to those people who are unable to make it here. Hopefully, they're sheltering in place or at airports, and

they have access to power and the Web so that they can follow these proceedings. And of course, later in the day, we will pose our questions to committee and have a discussion from our panelists.

Now, I want you all to pay very close attention over the course of the presentations this morning. Throughout all the presentations, there are going to be a couple of themes that I want you to keep in mind, and these themes will lead into the questions that will be for discussion later in the afternoon.

Firstly, we will be asking for advice on interpreting all this new scientific information, particularly in view of our previous evaluation of NSF, nephrogenic systemic fibrosis. You will hear a presentation of FAERS data, that is, adverse event reports that have come to us related to gadolinium exposure.

We will be asking if the evidence that we hear in these reports supports a causal relationship between that exposure and the reports that we will be talking about.

Next, we will ask about options for study to reduce any possible risk from retention. Some of these studies are ongoing, but we would like advice on the design of future studies so we can fill the gaps in our knowledge.

Finally, FDA currently plans to implement safety labeling changes. We will be asking the committee if this is felt to be the appropriate course of action, consistent with the risk. We ask the committee for other advice or other courses of action as they deem appropriate.

So that's our introduction, and at this time, I would also like to introduce Dr. Michelle Fedowitz. She is our associate director for labeling in the Division of Medical Imaging Products, and she will be giving a regulatory overview and a brief history of NSF.

Michelle?

FDA Presentation - Michelle Fedowitz

DR. FEDOWITZ: Good morning. Today I'm going to speak about regulatory actions and risk mitigation. I will discuss the following: What is

new safety information, what are the sources of this information, and how does FDA monitor safety of approved products? How does FDA address this new safety information once we have it? Particularly, how do we label new safety information?

I would like to review an example of how FDA addressed a previous safety finding, nephrogenic systemic fibrosis or NSF. Finally, I would like to open the discussion on the new finding of gadolinium retention.

New safety information is defined as a new serious risk or an unexpected serious risk that is associated with the use of the drug and that FDA has become aware of since the drug was approved.

How do we become aware of this new information? It is either by reanalyzing existing information or from new data, and I'd like to talk about the sources of this new data and how FDA monitors drug safety.

The sources can be either a clinical trial or a post-approval study, and this would be, for

example, a new efficacy study submitted to explore a new indication or a postmarketing study agreed upon at the time of drug approval. New data can also come from pharmacovigilance efforts both on the part of the FDA and the companies. FDA uses the FAERS data or the FDA Adverse Events Database, and Dr. Croteau will talk more about this later. Finally, FDA can review the peer-reviewed literature.

What actions may FDA take to address new safety information? In rare cases, FDA can withdraw a drug from the market, and I will be discussing this in more detail. FDA can also use a risk evaluation and mitigation strategy or what we call a REMS. This is a required risk management plan that uses risk minimization strategies beyond the professional labeling to ensure the benefits of the drug outweigh its risk.

We can also require postmarketing studies or PMRs, and these are studies or clinical trials that the applicants conduct to assess or identify a serious risk, and they are intended to further

refine the safety, efficacy, and the optimal use of the drug.

FDA can also communicate new safety information to the public. An example of this, which we have used, is a drug safety communication, and these outline information for patients, consumers, and healthcare professionals on new drug warnings, drug label changes, and other safety information. And finally, FDA can update a product's labeling information with safety label changes.

Discussing withdrawal, in rare cases, FDA can remove a drug from the market. Withdrawal is done for safety reasons in two instances. Either there is imminent hazard to the public health or the drug is unsafe for use under the conditions of use upon the basis of which the drug was approved. That is a long way of saying the risk-benefit profile is no longer favorable under any circumstances for any patient.

We can also use a risk evaluation and mitigation strategy or a REMS. These are tools to

minimize the risk outside the professional labeling. These can include a medication guide, a patient package insert, or a communication plan, and also, elements to assure safe use. We refer to these as ETASUs at FDA.

An example of an ETASU might be a requirement that, for example, healthcare providers who prescribe the drug have a particular training or experience in order to be able to prescribe that drug.

Finally, safety labeling changes. 2007 legislation authorized FDA to require drug application holders to make safety-related labeling changes based on new safety information. Safety label changes can better define the risk-benefit profile and typically will add or strengthen a contraindication, warning, or precaution.

This is useful if there are patients who benefit from the drug despite its risks because the drug labeling can also be used to distinguish vulnerable populations where the risk-benefit profile is not acceptable.

I would like to highlight some of the areas most pertinent to the label where safety labeling changes occur. On the left, the boxed warnings, contraindications, warnings, and precautions, drug interactions, and adverse reactions. On the right are other areas of the drug label where we have made safety labeling changes, including important information in the dosage and administration section and the specific population section.

Highlighting some of these specific sections of the label, adverse reactions. An adverse reaction is an undesirable effect reasonably associated with the drug. In general, the label should contain reactions that are frequent or severe. It should include clinically meaningful reactions that are most important to the practitioners in their prescribing decisions. An exhaustive list of adverse reactions not plausibly related to the drug should be avoided.

Warnings and precautions. So these are adverse reactions that are elevated, and what elevates an adverse reaction to the level of a

warning and precaution? Typically, these are clinically significant adverse reactions, so potentially fatal or serious ones. These are potential safety hazards or potential adverse reactions, and they are potential based on anticipated pharmacologic class reactions or based on anticipated toxicities seen in animal studies.

Importantly, the section includes information regarding any special care to be exercised by the practitioner. This section outlines the adverse reaction and ways to minimize the risk and allows prescriber discretion.

Contradictions. A drug is contraindicated in clinical situations or in patients, and these are situations where the risk from use clearly outweighs any possible clinical benefit to the patient. I think of a contraindication as a never. For example, never administer the drug to a pregnant woman. Specifically for contraindications, the association to exposure to the drug should be well established.

Boxed warnings. Not all adverse reactions,

contraindications, or warnings rise to the level of a boxed warning. This section is particularly important to highlight those that are especially important to the prescriber because they are essential to consider before prescribing the drug, and they may have implications for prescribing decisions or actions to mitigate the risk.

How has FDA handled a safety issue in the past? We would not like to re-adjudicate our NSF regulatory actions. Rather, I would like to outline the sources of evidence and the regulatory and risk minimization steps that were taken with a similar risk.

In 2006, FDA became aware of NSF. It was known as a scleroderma-type illness, sometimes fatal, related to gadolinium contrast exposure, and it was in patients with severe impairment in renal function. Importantly, there were many patients who received the drug safely and even many patients with impaired renal function who received the drug safely.

What evidence did we look at? We looked at

chemistry, preclinical data, clinical data, and published literature. The gadolinium contrast agents can be divided into two classes based on their chemical structure: either linear where the gadolinium is linked to a flexible open-chain ligand or macrocyclic where the ligand forms a rigid cage around the gadolinium.

We considered the physiochemical properties of the gadolinium contrast agents as they affect the binding strength and the rate of dissociation of gadolinium from the gadolinium chelator complex.

In general, the stability of the macrocyclic agents is more than that of the linear agents, and in vitro studies show linear structures release gadolinium much more readily and in far greater amounts than the macrocyclic ones.

We also considered preclinical studies evaluating animal models of NSF and clinical data, mostly FAERS database reports of systemic fibrosis. And finally, FDA had an analysis of the published literature.

What did we find? At the time, these were

the five approved agents that were on the market as we were learning about NSF. As we made our regulatory decisions, we felt these were the only agents with enough clinical use at the time to evaluate the clinical experience.

We looked at the physiochemical properties of the agents, and in general, for each agent, there were ranges with a general trend toward a higher thermodynamic stability, depicted on the slide, as well as an appreciation of the importance of in vitro kinetic stability as a measure of dissociation of free gadolinium.

However, the stability constants alone do not tell the whole story of gadolinium dissociation due to the complicated in vivo environment of the cell. Therefore, we also looked at preclinical studies evaluating animal models of NSF and showing histopathologic evidence of skin toxicity in animals.

Particularly in these two agents, we relied very heavily on the clinical case reports. The agency examined single-agent or unconfounded cases

of NSF. We found that these three agents had more clinical cases of NSF that could be verified as the single product the patient had received.

Not shown on this slide are the results of our literature review. There were limitations in the literature, which did not support a differential risk between the agents but did support both the refinement of the at-risk population to acute kidney injury and severe chronic renal impairment and dose, and there was an increased risk of NSF with increased single dose and increased cumulative dose of the gadolinium agents.

What did we do? There was a consensus to communicate new safety information to the public. The FDA and the product sponsors issued communications to the public to increase awareness of the possible association of NSF and gadolinium contrast agents and recommended actions to reduce the risk of NSF.

There were also professional society recommendations, and the FDA and the sponsors

increased their pharmacovigilance efforts. There were postmarketing commitments, which were changed to required postmarketing studies to evaluate NSF in patients with moderate and severely impaired renal function and to gather more clinical data.

After the 2009 advisory committee, FDA recommended safety label changes to warn and mitigate the risk of NSF. These included importantly a risk stratified contraindication of gadolinium contrast agents in patients most at risk for NSF with high-risk agents being contraindicated in the at-risk population. FDA also recommended strengthening the boxed warning and the warnings and precautions section.

The association of acute and chronic renal insufficiency was better defined in the label, and specific recommendations were made for screening these at-risk populations as well as dosing recommendations.

What did we find? We found that NSF cases dramatically decreased and the current risk minimization measures appeared to be effective.

Now we have a new finding of gadolinium noted in the brain, skin, bone, and organs in patients receiving gadolinium contrast agents now with normal renal function. And as Dr. Krefting noted, retention is known as the persistence of gadolinium for a longer period of time than would be predicted from the acute time course of gadolinium leaving the body in urine and feces.

How do we move forward? There is ongoing work by the sponsors, the scientific community, and the FDA to understand this new risk, its clinical consequences, and implications for patients. This is a challenging topic, and there are limitations in the existing data, and there are gaps in the knowledge.

In the coming talks, you will hear from FDA and the sponsors reviewing the various sources of evidence and ongoing preclinical and clinical studies. FDA will also present a review of the FDA safety database and epidemiologic studies for gadolinium retention. We will also hear from the patient community.

What are our regulatory options? What is the risk and what is the clinical outcome of retention, and how can we minimize this risk moving forward? Some possibilities might include better communication or education of patients in the healthcare community; also, labeling changes; and in particular, can we stratify these products by risk; and are there new risk categories that we need to consider?

Are there at-risk populations, particularly pediatric patients, pregnant patients, the elderly, or those with chronic illness who would receive repeat doses of gadolinium? Can we use increased pharmacovigilance or additional clinical and preclinical studies to fill knowledge gaps and characterize the clinical outcomes?

We are open to other considerations, and as I said, there are many challenges with this new finding, and we look forward to the discussion ahead.

Now, it is my pleasure to introduce Dr. Brent Wagner. He is our keynote speaker.

Dr. Wagner received his medical degree from the University of Mexico and trained in internal medicine and nephrology in San Antonio. He is a staff nephrologist at the Audie Murphy Memorial VA Hospital and director of the nephrology fellowship program.

Dr. Wagner researches the biologic effects of gadolinium and the basic mechanisms underlying the development of nephrogenic systemic fibrosis. In addition to publications, he has authored book chapters on NSF, and the title of his presentation is "Pathophysiology of GBCAs and the Retention of Gadolinium."

Dr. Wagner, thank you for coming, and I will turn the podium over to you.

Guest Speaker Presentation - Brent Wagner

DR. WAGNER: Great. Thank you, Michelle. And there's a correction. I am from the University of New Mexico.

I am a nephrologist in San Antonio. In 2006, when this disease reared its ugly head and was associated with gadolinium, this was very

concerning to me because I have got a number of at-risk patients. We've got patients with chronic kidney disease, acute renal failure. So I saw that there is a lot of people who had received gadolinium, and there was a good number of people at risk. This is already a vulnerable population. The patients are already suffering from severe illnesses.

With this talk, I want to talk about the elucidation of the mechanisms of gadolinium-based contrast agent-induced toxicity and that we are investigating this daily. The focus is the work in my laboratory about the biologic activity of these gadolinium-based contrast agents and how this is manifested systemically.

We have established a model in rodents. Mainly, I use one contrast agent to do the experiments, but I do believe that it is applicable to a good number of the contrast agents, if not all of them.

You will see today that there are many different chemical formulations of gadolinium-based

contrast. These agents have been linked to "nephrogenic systemic fibrosis." I use nephrogenic in quotes because nephrogenic proper means that the kidney is causing it.

In 2006, when it was clearly linked to gadolinium, we know that gadolinium is the cause, so that the kidney is a risk factor -- renal insufficiency is a risk factor -- but the kidney per se is not really causing the disease.

There is now evidence that gadolinium is deposited in the central nervous system. I believe that the central nervous system deposition warrants more study, and I am going to show that gadolinium-based contrast agents are biologically active.

Very little is known about the metabolism of these agents, their biologic effects, and the implications of retaining gadolinium in the tissues. The toxic effects and the mechanisms of how they impart their pathophysiology is a major gap in our knowledge.

If we understand how the disease processes occur, we are going to know quite a bit more for

stratifying patients who are at risk, and it will add to our future knowledge. How these different agents behave once they enter the body is an active area of investigation.

Here is the periodic table. We have seen this in high school. The lower row is the rare earth elements. They are not necessarily rare, but they are a very interesting group of chemicals. Some of them we use like lanthanum, which is the first member in the lanthanides there, and gadolinium, which is highlighted there in the middle. Now, gadolinium is a very unique element. As a cation, it has a number of unpaired electrons, which make it absolutely ideal for magnetic resonance imaging.

In 1997, Shawn Cowper and his colleagues in San Francisco discovered a unique sclerotic disease that only affected patients with renal insufficiency, and this was both acute renal insufficiency, and this was also chronic renal insufficiency, and end-stage renal disease. A lot of these patients actually had transplant.

These patients would present with marked pain of the extremities, especially the lower extremities. They had thickening of the skin. They had induration of the skin. The induration, the skin would turn into something that would resemble wood, so they describe it as woody.

If you try to pinch your skin right now, normal skin buckles. It has got elasticity. Well, these patients lost the elasticity of the skin. Some patients describe this disorder as the feeling of being encased in your own skin, as being entrapped in your own skin.

These patients also had joint contractures, and the disease could involve everything from the extremities, the thighs, the buttocks, and the abdomen. On occasion, some patients have yellow sclera plaquing. It does seem to spare the face and the neck for the most part, so it is the inverse of another disease that has been known called scleroderma. Autopsy studies showed that there was potential involvement of just about every organ study.

Since I was a medical student and a trainee in San Antonio, we knew that MRI contrast could also induce renal insufficiency. This is one case report where renal insufficiency occurred in a patient with preexisting chronic kidney disease, but they find unique features of this renal insufficiency once given a magnetic resonance contrast agent. So this has been known to be a risk factor for a good amount of time.

There are a good number of studies showing the biodistribution of these agents, and this is one of them. This is a radiograph of a rat after a single dose, and it's a clinically relevant dose of MRI contrast.

Initially, the contrast distributes throughout the entire body, the liver, the skin, and the kidneys. Then after some time, you can see the gadolinium being retained in the liver and the kidneys. And then after several days, it's still high in the kidney cortex. That's the outer rim of the kidney right there in the very last slide.

In our lab, we did a head-to-head comparison

of two gadolinium-based contrast agents that had different thermodynamic properties, which you just saw in the prior presentation. We compared Omniscan, which has this in vitro thermodynamic stability of 16.9, with ProHance, which had a higher thermodynamic stability of 22.9.

Now, these are on logarithmic scales, so practically very little gadolinium should be released from either one of them, but we wanted to see if you did a head-to-head comparison of these two, what would happen.

What you see here on the left are the histology of the skin from a control group, a group treated with Omniscan in the middle and a group treated with ProHance on the right. We did find in the skin from the Omniscan-treated group that there were features that looked exactly like the human condition. There was thickening of the outer layer of the skin, which is called the epidermis, and also there's a great amount of cellularity in the skin. Now, this is atypical, but it is found in the human cases of nephrogenic systemic fibrosis.

The skin from the ProHance-treated group did appear to have less of the cellularity, but we also wanted to look at markers of fibrosis, and those are the pictures on the right. The control group, which has very little of this protein called fibronectin, and in the middle, we've got the skin from the Omniscan-treated group. There is a high signal of this fibronectin being in the skin.

When you take a look on the far right, it is a representative skin section from a ProHance-treated animal, and there is an increase in this fibronectin protein even in the ProHance-treated group. On the lower right-hand corner is a technique that we used in order to quantitate proteins, and this is called a Western blot.

So we're looking at the fibronectin in the skin from these animals, we noted that there is an increase in the fibronectin in the skin from those animals treated with Omniscan. But this fibronectin also went up when the animals are treated with ProHance. So what we derived from this is that each one of these agents is

biologically active when you compare it with equivalent doses in a head-to-head comparison.

We need to look at the biologic effects using a mouse model. This permits us to define what molecules are being recruited and being used in order to cause the disease. We established this mouse model where we take mice, we randomize them, and one group serves as a control and the other group we treat with MRI contrast. In this case, it is the Omniscan.

We treat them with injections daily during the week, every day during the week, and we are aiming for 20 doses over a 4-week period. Then after that time, we analyze the tissues.

One of the first things we did was analyze the quantity of gadolinium that was in the tissues, and these are bar graphs that show the quantity of gadolinium that can be found in the kidney, the skin, and also, the brain.

We can look at the tissues with electron microscopy. This is a technique called transmission electron microscopy. We took the

kidney, which has a good amount of gadolinium accumulation, and we looked at the morphology of the tissues using this electron microscopy.

The panels on the left are the control, and on the right are the Omniscan-treated group. When we take a look at the filtering capillaries -- those are the two images on the left -- we see these depositions that occur within those capillaries. When we magnify them, we see those nanostructures, these little particles.

The two pictures on the right are from the cells that line the tubules. These are the cells that are responsible for filtering the urine, and we see a good number of these electron dense deposits in the cells of those treated animals. That's a higher magnification right there on the right. I'm going to show this again right here.

When you look at our experimental data on the left -- these are the deposits that we found in the kidneys of the Omniscan-treated group, and when you compare them to what happens to gadolinium oxide on the laboratory bench, this is what you

call an in vitro experiment where they took gadolinium oxide and they looked at how it would cluster in water, and that's at the top upper right. They also used a solution that was serving to mimic the internal environment of the cell, and that's what they call the phagolysosomal simulated solution there on the right.

They noted that when you take the gadolinium oxide and put it in this solution that mimics the internal environment, you start to have these nanostructures that start to form. This is striking to what we are finding inside of our filtering cells in the kidney.

This is an experiment where we had a control group and an Omniscan-treated group, and we looked at the tissue characteristics from the kidney. On the left side, we have got kidney from Omniscan-treated animals, and we notice with this PAS staining is to pick up scarring of a tissue. We find that there is an increase in the staining in the filtering units and also increased around the tubules.

Then we take sections of the kidney, and we stain it to detect fibronectin. Again, that is the protein that is associated with scarring. And we find an increase in that uptake in the Omniscan-treated group. Collagen type IV is also a characteristic protein that is increased in scarring, and we also find that going up in the filtering units and around the tubules in the animals that were treated with Omniscan.

Now, all these panels on the right are showing different characteristics of what we found in the contrast-treated animals. Again, we find scarring of the capillary units, and also we find what we call vacuolization of the tubules. Those cells that line the filtering tubules, they start to have a very unique characteristic appearance where it looks like they have got bubbles inside of them.

On the far right, we see that there is severe scarring around one of the filtering units. Again, this is a Western in the lower right-hand corner that shows that protein associated with

scarring is increased in the kidneys from the contrast-treated animals.

We know that oxidants participate in the scarring process, and we found that there was an increase in oxidant generation by two different methods. On the left is the stained method, so the increased red is detecting the oxidants, and this other assay over here, shown by the bar-gram on the right.

We also looked at skin. This is a systemic disorder in humans, and we are finding that it has a lot of impact on different organs in the animal. We compared the skin from control animals in animals treated with contrast.

In the animals that are treated with contrast, they have this increase in cellularity that looks just like you find in humans. It is actually the exact same order. Sometimes they will get thickening of their skin, shown there on the far right chart. We stained for that marker of fibrosis on the skin, and it goes up in the skin from the animals that are treated with MRI

contrast. In the lower right-hand corner is the Western blot showing these proteins that are associated with scarring going up in the animals that were treated with contrast.

We also looked for markers of inflammation. In this case, we used CD163, which is a white blood cell marker or a macrophage marker, and it goes up in the skin from the animals treated with MRI contrast. Then from the beginning of the description of the human disease, there was this thought that a special cell, a circulating white blood cell called a fibrocyte, participated in the disease.

This type of cell, this fibrocyte, will move into an affected organ and start to cause scarring. We looked at this specific marker, and we found that it was also increased in the skin from the animals that were treated with contrast.

Here is a representation of oxidants also in the skin. I showed it before in the kidney. These are an increase in oxidants in the skin using two different methods. And as you see, in both cases,

the oxidants go up in the skin from the contrast-treated animals.

Whether these cells that infiltrate the organs are from the circulation or if they are bone marrow-derived was a question that we wanted to test. So we took mice that have tagged bone marrow -- they have this green florescent protein -- and we took the bone marrow, and we transplanted it into animals and waited some time for that bone marrow to engraft. Then after a few weeks, were able to randomize this engrafted animal into two groups, a control group and a contrast-treated group, and then we can do the experiment where we take one group, treat it with contrast, and then we can compare it with a control group.

On the right, you see what happens in the kidney. The GFP is the green florescent protein. That is showing us the bone marrow-derived cells. So we see an increase of these bone marrow-derived cells in the kidney, and this also is correlating with that marker of fibrosis, collagen type IV.

This is what happens in the skin when we

examine the skin from the same animals. You see that the bone marrow-derived cells are being recruited into the skin, and this is also correlating one to one with the markers of that special cell called the fibrocyte. The CD34 and the CD45RO are both specific markers for fibrocytes.

This looks like exactly what happens in humans. In humans, one of the first markers that they found in the skin from these patients was that the skin had a lot of this CD34 in it. What we were able to prove experimentally was that it was indeed bone marrow-derived cells that are being recruited into these affected areas. Therefore, bone marrow is a player, and this also explains a lot of the systemic effects of the disorder.

We know that gadolinium retention can be detected in humans and in our models. This allows us to mechanistically study this type of injury. The pathologic effects are not well characterized at present, and our experiments also show that renal insufficiency is not requisite for this

fibrosis.

We are showing that there is recruitment of bone marrow-derived cells into affected organs, and this is what is mediating the deleterious actions. These are important because we can better understand and we can better study what is going on in the human condition by using these mouse models, and also, it will permit the discovery of rational biomarkers.

I do want to say that dechelation of gadolinium is a hypothetical pathologic mechanism. These animals have normal renal function. They have cleared a lot of that gadolinium contrast within 24 hours, and to what percentage these agents are releasing gadolinium really is of question, especially in vivo. And we've also found that one of those agents, ProHance, does cause fibrosis in the skin in our model.

Studies concerning the biologic effects of rare earth minerals in general and their retention in human organs are in the nascent stage, and the science on this topic is at ground zero.

This is our working hypothesis. We've got patients with normal renal function. They are exposed to MRI contrast. There may be some gadolinium retention in a variety of organs, and this retention is leading to organ injury. This is a stage where we could look for biomarkers.

There is something curious about this disease. Not all patients with end-stage renal disease, even when they are exposed to MRI contrast, acquire the disease. Yet other patients with acute renal failure, with chronic renal insufficiency who are not on dialysis, they've contracted the disease after just a single dose. Therefore, there is an avenue for personalization of medicine to detect why some people are at risk and why others are not.

Once an organ is injured the kidney, for instance, there can be impaired function. And if you have renal damage, this could increase your risk for gadolinium-induced disease, and it goes into this vicious cycle.

There is also preexisting conditions.

Patients just don't get MRIs for screening. They've got existing disease. They've got comorbidities that increase their risk for needing important diagnostic imaging. And this subset of patients then will be subjected to a gadolinium-enhanced MRI, and this could also feed into the cycle.

For instance, gadolinium retention in cardiac imaging is being used to characterize the type of fibrosis the heart has. There are other conditions like obesity. We have got great evidence that obesity is an important risk factor for increasing this damage and some of these other states.

I want to thank everybody in my lab, especially my lab technician Chuyan Tan, who has been with me since the start of this project in 2007, and also, Yves Gorin. He's my partner in all my scientific endeavors. And we've gotten quite a bit of help across a number of institutions. Thank you very much.

DR. HERSCOVITCH: Thank you very much,

Dr. Wagner, for this really informative presentation.

I'd just like to pause for a moment and have a committee member introduce himself, please.

DR. DAINIAK: Yes. I'm Nick Dainiak. I'm the director of REACTS, Radiation Emergency Assistance Center and Training Site in Oak Ridge, Tennessee. I have been there two and a half years. Prior to that, I was at Yale for 18 years, Bridgeport Hospital as chairman of medicine. I still have a lab at Yale and am still a professor of medicine at Yale.

DR. HERSCOVITCH: Thank you very much, Dr. Dainiak.

We will now move on to our industry presentations. Just as a reminder, each industry presentation will be lasting 15 minutes each, and again, please try to stay on time. We will begin with a presentation from Bayer HealthCare, please.

Industry Presentation - Thomas Balzer

DR. BALZER: Good morning, dear members of the FDA, dear members of the committee, ladies and

gentlemen. My name is Thomas Balzer. I am the head of medical for Bayer's radiology business, and it's my pleasure to be here. Thank you very much.

We estimate that about 450 million doses of gadolinium-based contrast agents or GBCAs worldwide have been administered to patients since its very first introduction back in 1988 with Magnevist by Bayer.

Out of those 450 million, close to 200 million are provided with our products, Magnevist, which was the first agent; Eovist, the first liver-specific GBCA at least here in the U.S.; and Gadavist, the first macrocyclic agent that also has a higher relaxivity.

I think overall, the benefit of these class of agents has been agreed upon. They provide frequently and consistently crucial medical information.

Overall, the safety is also favorable of these agents. We have very low reports of adverse events, and the most frequent adverse events we deal with are reactions in the group of

hypersensitivity.

There have been two observations in the past at least partially related to the stability of these agents that have been effectively addressed via label changes, and those were calcium interference only occurring with Omniscan and Optimark back in 2003, and then NSF, as we heard, back in 2006 in patients with severe renal impairment.

Now we have the latest observations of increased signal intensity in the brain or even presence in the brain and other tissues in patients with normal renal function, and the clinical significance is unknown.

There are about 39 studies now out addressing findings in clinical imaging relating to signal intensity in the brain, and they demonstrate differences based on the chemical structure and on the molecule stability of these GBCAs.

For all multipurpose agents as have been individually studied, and those are in alphabetical order, Magnevist, MultiHance, and Omniscan, there

has been shown a signal increase -- and that is important -- provided that a threshold of about five or more injections has been reached. I say that because there are a few studies out where the vast majority of patients received two injections, three injections, only very few more than five. The data are presented as a statistical mean across a group, and that may easily mask the effect.

The liver-specific agent Eovist is slightly different. It is administered as a quarter of a dose of the other agents, and there we see a signal intensity as well but only after about 20 injections or more.

The situations for the macrocyclic agents is very different. There is so far no visual proof of any signal intensity increase on an image in any of the studies for any of the agents. Also, up to 52 injections have been administered in those patients.

We are fully aware that there are some reports claiming that there are measurable effects, but we have also some concerns that there are

confounding factors like prior injections of other agents, like lack of standardization in those quantitative measurements are confounding these results, so we think, as presented, there is no evidence yet for signal increase with the macrocyclics.

There are a few studies also measuring gadolinium in human tissue, in bone, in brain, also in the skin as one report in patients with normal renal functions. To summarize all of the results, whenever a macrocyclic linear was administered and documented, traces were found in the tissues, in the bone, in the skin, as well in the brain for both classes of agents.

Just one word of caution here, to not overemphasize quantitative comparisons because if the sampling of the material was done shortly after the administration, we know there is a huge fluctuation among the values, so you don't reach a steady state until you have 6-8 weeks after the administration. Everything that is measured before is probably not representative.

The trace concentrations that we measure in the brain alone are probably not sufficient to explain this signal that we have seen on the images. That is why Bayer already back in 2014 initiated a really extensive research program to understand the underlying mechanisms better that started with establishing as a respective model but then addressing questions such as how does gadolinium enter the brain. What happens if it is in the brain, what's the localization, what's the chemical form, and is it eliminated, yes or not?

Last but not least, there is also one study ongoing that addresses functional effects of these agents on behavioral and cognitive abilities measured in this animal experiment, and I'm going to guide you through some of the key findings.

Here are the nonclinical findings on tissue measurements. You see with red color the linear agents, with green color the macrocyclic agents, and they can be summarized as follows here for skin, muscle, and brain.

Again, we find traces with both classes,

macrocyclic and linear, in each tissue, but we find consistently and a statistically significantly higher concentration with all the linear agents compared to the macrocyclic agents. And to put the situation in skin in perspective as what we know in the brain, the skin concentrations are about a factor of 100 higher than what we measure in the brain.

If it comes to the localization of gadolinium in the brain, the question was, is there a specific localization? And yes, there is. You see in the upper row, the linear agents; in the lower row, the macrocyclics. Red color on these images indicates a relatively higher concentration of gadolinium; blue is more the background.

You see a specific enhancement of gadolinium in the deep cerebellum nuclei, but you see it also beyond that in the granular layer. So it's not just limited to very specific areas. You see that comparably for all the linear agents. You don't see it for any of the macrocyclic agents.

Maybe the most important study and finding

is the following. We were looking for the chemical formation in the brain and did a gadolinium-tailored chromatography, and the first finding is what you would expect. You see a peak here on the right side that shows at 0.5 kilodalton the intact gadolinium chelate. That is expected.

What was not expected is a peak also more to the left showing at 250 to 300 kilodalton, macromolecule structures, which also contain gadolinium. The only explanation we can offer so far is that gadolinium is released from the intact chelate and binds to macromolecules only for the linear agents.

We see that here, and we have been challenged on that, whether that couldn't be the intact molecule also binding to the macromolecules. The answer is no. We have fairly consistent control experiments also trying to show a binding for the intact molecule. It was not possible. There is no binding of the intact molecule.

We find other hints for dechelation in the insoluble fraction, and it would also not explain

why we don't find any of that with any of the macrocyclic agents. There is no second peak. There is no release from those agents in that situation.

That is very much in line with our understanding of the stability of the data. Back to the forensic data that we also have seen in a previous presentation in humans, and we see for the non-ionic linear agents up to 20 percent release of gadolinium within 15 days; on the other end of the spectrum for the macrocyclic agents, zero.

One question, in that chart here, is there any immediately visible effect on the tissue level with this gadolinium in the brain? The short answer is no. Regardless of whether we talk linear or macrocyclic agent, we don't see changes, at least not those that we can capture on a histological level.

The last question on the nonclinical part is elimination in the brain in that nonclinical model, and here we observe now up to 52 weeks. Again, you have in red the linear; in green, the macrocyclic

agents. And you see that at least between week 5 and 52, there is essentially no elimination of any of the linear agents. But you see in the same time period a consistent and continuous elimination of macrocyclics almost down to the level of detection.

Now, these are all data that describe more mechanisms, but what does it mean? What does our own pharmacovigilance experience show us in the context of that discussion?

I think I want to point out one unique position that Bayer is in. Having also a therapeutic portfolio, it allows us to search a much larger database, and we have interestingly also an offering for a multiple sclerosis treatment. Therefore, we have up to 300,000 case reports in multiple sclerosis patients who frequently receive multiple MRs, which are an interesting other source for pharmacovigilance testing, be it qualitative, be it quantitative evaluations.

What did the search reveal with regard to the brain? The initial search that we did,

focusing also on cognitive and motoric changes, did not reveal any signal. There are a few things in the literature that could be seen as signal. There is a study from Welk, a retrospective cohort study that could not associate Parkinson's disease with the administration of GBCAs. That study is certainly not conclusive, but at least encouraging.

Looking into multiple sclerosis patients, we have two publications, one abstract and one paper, one from Terashima that doesn't show any effect here, and the other one, a questionable one, the so-called lower verbal fluency scores. But the control group are healthy, and this will not allow us to say is that a drug effect or is it normal disease progression.

We expanded our pharmacovigilance research on those 300,000 cases that we have with multiple sclerosis patients, and we didn't find any specific signal in this cohort either with regard to effects potentially associated with gadolinium administration.

Now looking into the situation in the body,

and that might be a slightly different entity. I think that's not clear yet, but there we have some signals from the literature primarily but also from patients communicating via social media, websites, and recently also reporting to us.

In the literature, we heard about the symptoms, burning in the extremities, pain, some skin changes, also, cognitive disorders. Those were things reported, and this was even proposed by one of the authors, Richard Semelka, to put that together and give it the term "gadolinium deposition disease."

I think that implies a causality that needs to be still established, but the symptoms really have to be taken seriously because they are real, they exist, and obviously show some really difficult situations for some patients.

What we first do because that is what is at our hand is we searched our pharmacovigilance database, and we have found 40 reports noting that patients report elevated levels of gadolinium in some kind of fluid, mostly urine, sometimes blood,

comes from fingernails, hair. Twenty-one of them reported also symptoms that are very similar to what has been published in these articles. There were also 13 reports reporting those symptoms without any evidence for an increased level of gadolinium in any of these fluids in the body.

Many of the reports unfortunately are not medically confirmed. That means we don't have any source data. We don't have any proof, medical proof, of what the findings are, what the lab results are, et cetera. So for us, the information is not sufficient yet to come to any causality assessment at this point in time, which doesn't mean that we discount any of the reports that are there. So we will follow up, and we do that already with the targeted questionnaires to gather more information. We really depend on what is reported to us.

Now, given the limitations that all the pharmacovigilance has, clearly, as it is voluntarily reporting, we are currently exploring options to go a little further for a so-called

signal detection in terms of pharmacovigilance. So please don't mix that up, the signal increase in the brain. That is a term in pharmacovigilance, to pick up a signal here, and to utilize retrospective screening studies in larger healthcare databases to identify those signals.

There are a number of questions related to that. It starts with an exposed cohort, which ideally has multiple MR exposures. There are not many that have very little confounding disease factors. For example, if you would go for the CNS population where you have a lot of these patients receiving multiple MRs, it is almost impossible to discriminate whatever you find from the disease.

One population that always has been mentioned and also has some problems are women that undergo regular screening for breast cancer when they are at high risk, and I think it would be also feasible to find an adequate comparison cohort.

Just still one word of caution with all of this, we can only detect what's recorded in those databases. We have to expect that there are

multiple signals coming out, many of them probably false positive, and in order to minimize such a random error, we probably need to look into more than one database. Whatever comes out would require a specific follow-up and a specific study.

In terms of risk mitigation from our perspective, we think right now communication is key, and communication also includes label. We actively support and propose changes in the label that addresses the findings that we have, in particular, to the situation in the brain.

We think there are a number of data out that would support and justify providing that information also with a clear piece in it that there are different findings for linear and macrocyclic agents. So we would see two classes here that need to be addressed appropriately, but also coming with the clear hint that there are no adverse clinical consequences that have been really confirmed as of yet.

In addition, communication to healthcare providers is necessary. We do that. We will

continue to do that. We will also continue to do it in our ongoing medical education, and we are certainly totally committed to continue with our research efforts and to consider whatever is necessary to clarify on the situation that we are facing now.

Just to summarize that, I think we should never forget the important role that these agents play in the diagnostic workup, and we think also that's not the main focus today, that the benefit-risk overall is favorable still, but yes, we are committed to find out what's really the underlying mechanism and what is any potential causality to what we see right now. And we'll move forward in doing this, and we'll move forward and transparently communicate our findings. Thank you very much.

DR. HERSCOVITCH: Thank you for this presentation.

We will move now on to our next industry presentation, and this will be from Bracco Diagnostics.

Industry Presentation - Alberto Spinazzi

DR. SPINAZZI: Good morning. My name is Alberto Spinazzi. I'm in charge of medical and regulatory for the Bracco Group, and I really thank the FDA on behalf of Bracco, and this distinguished panel for giving us the opportunity to present before you today. Bracco is a global pharmaceutical group, and we market two agents in the United States. One is a macrocyclic, ProHance, and one is a linear, MultiHance.

We decided many years ago to headquarter our clinical, medical, and regulatory operations here in the United States. This is why I was moved here. And I'm now a U.S. citizen -- I apologize for my thick accent -- my family also. And I'm so glad that the FDA is taking this really seriously and continues to take this seriously about the long-term retention of gadolinium, and I can assure you that Bracco is taking that very, very seriously.

As you have heard before, a lot is unknown, the potential risk factors, the association with

adverse health effects. We do believe it is important to inform the public and the healthcare providers further.

Therefore, we fully support the FDA initiative to on one side update and enhance the labeling. This is very important to be done also with assessing each individual agent and the benefit-risk balance of each agent; and also the effort to develop a collaborative effort to better understand this phenomenon of gadolinium retention, but also to mitigate the risk.

This is very important to us. There should be ways to reduce exposure, which is critical, without any way compromising efficacy because in the end, you want a diagnosis to treat patients. So what could be followed is what was done with radiation exposure in CT and follow the principle of as low as reasonably achievable principle, so the ALARA principle.

It was mentioned before, NSF. NSF is a serious medical condition, the only one currently associated with gadolinium retention, which is the

topic of today, gadolinium retention in body organs.

What the FDA did years ago was extremely effective, and there were specific labeling changes. There were warnings introduced in the labeling of all the agents, restrictions for specific agents, contraindications that were based on clinical evidence. So there was no segregation of products based on their chemical structure or animal experiments. This was only supportive evidence.

Eight years later, this approach has been shown to be extremely effective. Since that point, it was mainly spontaneous reports of unconfounded single-agent cases of NSF. Now there is a much larger body of evidence.

Here what I am going to show in this table are the specific studies that followed prospectively patients at high risk for NSF. They were medically monitored, and each lesion suspicious of NSF was assessed by specialists.

You can see here the number of patients

overall in the biostudies of these agents, and you can see that there is not a clear line between macrocyclics and linears. Actually, the largest body of evidence, probably because it is a linear agent, has been with MultiHance, and no cases of NSF over 8,000 patients at high risk.

The NSF, the actions by the FDA, and also the overall assessment of the benefit-risk profile of different agents have changed the practice and also changed the use of the linears, so Magnevist, Omniscan, OptiMark declining continuously and markedly while MultiHance showed a steady progressed increase in usage. This is both in adult and the pediatric population.

What is the problem today, as was stated before by Dr. Krefting, is the retention of gadolinium complexes in tissues. The main focus today is patients without impairment of renal function, but beyond NSF, these could also affect patients with impairment of renal function. You might have retention in brain tissues. One is to change the signal intensity in deep brain areas and

make them wider so you see also enhanced images. This is called T1 hyperintensity, and the potential for adverse neurological effects.

As far as body retention beyond NSF, there is this group of events, group of symptoms, that usually start hours or days after administration, even a single dose of any gadolinium chelate, and it should be important to understand a possible, a potential association with exposure to gadolinium agents or retention in tissues.

What is the summary of available evidence? You got before some selected studies in animals. We suggest that since the main problem is retention of gadolinium in human tissues, that direct demonstration of gadolinium in human tissues should be the highest level of evidence. So those studies are probably the most important to understand what happens in humans, and a few can retain gadolinium long term.

If you look at the brain tissues, besides ProHance that has very low levels in the brain at the limit of quantitation, for all the other

agents, there is not that much difference, probably from Omniscan. In body tissues, it has been seen, gadolinium following the administration of all the agents.

If you look at this study here, for instance, the tissue sample studies and the autopsy study, you can gadolinium is on top. And you can see that when you normalize exposure, even in a patient at an interval of more than one year between exposure and death, you still have the highest level in this series, higher than the linears Eovist and MultiHance.

The second level is definitely animal studies because there still is a direct demonstration in tissues. Similarly to men, the levels in the brain are extremely low and can be measured only using the most sensitive analytical techniques. They are usually in the brain much lower than what you observe in the body tissues.

In brain tissues at the lowest levels, there is a difference among the macrocyclic agents with the lowest levels found with ProHance, lower than

with Gadavist and Dotarem. The lowest levels among the linears are with MultiHance, so there are differences among these agents.

In body tissues, you cannot draw a demarcation line. You might have sometimes higher levels with the macrocyclics, sometimes higher levels with the linears. It's kind of a rollercoaster. It depends on the organs and depends on the experimental models.

The only two studies that are similar -- because actually Bracco copied a previous experimental design in juvenile animals -- was same doses, same design, same methodology in juvenile animals. If you look at the retention in the body in juvenile animals, you do not see remarkable differences between Dotarem and the linear MultiHance.

The lowest level of evidence is assessment of signal intensity on the images. There is a lot of variability, depending on the method of quantitation. There is a lot of variability, depending on the readers, and most important,

imaging cannot measure gadolinium in tissues. Since the chemical forms are retained and their relaxivity is not known, you cannot infer from the signal intensity or airway relaxation rate the possible levels of gadolinium.

There are many sources of bias. There is a flurry of small scale retrospective studies. And if you see a systematic trend, that might be important, but you do not see that apart from ProHance, Omniscan, and Magnevist.

If you look at this, here are all the studies that were mentioned before. With ProHance on the red column is when you see a change in signal intensity, even a mean change, and on the right, you have when you do not see a change in signal intensity. So you can see never seeing a change in signal intensity with ProHance, always with Omniscan and Magnevist, but for the other agents, there are mixed results with the majority of the studies not showing an effect on signal intensity independent of the chemical structure.

Retention, but is there any toxicity? I

followed very carefully the presentation that was given before by the distinguished expert, and data so far in brain tissues is you cannot find signs of toxicity, either with structural or neural pathology, and electron microscopy. And following these animals clinically with assessment of behavior, their neurological testing, there have been extensive studies done in juvenile animals with MultiHance, and there were no signs of toxicity.

In body tissues, as given by the distinguished experts, there are skin changes but only seen with two agents, Omniscan and Optimark, and nothing with the other agents.

Now, in humans, there is no sign of neurotoxicity from tissue sample studies. There are two large population studies now, one the study from the Ontario database not showing an association and any effect on motoric skills or Parkinsonism in elderly patients, and a new study that has been reported by Dr. McDonald, who is here, not showing any potential effect on cognitive

function and motoric skills.

As you heard from previous presenters, we had this group of symptoms and events that are heterogenous with some clusters of symptoms, and this is also as stated by the FDA in the briefing material, there is not still a clear association with exposure and/or retention of gadolinium agents.

Coming back to the risk assessment, there is retention. There is retention with all the agents. And in brain tissues, what is clear is that you might have T1 hyperintensity. That could be seen on the images of patients on unenhanced images and has to be interpreted. But there is no evidence of adverse neurological effects. For body tissues, there is not a clear association between event and the exposure to gadolinium agents.

What is our proposal for mitigation? To minimize the risk of gadolinium retention, certainly labeling should be enhanced with tailored and clear warnings. It is important for people to understand gadolinium is retained also in patients

with normal renal function to make sure that they are aware and possibly use the ALARA principle also for use of gadolinium agents.

We believe it would be important also to inform users about the potential for T1 hyperintensity, not to lead to any error in the interpretation of the images. Getting the history of the patients, that should be easy.

Also, out of an abundance of caution, there should be also information about this latent set group of symptoms that have been mentioned previously, even if the association with exposure is still unknown; and certainly, FDA-approved information to healthcare professionals and educational progress validated by the FDA.

In conclusion, we are taking this very, very seriously. Gadolinium retention should not be just based on the chemical structure or segregating agents based on that. It is important instead to look at classes of products, to look attentively at individual agents.

We fully support the FDA's initiatives, one,

to improve information and warning to healthcare providers but also to encourage further research in this area. We are ready to follow your guidance and to work collaboratively with the agency, with the scientific community, and also the other sponsors. Thank you for your attention.

DR. HERSCOVITCH: Thank you very much for that presentation.

We will now move on to a presentation from GE Healthcare.

Industry Presentation - Mark Hibberd

DR. HIBBERD: Good morning, Mr. Chairman, members of the panel, members of the public, and the FDA. I am Mark Hibberd, chief medical officer for GE Healthcare Life Sciences.

Substantial data and decades of use, as well as administration of tens of millions of doses to patients, support the safe use of gadolinium-based contrast agents and Omniscan. Omniscan was first approved in the U.S. in 1993 and is currently approved in 107 countries. Over 100 million doses have been administered worldwide.

We agree with the FDA that trace amounts of gadolinium are detected in the brain and in other human tissue with all of the gadolinium-based contrast agents, including both linear and macrocyclic agents. We also agree that in the normal renal function setting, adverse effects have not been causally linked with retained gadolinium in animal or human studies, however, uncertainties still exist.

We have addressed some of these uncertainties in our research, however, we agree that more research is needed. Thus, we have initiated a robust research program to better address these uncertainties, and we are committed to label changes to support the appropriate use while research is going on. Overall, the safety profiles of gadolinium-based contrast agents differ, and so the availability of different agents allows a choice to best fit patient needs.

Given the limited time available today, we will focus on data that answers key questions about retained gadolinium and the safety of GBCAs. NSF

is not in scope for this presentation as we are focusing on patients with normal renal function.

Dr. Robert McDonald, who has been extensively involved in contrast safety research, will provide an overview of the clinical and nonclinical data on tissue gadolinium and any potential effects. Dr. McDonald is a scientist and neuroradiologist at the Mayo Clinic and is also a member of the contrast safety committee at the American College of Radiology. I will then return to summarize GE's risk mitigation plans.

Thank you, and I now invite Dr. McDonald to the lectern.

Industry Presentation - Robert McDonald

DR. McDONALD: Good morning. I'm Bob McDonald. I thank the panel for the opportunity to speak today about the safety profile of GBCAs. In terms of my financial disclosures, I am currently a consultant to GE Healthcare. Additionally, I've received support from all four sponsors here today but have no financial stake in any of the companies nor the outcome of this meeting.

Let me now review important research related to gadolinium retention. At the Mayo Clinic, we took great interest in the initial observations showing a correlation between progressive MR signal intensity in the brain and cumulative GBCA exposure. Since MR signal analysis is a relatively insensitive and indirect assessment, we sought to use more sensitive quantitative tissue analysis techniques to validate this observation.

Our group provided the first confirmation of these initial observations in post mortem human tissues that these signal changes were a result of gadolinium retention in patients with four or more GBCA doses. Using inductively coupled plasma mass spectrometry, we confirmed a strong correlation between cumulative GBCA exposure, T1 signal change in specific neuroanatomic regions, shown at left, and gadolinium concentration in these same regions, shown at right.

It should be noted that most patients receive far fewer doses than shown in this study. Thus, any gadolinium retention would be at or below

the limit of detection, as noted in the red circle.

Despite clear evidence of gadolinium retention in brain tissues comparing panels A and B, we have not observed histological evidence of injury to neural tissues comparing panels C and D in patients exposed to as many as 29 cumulative doses of Omniscan in humans.

Subsequent studies have demonstrated that gadolinium retention is seen with both linear and macrocyclic agents and appears to vary both between and within classes. Here we see results from our recently published preclinical rat study showing measurable increases in gadolinium concentrations compared to control for 2 linear agents and 2 macrocyclic agents.

Although slight different in study design, these findings were replicated in a separate rat model showing that this retention is observed with all macrocyclic agents with differences within the subclass.

Despite administration of 80 human equivalent doses in our animal study, we did not

observe evidence of toxicity in the brain and other tissues except for the kidney.

At the supratherapeutic dose in our rat study, we observed evidence of reversible histopathological changes in the proximal convoluted tubule of the kidney with all agents. However, we were surprised to observe irreversible injury only from the agent associated with the lowest amount of gadolinium retention in the brain, liver, spleen, and kidney, shown here.

While these findings are only observed at these supratherapeutic levels, they show that toxicity is not related to the amount of gadolinium retained in the tissue.

Many subsequent animal studies have reached the same conclusion. Gadolinium retention from GBCA administration is not associated with histopathological evidence of neural tissue injury. In addition to these findings, recent clinical research sheds light on the effects of retained gadolinium in brain tissues.

Results from a retrospective population-

based study of almost 250,000 Canadian patients published in JAMA found no significantly increased hazard in the development of Parkinson's symptoms amongst patients exposed to GBCAs for contrast-enhanced MRI compared to those never exposed to a GBCA.

This study reflects real-world clinical practice as the majority of the patients in this study received only 1 dose of gadolinium rather than the high exposure groups such as multiple sclerosis and oncology patients where much of the retention data is drawn from.

I'm now going to show you some early data looking at the effect of gadolinium exposure on neurocognitive function. The Mayo Clinic Study on Aging is a large, ongoing, prospective, longitudinal, observational study on the natural progression of cognitive aging and cognitive function in a population-based cohort. Endpoints include a comprehensive catalogue of clinical evaluations, including cognitive and neuropsychiatric assessments; neurologic

examination, including assessment of movement disorders; imaging with MRI and PET-CT; and laboratory evaluation performed at 15-month intervals.

We used this large database to conduct a retrospective analysis of the potential relationship between Omniscan exposure, the agent previously used in our medical center, and neurocognitive function. A cohort of over 1300 patients who had exclusively received Omniscan were compared to almost 3,000 well-matched controls who never received a contrast agent. Forty-four percent of the exposed cohort received 5 or more doses of Omniscan and thus represented a higher exposure group than typically seen in clinical practice. The average length of observation was approximately 5 years in both groups.

A multivariate analysis was performed adjusting for various demographic factors. We found that Omniscan exposure had no effect on neurologic outcomes. We also did not find evidence of a dose-response relationship with these

outcomes.

Now, I would like to switch gears to discuss a known serious adverse clinical event from GBCAs, hypersensitivity reactions. While usually mild, hypersensitivity reactions can be severe and may cause death. A recently published meta-analysis combining data from nine studies representing more than 700,000 patients revealed that Omniscan has a significantly lower rate of hypersensitivity reactions.

Agents with different characteristics such as protein binding, ionic charge, and macrocyclic structure were associated with significantly higher hypersensitivity reaction rates than Omniscan. Similarly, using data reported to the FDA, linear non-ionic agents also had the lowest rates of hypersensitivity-related mortality.

Although these events are rare, when you extrapolate across millions of doses, this translates into an approximately 4- to 18-fold increase in death every year when using linear ionic or macrocyclic agents compared to linear non-

ionic agents such as Omniscan.

In summary, preclinical studies have shown no evidence of acute or chronic brain toxicity at doses far above standard clinical equivalent dosing following intravenous administration. Although we have not yet found evidence of chronic toxicity nor clinical effects from gadolinium retention, there remains significant uncertainty, requiring further research on many issues, including the chemical form, mechanism, biological activity, and potential clinical significance of retained gadolinium in the brain. With regards to hypersensitivity, linear non-ionic agents such as Omniscan have significantly lower rates of allergic reactions across the entire class.

Finally, since 1988, between 3 to 400 million GBCA doses have been administered worldwide without evidence of retention-related toxicity. Notably, these agents have helped countless patients by identifying disease that can expand and save lives. Thank you, and I'll now turn the lectern back to Dr. Hibberd.

Industry Presentation - Mark Hibberd

DR. HIBBERD: Thank you, Dr. McDonald.

While the evidence to date shows no harm from retained gadolinium in patients with normal renal function, we also recognize that uncertainties still exist and have developed a risk mitigation plan to advance scientific understanding of gadolinium retention.

Our risk management plan has three components. First, we have intensified our monitoring of adverse events, placing special emphasis on delayed events, persistent events, and all events that may have a relationship to retained gadolinium. Data from all sources are reviewed weekly by a team of nonclinical, clinical, imaging, and statistical experts and monthly biosafety management team.

Second, based on the highly successful approach taken for NSF, we support labeling revisions that reflect the most up-to-date evidence around gadolinium retention and focus on the appropriate use and dosage of these agents. We

will communicate all label updates through direct communications to healthcare providers.

Lastly, while the evidence to date does not suggest harm from gadolinium retention, we have a robust clinical and nonclinical program to address uncertainties related to this retention. Let me briefly describe this research program.

Currently, we have five clinical studies that are underway or being planned, and they include autopsy analyses of brain gadolinium distribution, histology, toxicologic examinations, as well as long-term clinical studies of motor, cognitive, and neurological function among patients receiving gadolinium.

We have also six nonclinical studies completed or underway. These quantify retention and washout of gadolinium for all of the available agents with a single protocol; also, with behavioral evaluations after short- and long-term exposure, and with blinded independent tissue toxicity assessments. We are also trying to identify the chemical state of gadolinium and its

location in the brain together with multiorgan toxicity assessments.

In summary, scientific evidence supports the safe use of Omniscan and shows no causally-related adverse effects from the long-term retention of low levels of gadolinium after administration of both linear and macrocyclic agents. GE Healthcare is committed to research and to working with the FDA, with patients groups, and all manufacturers of GBCAs to better understand the unknowns around gadolinium retention.

In addition to gadolinium retention, all adverse effects should be considered when looking at the overall safety of GBCAs, including Omniscan's low rates of hypersensitivity reactions.

Before closing, I want to recognize that there are some people who have experienced adverse effects following contrast administration. Listening to them will help us improve how contrast agents are best used.

We must continue to work together to help patients who are negatively impacted by GBCAs as

well as patients who experience improved health due to the improved diagnostic from GBCAs enhanced imaging. Thank you, and we look forward to your questions.

DR. HERSCOVITCH: Thank you very much for that presentation.

We will now move on to our last industry presentation from Guerbet.

Industry Presentation - Pierre Desche

DR. DESCHE: Good morning, everybody. My name is Pierre Desche. I am speaking on behalf of Guerbet where I'm in charge of development, medical, and regulatory affairs. And I would like to thank the FDA for the invitation and giving us the opportunity to present the company's position on this important question about gadolinium retention.

We have two GBCAs on the U.S. market, Dotarem, which is macrocyclic and ionic GBCA which was approved in the U.S. in both adult and pediatrics, including term neonates, for a CNS indication. Based on the extensive review of all

clinical, nonclinical, as well as pharmacovigilance data, we have concluded that the risk-benefit balance of Dotarem is favorable.

We have also Optimark, which is a linear non-ionic GBCA, which is also approved in the U.S. in adult patients for CNS, spinal, and liver disease imaging. This compound was integrated in the Guerbet portfolio when Guerbet acquired the contrast media and delivery system business from Mallinckrodt.

Optimark has been approved in 33 countries and approximately 22 million doses have been administered so far. Based on the increasing demand for macrocyclics worldwide, Guerbet has decided to progressively phase out Optimark worldwide, and this has already started in Europe.

It is important to note that in 2016, Guerbet voluntarily proposed a labeling modification of Optimark in order to inform the medical and the patients' communities on the potential brain gadolinium deposition after multiple administration, and this labeling change

has been approved by the FDA in August 2016.

As it has been already said during this morning's session, gadolinium is highly toxic. So before administration to human, it should be chelated, and there, there are two options, the linear chelation or the macrocyclic chelation. The chelation dramatically decreases toxicity, ensures biocompatibility, and allows rapid expression, but it should be noted that the macrocyclics are much more stable than the linear compounds.

Now I am going to focus on the long-term reaction observed with the GBCAs. We need to talk about the chemistry, and we need to talk about stability.

The stability, there are two components, thermodynamic stabilities, and the macrocyclics are much more stable than the linear compounds, and also, the kinetic stability. Again, the macrocyclics are much more stable as far as kinetic stability is concerned compared to the linear compounds.

This is important when we consider the

occurrence of NSF. Most of the cases of confirmed and confounded cases of NSF have been reported with linear GBCAs, and very few have been reported with macrocyclics. There is the same trend with the brain hyperintensities. Most of the reported T1 hyperintensities have been reported with linear compounds, and there is no case of T1 hyperintensities reported with the macrocyclics. We think that both are due to disassociated gadolinium, and both show differences between stable and less stable GBCA.

As you know, NSF is a clinical syndrome. It is a consequence of the instability of some GBCAs in patients with severely impaired renal function. On the other side, hyperintensities in brain should be considered biomarkers of the instability of some GBCAs, mainly linear GBCAs, in all types of patients, including the patients with normal renal function.

However, in patients with a NSF-like syndrome, this syndrome has been reported despite the patient has normal renal function. Conversely,

in patients with NSF, documented NSF, there are cases where there is also brain T1 hyperintensities.

So our conclusion is that brain hyperintensities and NSF are, in fact, part of the same continuum from gadolinium retention to gadolinium toxicity, and renal dysfunction acts as a catalyst.

Now, we would like to spend a few minutes on some inconsistency in the literature data about the T1 hyperintensities. There have been reports of no brain T1 hyperintensity with linear GBCAs. However, if we go back to the Weberling publication, it's clear that with linear GBCAs, the more you give to the patients, the higher the proportion of patients with T1 hyperintensities.

There are some publications showing with [indiscernible] that there is no T1 hyperintensities, but these publications are using a low number of injections or a half dose as in the Schneider publication.

When we look at publications on the T1

hyperintensity, the methodologic aspect, the method used in that study, even if it is retrospective, it is very important, and at least two key factors should be taken into account, the number of the injections as well as the cumulative total dose of the GBCA administered. When we took into account the methodological aspects, we can conclude that all linear GBCAs may induce brain hyperintensities.

On the other side, there has been some reports of T1 hyperintensities with macrocyclic compounds such as recently in the Rossi-Espagnet study in children, that in fact despite a high signal intensity increase comparable to the previously reported increase with the linear GBCAs, in the publication itself, there is no visible T1 hyper signal, which has been reported in this publication.

In this study, in fact, there is a big confounding factor, which is aging, which is not taken into the interpretation of the results. So we conclude that there is no brain T1 hyperintensity reported conclusively with the

macrocyclic GBCAs.

Now, moving to another inconsistency into the literature data, which is all gadolinium chelates could deposit in the brain. We think that there is a confusion between a transitory presence of chelated gadolinium, which is observed with all GBCAs and the permanent of disassociated gadolinium, which is only observed with linear GBCAs.

For instance in the McDonald studies, there are gadolinium deposition in the rat with both the macrocyclic and the linear gadolinium, but this is observed 7 days after the last administration.

Now I am going to present some unpublished results from Guerbet. When we took a longer period of time of observation, it is clear that after 1, 2, 3, 4, 5, until 12 months of observation in rats, there are clear distinctions between the elimination kinetics of the gadolinium between the linear, which is Omniscan, and the macrocyclic, which is Dotarem. It is also the same for the form of the gadolinium chelate. After Omniscan, there

is gadolinium associated with macro molecules, and here we confirm the results obtained by our team.

In contrast with the macrocyclic, there is no gadolinium associated with the macro molecule. In fact, the intact complex is clear rapidly all of the time. So in conclusion, with the macrocyclics, there is a faster washout of gadolinium, and there is no detectable disassociated gadolinium, also.

We think that there is a complex set of evidence of gadolinium disassociation deposition related to the GBCA structure, and there is a clear distinction between the linear GBCAs and the macrocyclic GBCAs as far as the chemical stability is concerned, the individual stability and physiological conditions; the occurrence of NSF in patients with renal failure; the occurrence of brain hyperintensities in adults and children with normal renal function; and finally and most importantly, the chemical form of gadolinium in the brain.

But there are differences between brain T1 hypersignal and NSF. First, brain T1 hypersignal

occurs in patients with normal renal function. The linear GBCA in MultiHance induces brain T1 hypersignal, and so far, there is no evidence of a clinical impact of gadolinium deposition in the brain.

As you know, the gadolinium retention question is an overall question which has been handled by a number of countries in Europe but also in other countries, which has already started to react to these serious questions.

Now I will move into the acute phase reactions, which has already been mentioned. This is the meta-analysis of nine publications, which has been recently published by the group of Dr. Prince, that suggests that with linear non-ionic compound Omniscan, there is less immediate adverse reactions than with the linear agents, ionic or the macrocyclic agents non-ionic. But when we take into account the adverse event rate, which has been measured with Dotarem, it seemed that the distinction between ionicity and the macrocyclic ionic structure is not so clear.

Also, it is the same when we look at a greater number of patients looking at the pharmacovigilance database, which has been published with several compounds. You can see that with several millions of injections, the adverse drug reaction rates with Dotarem, which is a macrocyclic ionic compound, is very close the adverse reaction rate observed with Omniscan, which is a linear non-ionic compound.

So our conclusion is that there is no link between acute reaction and ionicity, non-ionicity, as well as no link between acute reactions and linear, macrocyclic structure.

We are seeing there is a clear difference between the linear and the macrocyclic agents when we are looking at the long-term reactions. On the opposite, there is no difference between linear and macrocyclic GBCAs, looking at the acute phase reactions.

What about the impact on patient management? There are a number of comparative studies using crossover design, mainly in the CNS indication, as

well as angiography, breast imaging, or cardiac imaging. I have to note for those indications, Dotarem is not approved in the U.S., but there is no demonstration of a significant impact on the patient management from those comparative studies.

This is the summary slide. GBCA injections improve diagnostic accuracy of MRIs. There is no doubt about that. The clinical impact of lower stability GBCAs, that is linear GBCAs, is demonstrated with NSF. Brain hyperintensities and NSF are part of the same continuum. The GBCA's stability is directly related to the chemical structure, so we are going back to chemistry. Macrocyclics are more stable than the linear agents.

Our proposal for risk mitigation, the first one is adopt a precautionary approach. As a reminder, it took nine years to link NSF with the gadolinium. So to change labeling of the GBCAs, restrict the use of the linear GBCAs as second-line agents in accord with the NIH recommendation regarding clinical studies. So include the same

statement as we did with Optimark, same statement on retention, and as all correlates, continue prospective mechanistic, non-clinical studies and also to continue retrospective large-scale clinical studies. Thank you for your attention.

Clarifying Questions to Presenters

DR. HERSCOVITCH: I'd like to thank all the industry speakers for their very thoughtful presentations. We will now proceed with the opportunity for clarifying questions from the members of MIDAC.

I will ask you all, do you have any clarifying questions for any of the industry presenters, and if you do, please state your name for the record into the microphone before you speak, and also please identify which presenter your question is for from which of the four industry presenters, or if it is a general question to all presenters. We have about 15 minutes for these questions.

I'd like to start on this side. Please raise your hand, identify yourself if you have a

question, and we will just go around the table.

Moving around, yes, please put on your microphone, identify yourself. Thank you.

DR. DAINIAK: Dr. Dainiak from REACTS, and I have a question for Dr. Wagner.

Dr. Wagner, have you found any evidence for CNS deposits in your mice or clinically in patients who have NSF?

DR. WAGNER: Well, I'm a nephrologist, so I am not ordering a lot of unenhanced brain scans, so I can't speak for the patients. But for the mice, we do have an experiment ongoing.

We have taken some of the tissues and sent them for analysis for inductively coupled plasma mass spectroscopy, which is the method that is very sensitive for detecting the gadolinium. And we're finding it in just about every tissue that we send to them.

I am not a brain pathologist. I have begged our brain pathologist in San Antonio to take a look at the slides, and he's just not interested. So I have looked at what would be the equivalent of the

dentate nucleus in the animals, and I can't see any difference but --

DR. DAINIAK: I'm sorry. You cannot find evidence in animals? Is that what you're saying?

DR. WAGNER: Well, you do find gadolinium in the tissues for sure.

DR. DAINIAK: In the brain?

DR. WAGNER: In the brain, both in the cerebellum and in the cerebrum.

DR. DAINIAK: You're doing mass spec on that now

DR. WAGNER: Actually, my next step is I want to do the transmission electron microscopy, which is exactly what I showed for the kidney. Those kidney results were just last week, so it is in my plan.

DR. MARZELLA: This is Lou Marzella. If I may respond to that question as well, in animal models, there has been fibrosis observed up to the level of the dura, but none in the brain. To the extent that astrocytic changes have been looked for -- and I think it was shown by one of the

sponsors -- no evidence of astrocyte activation has been shown in the brain.

Although patients that developed NSF have not been looked at carefully, to my knowledge, there is no signal that the development of systemic fibrotic changes was correlated with neurologic findings.

DR. JACOBS: Paula Jacobs, National Cancer Institute. My question is a general one to all of them, which is what kind of validation has been done on the assays used in both animals and human autopsy samples and human skin samples to validate the assays so that we can know that one of these graphs presented by one researcher represents a number that is similar to a graph presented by another researcher?

DR. HERSCOVITCH: Please identify yourself again.

DR. McDONALD: Of course. Bob McDonald, Mayo Clinic, so not an industry sponsor, but I can provide some insight. So one of the reasons we went to mass spectrometry is because I initially

looked at the T1 signal and then thought, huh, this is interesting, but it's like trying to measure the width of a hair with a ruler when you have a micrometer.

It is irrelevant whether or not MRI sees this or doesn't see this at this point because I don't think we have the data to say whether or not that means anything because we can measure it with all the agents.

We have one of the only clinically validated labs in the world that can measure gadolinium and do so on a clinical basis, so a lot of the clinical testing samples come through our multimillion, maybe billion-dollar medical lab to do these sort of tests, and we are very rigorous.

I now work with the metals lab, and they perform very rigorous standardization and QC every day on it. But again, that's the problem we see with the MR data because my MR scanner is not calibrated to anyone else's, and so that is a very good point about going forward, we need some standardization.

DR. MARZELLA: If I may comment -- Lou Marzella -- I think that is a critical point that is being raised, which is going to be important to allow us to do comparisons between different agents. Ideally, this should be done with side-by-side comparisons, but to the extent that protocols can be standardized and validated, that this would be an enormous achievement.

DR. BALZER: Thomas Balzer, medical for Bayer, and I will ask our head of research, Dr. Pietsch, to answer that question.

DR. PIETSCH: This is very important to standardize, first of all, to use sequences in MR, but also to align them with preclinical measurements. Here, the way, first of all, to take the biopsies from the respective analysis, it's very important to allow a very high quality in the measurement afterwards.

As we have seen, we detect gadolinium today in the nanomolar to the picomolar range. It is of importance to take the biopsies in a very high quality, and here, standardization is the key

afterwards to allow really robust measurements. Thank you.

DR. HERSCOVITCH: Other industry representatives? Again, please identify yourself.

DR. DESCHE: Dr. Philippe Robert to answer that question.

DR. ROBERT: Thank you for your question. Philippe Robert, head of imaging and biological research. The rendition of techniques regarding the dosage of gadolinium has been extensively studied for many years, and we are using in each experiments blank, so animals with no injections so we can control the background gadolinium signal.

I have to add that our nonclinical studies have been also reproduced by other sponsors, and the level of gadolinium that is measured in the other studies independently are in the same range very precisely as compared to ours.

DR. TEDOLDI: Fabio Tedoldi, director of the Bracco Research Center. As for the previous speaker, also in our labs, we always use validated methods, in particular for ICP MS with internal

standard, and normally, we try to run study comparing at the same time in the same condition different agents at the same time.

DR. HERSCOVITCH: Thank you very much.

Moving around the table, Dr. --

DR. FOTENOS: Just one quick comment from the FDA also in response to the question.

DR. HERSCOVITCH: Sure, please.

DR. FOTENOS: Anthony Fotenos, medical officer. I would also emphasize that the question about assay sensitivity potentially goes beyond just a quantitative validation. There is also the sense of -- particularly when you have negative findings, it's very helpful to have a positive control.

For a nonclinical behavioral study, when I see no effects or no histological changes, is that at a level where, for example, with a known neurotoxin that you would -- would that same experiment also show no effects? So is the assay insensitive to subtle findings? And having do positive and negative controls, which I don't think

we've seen as much as we might, would help further those questions.

DR. HERSCOVITCH: Thank you for that comment.

Dr. Applegate, please.

DR. APPLEGATE: Kimberly Applegate. I had a question for Dr. Wagner, or actually two questions. One is, in the research you presented, did you have any information about whether the animal models that you looked at had any protective effect if they were younger, so as in children or infant, or even fetal, any protective effect? That's the first question that you could share with us.

The second question is in the other presentations that you just heard, were there any surprises or discrepancies in your findings versus what they presented? Thank you.

DR. WAGNER: That's a great question, and I have finite resources. But that is a critical question. And of course, these types of questions are coming up all the time.

Right now, my design is entirely adult, but

we are exploring not just that -- or we're proposing to do such studies. But we also want to see gender differences, too, because the patients that I see with chronic kidney disease, with end-stage renal disease, the females are in a medically postmenopausal state, and that may have some bearing on how the disease presents as well.

With respect to the results that I have done, the second question, my results compared to what was presented by the industry speakers, there's a lot of weight put on this dechelation of gadolinium versus the chelated form. This is what really compelled me to do research in this area is because I don't have a dog in the fight. I think this is a fantastic opportunity to conduct science, non-biased science.

When I initiated the experiments, I think many clinicians were expecting that bone marrow cells would infiltrate the skin, but that wasn't experimentally proven. We're dealing with case reports. We're dealing retrospective data. That's not prospective scientific data.

The only way to answer a question and get the truth is with prospective trials, and we will never get that with patients. The disease is too rare for us to test these hypotheses. So we need preclinical trials to do so.

A lot of the narrative reviews took advantage of these differences in thermodynamic stabilities, which are measured at a pH of 1 in non-physiologic conditions.

There is a paper by Dr. Frenzel in 2008 that showed that in vitro, these agents are prone to releasing gadolinium more than some others. However, of note is the very first paper that linked gadolinium to nephrogenic systemic fibrosis was with Magnevist, I believe, is gadolinium DTPA.

Well, in Frenzel's study, that was one of the agents that was least likely to release gadolinium. So I've always questioned how much of the dechelation of gadolinium, how much of that is responsible for the disease. Is it possible for chelated gadolinium agents to cause disease on their own?

Some of our in vitro cellular culture experiments show that these things have biologic activity and in a short amount of time, in such a short amount of time, that the gadolinium should be largely chelated. That, and also in patients with some residual renal function, they've cleared a lot of the gadolinium contrast within the first day, within the first couple of days, and yet we're seeing profound systemic effects years later.

The patients have contracted the disease 24 hours after gadolinium exposure. There are cases of patients getting the disease years after the gadolinium exposure, and there are two cases -- not in the highest impact factor journals, but there are two cases where patients received solid organ transplants, and they had no history of gadolinium exposure, and yet, they contracted what looked like nephrogenic systemic fibrosis.

These patients that received solid organ transplants, they don't know if the donors were exposed to gadolinium, and that's one of the first thoughts that comes to my mind because if

dechelation of gadolinium, if that is an important part of this mechanism, and that hasn't been proven -- if that's an important part of the mechanism, then it is frightening to me that you just need a few atoms of gadolinium to be freed in order to precipitate a profound incurable systemic disease that affects the brain, it affects the skin, it affects all these organs that have been analyzed by autopsy. That's about it.

Does that answer your question?

DR. APPLEGATE: Thank you.

DR. HERSCOVITCH: Dr. Marzella, do you have a comment?

DR. MARZELLA: Yes. You raised a number of important questions. I think that the susceptibility of pediatric patients to toxicologic effects of gadolinium agents is an important concern that we are asking for the committee to comment on.

To the extent the experience with the clinical manifestations of NSF do not suggest an association with pediatric patients, the agency has

also requested that manufacturers conduct studies comparing juvenile animal models and adult animal models, and these are still in infancy.

Our concern initially began because of concerns about potentially increased exposure due to renal handling in these patients, in juvenile, in young pediatric patients. So the concern about increased exposure based on pharmacokinetic data has not panned out. We also haven't seen any evidence of increased susceptibility to fibrotic responses in juvenile versus adult animal models.

Now, we are also asking sponsors to do neurologic function testing because of the potential concerns about retention of these metals in the developing brain.

I should add that the data so far are negative, that we don't see any evidence of functional or behavioral abnormalities.

DR. HERSCOVITCH: We have a few more minutes for questions. Dr. Toledano?

DR. TOLEDANO: Thank you. It's Dr. Toledano. I have a question for Dr. Balzer at

Bayer.

Biologically, I'm a statistician, I'm thinking about these metrics, and we've seen these numbers after you have more than 5 doses. Does that number have the same impact independent of timelines? So somebody who is being monitored during oncology is having these doses rapidly and somebody who has MS is getting annual scans.

Do we know?

DR. BALZER: Well, first of all, these are all retrospective studies, except I think, three or four of those 39 that have a prospective component. So that is a factor that was not really controlled in any of those studies. Sometimes the time span between the injections is years. Sometimes it's within a few months.

I could not identify from our search in the literature a clear pattern here. The only association that we could find is that in patients with renal impairment, you may see it at a lower number of injections than in the other patients. But that's, I think, all we can conclude so far.

DR. TOLEDANO: Thank you.

DR. HERSCOVITCH: Dr. Brent?

DR. BRENT: If I might, Jeffrey Brent, and please indulge me, I have three questions. Hopefully, they'll be easily answered.

The first one, I'm going to address this to the industry group in general. The first one is what extent have you looked at any animal model experiments where you've done administration of free gadolinium, not associated with a contrast agent, to get an assessment of what that effect would be?

The second is, do you see any reasonable analytical technique that would be very helpful for determining whether gadolinium that is present, is in its free form or in its chelated form or bound to a contrast agent?

The last one is a little bit different. I'm aware of the European action where they basically suspended a number of linear agents and restricted the others to hepatic indications. By doing that, do you think that they have created any diagnostic

gap, any circumstance where there might be a diagnostic need that would not be fulfilled by those kinds of restrictions and suspensions? Thank you.

DR. BALZER: Maybe I'm starting, and I probably forgot the second question. I will refer the third one to our preclinical --

DR. HERSCOVITCH: Brief answers, please.

DR. BALZER: -- just quickly, in Europe, that was one of the key questions.

DR. MARZELLA: If I may interrupt, I think this is more appropriate perhaps for the discussion period. We are focusing here on clarifying questions, and I think instead of asking ad hoc, we should reserve this for a broader discussion, if you don't mind.

DR. BALZER: I don't mind, but then I hand over to for the preclinical question to my colleague.

DR. MARZELLA: Sure, yes. Thank you.

DR. PIETSCH: Coming to your first question regarding the toxicity of gadolinium, in the early

days of the development of our contrast medium, there were, for example, experiments done regarding gadolinium EDTA. Here we know also from tests with gadolinium chloride that the stability is the most important key. After immediate IV administration, disassociation was observed, and gadolinium phosphate particles were built. This afterwards was taken up by a macrophages in the liver, for example. The system has taken up those particles, and afterwards, the focal liver necrosis was observed. That was the early effect of stability might be a very important role here.

Therefore, it was clear to have a very efficient but also very tolerated contrast media, the chelation is the most important key here to increase the tolerability. Maybe that answers your first question.

DR. HERSCOVITCH: Yes, please?

DR. EVANS: Hello. My name is Paul Evans. I am head of nonclinical science at GE Healthcare.

With respect to your first question, toxicity of gadolinium chloride, indeed that was

included as a control in some of our development studies, and of course it's important to remember, I think, the bio-distribution of gadolinium chloride is very different to the GBCAs.

It very quickly precipitates in vivo, and it's taken up by the liver and spleen predominantly, and you do see some toxic effects there at certain doses and also in other tissues.

We are intending to include gadolinium chloride as a positive control, referring to a previous question, in our upcoming studies, particularly looking at neurological function and behavior in rats. So that will indeed provide a control for gadolinium in tissues but also may show some functional effects as well. And I thought it was a good comment to potentially include something that actually we know should impair neurological function.

Your second question on methods to look at the form of gadolinium, it's a very difficult question. I think it will take multiple different technologies and methods in combination. Some have

tried methods where you homogenize and sonicate tissue, and then you produce a sludge that you put down a color chromatography and try and separate and see what form that's in. But I think it's important to remember here you're destroying tissue architecture. You're lysing cells. You're exposing the gadolinium presence to compartments it wouldn't usually see. So it's very prone to artefactual results.

We have some work ongoing looking at new methods, mass spectrometry methods where you could look at the form on tissue slices in situ. There's a technology called lesser liquid extraction surface analysis, which is much more gentle, and we're hopeful that a combination of those methods might add to the knowledge in this space.

DR. McDONALD: Very briefly, we also independently are working with the Department of Energy and its spectroscopy technique to do the same because destroying the tissue creates an artefact that may not reflect reality. So we're looking for a way to do it in tissue to avoid that

confounder.

DR. HERSCOVITCH: Thank you, Dr. McDonald.

Yes, please?

DR. FRANK: My name is Richard Frank with Siemens Healthineers. I have three questions, one for Dr. Wagner, one for industry, and then one for FDA.

The question for Dr. Wagner is, you recommended stratifying patients according to risk, and you have recommended the development of biomarkers. In the absence of any known actual clinically relevant effects, how would you direct that research, and how would you propose to stratify patients according to risk?

DR. WAGNER: That's difficult. I'm studying nephrogenic systemic fibrosis, and so we've got two risk factors, renal insufficiency and gadolinium exposure. There have to be --

DR. FRANK: I mean relevant to the brain retention, yes.

DR. WAGNER: Relevant to the brain retention, I'm approaching it from a different

state. We don't know what the toxic effects are of this retention, if there are any. On my side, though, I know exactly what the clinical effects are in systemic fibrosis, and there are risk factors out there that have not been defined. Like I mentioned earlier, it's going to be impossible to find using observational data or retrospective patient data because the numbers of cases are just so low.

I think that disease is also under-recognized clinically. To diagnose nephrogenic systemic fibrosis, it's very complex on a subjective scale of clinical signs and symptoms, and that goes along with a histological matrix.

I think what has been presented today shows that there seems to be a subclinical type of -- and I hate to say nephrogenic systemic fibrosis, too, because we're finding these systemic effects in animals with normal renal function. There's more evidence that there's some kind of shared pattern, especially when the symptoms cluster with skin complaints.

Now, there are other risks out there, which is why some patients that receive just a single dose contract the disease, and we've got dialysis patients who've received 6 doses of gadolinium contrast, and they don't acquire the disease. So there's more out there.

DR. FRANK: But in terms of the matter --

DR. HERSCOVITCH: Excuse me. Could I just request that the answers be relatively brief. We're falling a bit behind in time.

DR. WAGNER: I'm sorry.

DR. FRANK: I didn't mean to explore the NSF situation but to identify whether there were any clinical risk factors that could be identified relevant to accumulation in the brain, and it would appear it's only related to the number of doses.

DR. WAGNER: That's not my area. I can't say.

DR. HERSCOVITCH: We have two folks on the phone who would like to pose questions.

DR. FRANK: Peter, I'm sorry. I had two other questions, if I could.

DR. HERSCOVITCH: I'm sorry. If they could be brief with very brief responses.

DR. FRANK: So this question has to do with the hypersensitivity reaction. I understand that each of the industry reps have highlighted the occurrence of hypersensitivity reactions. Is there any way to predict who might be at risk of that, or is it only after they've had a hypersensitivity reaction that they would take this into account?

DR. HERSCOVITCH: In brief, and remember, we're focusing on the issue of gadolinium retention at this meeting, not broader assessments.

DR. McDONALD: Bob McDonald, Mayo Clinic, and apologies for the slight diversion, but hypersensitivity reactions are a very big deal because they are a known risk. Although rare, there are known differences. This was codified better in the last few weeks with that recent publication.

There are some predictors like previous allergic reaction and atopic disease that can be predictive, but the truth is this is yet another

area where we don't know that much because we don't quite understand the mechanism because we call them allergic-like anaphylactoid reactions because the mechanism is not clear.

But I would submit those differences still matter clinically because even a mild reaction and different system can logistically make huge changes to how we practice medicine. If people are having more of those mild reactions, we have to stop the scan, evaluate them, do --

DR. MARZELLA: I think we're getting a little bit off topic. We do have to restrict our questions to the gadolinium retention issue, please.

DR. FRANK: The third question has to do with the point Guerbet made in coming to the FDA and proposing label changes. It seems like all the industry have been responsible in pursuing this question from a scientific and clinical standpoint, but one of them has actually changed the label.

Was there anything unique about that particular product, or was there anything unique

that led to the change for the one compound and not the others?

DR. MARZELLA: Maybe I can address that. It's a question of timing. I think that companies can make labeling changes any time that they choose to do so, but given the timing of this advisory committee, I think the FDA as well as companies thought that in the interest of gaining consistency and being able to factor in the advice that we'll receive at the advisory committee, that it would be better to delay any changes until we've heard the discussion today.

DR. FRANK: Thank you.

DR. MARZELLA: If I could go back, I'd like to go back to the issue of assay sensitivity. I think that's independent on what the specific positive control would be, and I would think that gadolinium chloride would be a terrible control to try to have.

Markers of susceptibility I think are very critical. It seems as though, based on the NSF experience, that the existence of the exposure is

one factor, that the presence of renal failure is another factor, but they're not sufficient. There's something else that accounts for this susceptibility. So Dr. Wagner's research is very important because it shows the potential for identifying markers that could suggest increased sensitivity.

The other point I would like to make is that it's not clear that the systemic fibrogenic reaction is going to be the same mechanism, which would be affecting brain changes, whatever they might be.

DR. HERSCOVITCH: Thank you very much.

I'd like now to ask Dr. Bolch, who is on the phone, to ask his question, please.

DR. BOLCH: Yes. This is Wes Bolch, University of Florida. Just a quick question. In the briefing documents, it was mentioned the deposition to bone. Can someone comment on specifics? Is it bone surfaces, active marrow, adipocytes? What is the implications for bone deposition?

DR. HERSCOVITCH: Would anybody from industry care to answer that clarifying question?

Yes, please identify yourself.

DR. DESCHE: Pierre Desche, I'm calling Dr. Eric Lancelot to answer that question.

DR. LANCELOT: Good morning. I'm Eric Lancelot, head of pharmacovigilance. It's true that in the scientific literature, there are some preclinical studies showing accumulation in bone of gadolinium.

In fact, we performed a meta-analysis of all these published papers showing that this gadolinium concentration in bone is actually decreasing over time, so in a time-dependent manner. But there are clear differences between different contrast agents, depending on their stability with linear agents remaining much longer in the bone than the macrocyclic agents.

There are also some reports, some studies suggesting that you may also find gadolinium for some days and weeks or so in the bone marrow, and probably the kinetics of gadolinium washout from

the bone marrow is following more or less the one in the mineral bone. I hope it answered this question.

DR. SPINAZZI: This is Alberto Spinazzi from Bracco. Deposition in bone is still a complex issue. Again, starting from what has been seen in human patients, if you look at the short term and you compare the agent that causes the highest level of retention, which is Omniscan, and compare that to the agent that causes the lowest level of retention, ProHance, short term, 3 or 4 days after injection, data shows that there is a difference, so 3 times higher levels following a standard dose of Omniscan.

When you go to eight years later, the levels of gadolinium retained in bone after ProHance and after Omniscan are identical. When you look at animal data and you look to see retention in bone, this clear demarcation between the linears and the macrocyclics is not there, especially from the studies that have been mandated by the FDA now to study in juvenile animals.

I guess we have been the first company to also study the effects on the brain, at least this is based on my knowledge. It's easy to make claims like the ones that have been made. It's way more complex, the retention.

Also, the comment was made that you have five administrations, and then you see a change in signal intensity. That is not correct at all.

DR. HERSCOVITCH: Thank you.

We have a question from Dr. Weisman on the phone. Dr. Weisman, please?

DR. WEISMAN: Hi. Michael Weisman from Los Angeles. I have a question predominantly for Dr. McDonald, and that has to do with the postulated mechanism in NSF has to do with the CAT space and the narrow pathways.

Have those pathways been examined in the subclinical animal models? Are they activated at that level?

DR. McDONALD: That's a great question, and again, keep in mind this is at 80 equivalent human doses in rapid succession, which could change the

equilibrium of what's going on in the organism. We have looked at it for the kidney, but we have not really expanded that out to other tissues.

We really didn't think to do that in the brain because it's a G0 organ. It's not cycling through the cell cycle, at least the neurons aren't. But that's a great thought.

DR. WEISMAN: Just a follow-up to that, though, if it's possible to explain some of the heterogeneity that you're seeing in the clinical findings, could there be other environmental triggers that might affect the brain that could in fact produce clinical findings or not?

DR. McDONALD: Absolutely, that's a possibility. I think Dr. Wagner summarized this best. This is very nascent work. We're taking single studies and drawing massive conclusions, and I don't think we're there yet in terms of chemical stabilities and macrocyclic versus linear. There's just not a lot of data, and that's a great observation.

DR. WEISMAN: Thank you.

DR. HERSCOVITCH: Thank you, everyone, for these very thoughtful questions and replies.

We are a little bit behind, but we will take a 10-minute break. So we will reconvene at 10:15, and reminder for members of the committee not to discuss this during the break.

(Whereupon, at 10:04 a.m., a recess was taken.)

DR. HERSCOVITCH: Can everybody please be seated? We will now proceed with presentations from the FDA, and I know they will all keep to time. Our first speaker is Dr. Croteau.

FDA Presentation - David Croteau

DR. CROTEAU: Good morning. My name is Dave Croteau. I'm an adult neurologist by training, and I'm a medical officer in the Division of Pharmacovigilance in the Office of Surveillance and Epidemiology.

I will be covering today the results of the FDA Adverse Event Reporting System, or FAERS, and the medical literature review on adverse events with gadolinium retention after exposure to

gadolinium-based contrast agents abbreviated as GBCA. My presentation will be followed by Dr. Steven Bird, who will discuss epidemiologic considerations, and Dr. Patty Greene, who will present GBCA utilization data.

What I would like to do over the next 20 minutes is to present the purpose of our review. I will then outline the methodology used. The results will consist of data identified in FAERS and in the medical literature, including case reports, case series, and other report types. Two case report examples will be provided, and lastly, I will wrap up with a discussion, including an interpretation of the data and a summary of the findings.

The primary purpose of our review was to identify and describe clinical adverse events in patients with gadolinium retention after GBCA exposure without reported renal impairment. A secondary purpose was to evaluate the supporting medical literature available on gadolinium retention. Please note that nephrogenic systemic

fibrosis, which occurs in patients with renal impairment, and hypersensitivity reactions are not addressed in this review as they are well characterized adverse events or reactions in the various GBCA labels.

Before moving to the methodology, a word on FAERS. So FAERS is an electronic database of spontaneous reports for human drugs and biologics. Manufacturers have specific reporting requirements. However, reporting by patients, consumers, and healthcare professionals is voluntary. They can either report to the manufacturer who in turn reports to the FDA or directly to the FDA. That direct reporting represents approximately 5 percent of all reports received in FAERS.

Since 1968, there have been more than 14 million reports, including duplicates, and in 2016 alone, there were over 1.6 million new reports in FAERS.

FAERS is a drug safety surveillance tool with many strengths, which are outlined on this slide. I want to highlight that FAERS is most

useful for detecting events with low background rates, clinically serious events, events that occur shortly after drug exposure, and early in the postmarketing phase. Based on these strengths, FAERS may not be the best method to assess many of the adverse events identified in our review, as I will discuss later.

While FAERS has a number of strengths, it also has its limitations, which are outlined on this slide. I will go over some of those limitations in the discussion section, more specifically, variable report quality, some reporting biases, and potential confounding effect of intended drug indication. It's also important to mention that a causal relationship between a drug and an event is not required for reporting to the FDA.

Now the methods. FAERS cases were identified by selecting cases reporting gadolinium retention with or without clinical adverse events. Gadolinium retention evidence criteria were fairly liberal, including any body fluids or tissues with

detectable gadolinium. No quantitative data was required. Inferred retention based on specific brain MRI abnormalities was also used as evidence of retention.

The medical literature was reviewed using PubMed and EMBASE search engines. The search strategies included keywords relating to clinical manifestations reported in conjunction with gadolinium retention already published in the medical literature, as well as hypothetical clinical manifestations based on brain retention patterns.

A total of 139 cases of gadolinium retention were identified. The FAERS search identified a total of 41 cases, and the medical literature searches, 98 cases. FAERS included 34 cases with clinical adverse events and 7 cases without clinical adverse events.

Among the 98 medical literature cases, only 5 had documented supportive laboratory evidence of gadolinium retention, meaning that gadolinium measurement was performed by the publication

authors or outside laboratory reports were collected and verified by the publication authors.

One was reported as a single case report and 4 as a case series, 93 as unverified self-reported laboratory evidence of gadolinium retention. One was published as a single case report, and 92 were from two online surveys posted to a private blog on a gadolinium toxicity support group website and a public gadolinium toxicity Facebook page.

Even though published in peer-reviewed journals, those two surveys could have been excluded from the review given the nature of the data provided, but it was felt important to include all the data published, given the overall paucity of data on the topic.

It's also important to point out that the bulk of the medical literature cases, that is, 96 out of 98 cases, were authored by the same UNC Chapel Hill radiology group, leading to possible duplicate cases and an actual total number of medical literature cases lower than 98.

This table shows the aggregate case

characteristics. A substantial number of patients or cases had unreported data, as shown in the first column, due to inclusion of the results of the two online surveys mentioned earlier.

The predominant characteristics are in bold. There was predominant U.S. reporting with the majority of reports received after 2014. Important to consider in the interpretation of the year of initial report is the increasing awareness of the potential problem, the event of gadolinium measurement assays, and change in GBCA landscape.

There was predominant consumer reporting representing approximately two-thirds of all FAERS cases. The age range was wide with the median at 49. Female sex, and Caucasian race were preponderant.

Brain was the most frequently imaged body region. Neoplasm or screening for a neoplasm was the most common indication for GBCA administration, although the majority of patients had no reported data for those two characteristics. Urine was the most frequently used body fluid to demonstrate

gadolinium retention.

Patients had typically multiple adverse events with a range of adverse events with a range of 1 to 39 and a median of 7 adverse events per patient. Adverse event onset was typically within 6 weeks of the last GBCA exposure with the majority developing adverse events immediately after the last GBCA exposure.

Those time intervals may be misleading as patients may have had one or more MRI with GBCA prior to the index or the so-called last GBCA exposure. However, that's how most of the data are reported. Adverse event duration at the time of the report ranged from 1 month to 9 years with a median of 5 months.

This graph shows the number of patients with reported clinical adverse events and/or gadolinium retention by GBCA type and class. Linear GBCAs are located in the pink or purple shaded area, macrocyclic in the blue shaded area, and multiple, mixed, unspecified, or unknown GBCAs in the green shaded area. The medical literature cases are in

blue, and the FAERS cases in orange. The linear and macrocyclic GBCAs are in increasing order of thermodynamic stability from the top down.

While the majority of patients with clinical adverse events received linear, multiple, unspecified, or unknown GBCAs, only a few received exclusively macrocyclic GBCAs. Most patients seem to report clinical adverse events and/or gadolinium retention with the less stable GBCAs. However, all those findings may need to be considered in light of a number of factors, including drug utilization data, which will be discussed in the last OSE presentation this morning.

This graph shows the number of patients by adverse event clinical category with medical literature cases in blue and FAERS cases in orange. Most patients experience more than one clinical adverse event, often falling in multiple clinical categories. While clinical adverse events identified lack a consistent phenotype, some clustering was observed around pain syndromes, neurological, cutaneous, and musculoskeletal

clinical categories. However, the clinical category "other" accounted for the highest number of adverse events. All those findings suggest heterogeneity of the clinical adverse events reported.

This table provides a more granular overview of the different adverse events by clinical category, including events occurring in at least 10 cases. Please note that some events were reported in cluster in the two online surveys and couldn't be broken down into individual adverse events.

The most common pain syndrome was limb or central torso painful sensations often characterized as burning. The most common neurological adverse event was clouded mentation. A number of cutaneous adverse events were reported, including skin discoloration, skin changes, and skin thickening.

Bone and joint pain were the most common musculoskeletal adverse events, and lastly, fatigue and asthenia, the most common adverse events in the category other. Again, those findings highlight

the heterogeneity of the clinical adverse events reported.

This graph shows the number of GBCA administrations before onset of reported clinical adverse events with medical literature cases in blue and FAERS cases in orange. A substantial number of cases in our review reported adverse events after a single GBCA administration, suggesting no apparent GBCA dose effect on adverse events, although the great majority had an unspecified number of administration.

Two case report examples are provided here to give you a flavor of the reports retrieved in our review. The first case is from FAERS. It is a 53-year-old Caucasian woman with normal renal function and reportedly unremarkable past medical history. Her GBCA exposure included 6 contrast-enhanced MRIs over 9 months with Gadavist, MultiHance, and Magnevist for a transverse myelitis indication. In addition, she underwent 3 contrast-enhanced MRIs with unspecified GBCA and indications over the preceding 9 years.

Her symptoms developed 2 months after the first of the six most recent contrast-enhanced MRIs and included bone pain, generalized muscle tightening, weakness, fatigue, and other unspecified symptoms. The only investigation reported included two 24-hour urine gadolinium measurements, which had detectable gadolinium above the referenced ranges provided by the respective laboratories.

The second case is from the medical literature. It is a 29-year-old Caucasian woman with normal renal function and past medical history significant for medullary sponge kidney. Her GBCA exposure was limited to one contrast enhanced MRI with Magnevist for suspected complex renal system served on ultrasonography.

Her symptoms developed with 24 hours of the contrast-enhanced MRI and included flu-like body aches and painful sensations characterized as burning, as well as sharp pins and needles involving her central torso and all four limbs. Later on, she developed clouded mentation, severe

headaches, and arthralgias.

The only investigation reported included one blood and one 24-hour urine gadolinium measurements one month after GBCA administration, and both had detectable gadolinium above the referenced ranges provided by the respective laboratories.

Her physical examination was reportedly unremarkable 2 months after GBCA administrations, and an outcome was provided 2 months as well after GBCA administration and included progression of the symptoms over days with subsequent reduction, although she remained with sporadic painful sensations and persistent clouded mentation, severe headaches, and arthralgias.

Given the concern around special populations, the number of cases in each population was examined. Our review included 2 pediatric cases, 3 geriatric cases, no pregnancy or lactation cases, and no hepatic insufficiency cases.

Given the potential concern of exacerbation of preexisting inflammatory conditions by gadolinium retention, those were also examined, and

only one instance of preexisting systemic inflammatory condition was identified, including pelvic skin xenograft rejection, ITP, rheumatoid arthritis, and unspecified autoimmune symptoms. This was only in one patient. In addition, one case had a preexisting inflammatory neurological condition reported as encephalitis, which was not otherwise specified.

Despite clustering around certain clinical categories, the marked heterogeneity of clinical adverse events reported makes interpretation of the data challenging. In addition, many factors may influence the interpretation of the data and may result in either an over- or underestimation of the importance of the problem.

An important factor is the self-reported information in most reports. The self-reported information in many but not all cases include assessment of the clinical adverse events by a healthcare professional and the laboratory results supporting gadolinium retention. Cases with such unverified self-reported information predominantly

originated from the published online surveys discussed earlier and some FAERS consumer reports.

In addition, alternative etiology investigation was generally not reported. For example, patients with certain pain syndromes should have been investigated for peripheral neuropathy. Another factor is the fact that adverse events reported could be symptoms related to MRIs study indication. That information was only available in a minority of cases. A good example is the FAERS case report example presented with transverse myelitis, which may result in some but not all symptoms reported such as muscle tightness and weakness.

Concordant site of gadolinium measurement and symptomatic body region, for example, cutaneous adverse events and a skin biopsy, would be best for characterizations of potential clinical and laboratory manifestations of gadolinium retention as well as causal association assessment.

A number of internet website and social media with interests in gadolinium retention exist,

mainly to report simulation. In fact, we have observed an increase from 5 percent to 50 percent in direct reports in FAERS. In addition, there was also a high proportion of consumer reports representing approximately two-thirds of all FAERS reports in our review. All those findings suggest a reporting simulation.

Lastly, although the potential clinical manifestations of gadolinium retention are not known, an insidious or deadly onset or nonspecific clinical manifestations would make those potential clinical manifestations challenging to recognize and link to GBCA exposure by patients and by healthcare professionals and may lead to an underestimation of the importance of the problem.

In summary, we acknowledge the growing concern for untoward effects of retained gadolinium within the lay public and the medical community. It is also important to acknowledge that clinical adverse events reported, although lacking a consistent phenotype, seems to cluster around certain clinical categories, including pain

syndromes, neurological, cutaneous, and musculoskeletal.

However, at this juncture, considering the totality of the data, including case reports, case series, and published online surveys identifying our review along with the data limitations outlined earlier, we are unable to determine a causal association between reported clinical adverse events and GBCA exposure. This being said, we are continuing to monitor adverse events reported in FAERS and in the medical literature for a potential safety signal linked to gadolinium retention after GBCA exposure.

Thank you for your attention. Dr. Steven Bird will present next on epidemiologic considerations.

FDA Presentation - Steve Bird

DR. BIRD: Good morning. My name is Steven Bird, and I'm a pharmacoepidemiologist at FDA. I will be discussing epidemiologic studies on the safety of gadolinium contrast.

We reviewed the literature and identified

two additional epidemiologic studies on the safety of gadolinium. The first study by Welk, et al. evaluated the associated between gadolinium contrast exposure and risk for Parkinsonism. This was a retrospective cohort conducted using administrative databases in Ontario covering 2003 through 2013. Patients 66 years of age and older were identified who had an MRI with or without gadolinium contrast for all imaging locations except the brain and spine.

The study observed a rate of 3.17 cases of Parkinsonism per 1,000 person-years following contrast MRI and a rate of 2.71 cases of Parkinsonism per 1,000 person-years following non-contrast MRI. The adjusted relative risk for Parkinsonism per additional contrast MRI was 1.04 and was not significant.

While this was a well-done study with a large sample size, its approximate 4-year average follow-up may not be sufficient for a potentially longer latent period anticipated in the development of Parkinsonism.

The second study by Ray, et al. evaluated infant and childhood outcomes following gadolinium exposure in utero. It was a retrospective cohort conducted using administrative databases in Ontario between 2003 and 2015. Among approximately 1.4 million linked mothers and infants, 397 were exposed to gadolinium during pregnancy. Stillbirth and neonatal deaths occurred among 7 pregnancies exposed to gadolinium contrast and in 9,844 pregnancies not exposed to MRI.

This study observed a 3.7-fold increased risk for stillbirth and neonatal death with gadolinium contrast during pregnancy compared to women not having any MRI during pregnancy. While well done, this study had a small number of exposed outcomes, was not powered for a comparison of contrast MRI versus non-contrast MRI, and needs replication.

An internal FDA study in the Sentinel distributed database evaluated use of gadolinium in a sample of 3.7 million pregnancies between 2008 and 2015. We identified 8,842 total gadolinium

exposures during pregnancy, which produces a rate of one exposure per 421 live-birth pregnancies. Sixty-four percent of all exposures were during the first trimester, a time period where women may not have yet recognized pregnancy.

The rate of exposed pregnancies in this U.S.-based study is approximately 8-fold larger than the rate of pregnancy exposure in the Canadian study by Ray, et al. FDA is evaluating repeating this study in the future.

The following discussion presents a brief perspective on design considerations and types of studies that may inform safety risks associated with gadolinium retention. In the context of gadolinium, the study outcome is likely the most crucial consideration.

All tissues may retain gadolinium. Gadolinium causes tissue fibrosis, and this creates a large number of potential adverse outcomes, possibly unpredictable in nature. Studying any specific outcome is resource intensive, typically requires a customized study design, and requires

validation to show the outcome can be accurately and completely captured.

We must also decide if more subtle outcomes such as cognitive function tests are sufficient or whether more robust clinical endpoints such as dementia must be evaluated. One logical approach to hypothesis generation is to identify patients who have reported adverse events from gadolinium retention. This could include questionnaires, focus groups, and clinical examination of patients with spontaneous reports of adverse events.

Furthermore, adverse outcomes presumably depend on dose exposure as expressed by the amount of gadolinium retained at the tissue level and over time. Focus should be placed on patient populations who required a multitude of MRIs for conditions unrelated to adverse outcomes under investigation.

Study designs must also take into consideration that dose exposure varies from one tissue type to another, from one type of gadolinium contrast to another, and over time post-

administration. Follow-up time is also a critical component for epidemiologic investigation. We do not know the latency for adverse outcomes for gadolinium, and studies with long follow-up are required.

As core principles, we should expect all studies to use the most rigorous methods possible, present results in a fully transparent manner, enable the independent verification of study results, and conduct research ethically by protecting the rights and welfare of patients.

As an additional guide to thinking, OSE reminds the panel members that an informative study should include sufficiently large and susceptible study populations with adequate exposure to diagnostic gadolinium followed in settings that capture relevant health outcomes. We recognize that most sponsors have initiated hypothesis-generating assessments to inform future studies, but FDA has not yet received any formal proposed studies for review.

As we consider future studies, we ask the

panelists whether we can resolve health concerns related to gadolinium retention by relying solely on opportunistic data. These data sources are compiled and collected for reasons unrelated to the primary study question. Examples of opportunistic data sources often used to address drug safety concerns include administrative healthcare claims databases and electronic healthcare records, as well as ongoing prospective observational studies.

Administrative database pre-2006 may be uniquely suited to study patients with chronic kidney disease who may be more susceptible to the study of gadolinium adverse events. Databases with good mother-baby linkages may provide the best source to study the safety of gadolinium in pregnancy.

Ongoing prospective observational studies are likely the best opportunity for long-term follow-up if they capture the right information for a given study question.

Opportunistic data sources often carry advantages related to the number of persons

immediately available for study and the amount of time required to complete. However, these opportunistic data sources vary substantially, not only in data quality but also in the availability of data elements essential to the research question.

In contrast to opportunistic data sources, new prospective observational studies designed for the study of gadolinium retention could be a good avenue to identify and study high-risk patients who require continued gadolinium contrast scans. This could be conducted with parallel arms for enrollment by each sponsor in populations including women with breast cancer and children with multiple sclerosis.

While these studies can provide valuable information, their conduct will be lengthy, and this information will not inform regulatory decisions at the present time.

Finally, randomized control trials are the gold standard for clinical evidence, but ethical and feasibility requirements need to be taken into

consideration.

With respect to direct evidence of harm to health from gadolinium retained by patients with normal renal function, conclusive data are lacking. Focus on highly exposed patients may provide insight on to the safety of gadolinium contrast. Vulnerable populations and pregnant women also require special attention. The desire for perfect or ideal studies should not delay execution and interpretation of feasible studies. However, all studies must be evaluated in the context of their limitations.

Finally, a multitude of studies are likely required to address current concerns with gadolinium retention, and there is no guarantee of definitive answers in the near term.

Now Patty Greene will be presenting data on the utilization of gadolinium.

FDA Presentation - Patty Greene

DR. GREENE: Good morning. My name is Patty Greene, and I'm a drug utilization analyst in the Division of Epidemiology, Office of Surveillance

and Epidemiology. I will be presenting data on U.S. sales of gadolinium-based contrast agents from 2006 through 2016. The purpose of this presentation is to provide a descriptive analysis of U.S. trends in the use of GBCAs by type since the last advisory committee meeting in 2009 and to provide context to other information you will hear today.

Let's start with the description of the data source used. We used sales data as a surrogate for use because it provides nationwide trends in the type of GBCA, that is, macrocyclic versus linear. The database was used to measure the number of packages sold from manufacturers to hospitals and clinics nationwide is provided here. Please note that U.S. sales are not a direct measure of patient utilization, and demographic information is not available.

This graph shows that total sales of GBCAs range from 7.5 to 8.8 million packages sold annually. Since the last advisory committee meeting in 2009, sales of linear GBCAs accounted

for 94 percent of total sales as represented by the blue bar. However, by 2016, sales of macrocyclic GBCAs increased to account for 51 percent of total GBCA sales nationwide.

Next, we examine sales to pediatric specialty facilities. This database was used to measure the number of packages sold from manufacturers to a sample of 50 pediatric specialty hospitals and five pediatric clinics in the U.S. This database does not include a national estimate of utilization or demographic information.

Of the sales for manufacturers to 50 pediatric specialty hospitals and five pediatric clinics in the U.S., sales of linear GBCAs, as represented by the blue line, accounted for 98 percent of total sales in 2009. However, trends reversed sharply in recent years. By 2016, sales of macrocyclic GBCAs accounted for 82 percent of sales while linear GBCAs accounted for 18 percent of sales.

In summary, national trends show an increase in the use of macrocyclic GBCAs and a decrease in

linear GBCAs to a nearly evenly distributed market share by 2016. In 2016, sales to a robust sample of pediatric specialty hospitals suggest a higher proportion of macrocyclic GBCA use in this vulnerable population compared to trends nationwide.

Finally, I would like to comment that in the context of all the information you will hear today, use of macrocyclic GBCAs is increasing in the U.S.

The next speaker is Karen Bleich from the Division of Medical Imaging Products.

FDA Presentation - Karen Bleich

DR. BLEICH: Good morning. I'm going to give a brief overview of the highlights of the emerging science related to gadolinium retention. Please note that most of the studies here are published and unpublished studies without a review of the primary data by the FDA. I'm also going to talk about the regulatory evaluation of the GBCAs in terms of NSF and gadolinium retention.

We're all familiar with the remarkable observation made by Kanda and others in 2014 that

the increased signal intensity in portions of the brain related to prior GBCA administration, and shown here on the right is the increased signal in the dentate nucleus.

It was reported in the context of the patients who received multiple doses and just of the linear agents, as we heard earlier this morning. Previously, it was believed that the gadolinium agents did not cross the blood-brain barrier, so the next step was verification because there are other known causes of this imaging finding.

In 2015, human autopsy studies confirmed the presence of gadolinium in the brain, and we saw this earlier today. This is Dr. McDonald's study, and we can see that in this autopsy study on the Y-axis in the top graph, there's an increase in the signal intensity in the dentate nucleus as the total Omniscan dose on the X-axis increases. On the bottom graph, the amount of gadolinium found in the dentate nucleus on autopsy increased as the total Omniscan dose increased.

At this point, the FDA released a drug safety communication stating that the FDA was evaluating the risk of brain deposits with repeated use of GBCAs. The EMA took similar action at this time and also removed from the product labels the statement that GBCAs do not cross an intact blood-brain barrier.

How do we evaluate the issue of gadolinium retention? In response to NSF, the GBCAs were risk stratified based on this list of parameters and risk mitigation steps were taken that allowed for the continued safe use of GBCAs. We're going to look at this same list in terms of gadolinium retention.

The first two parameters refer to how tightly the gadolinium ion is bound to the chelating agent, and we have already heard a lot about this, this morning. We don't know whether or not it relates to toxicity, but we do know that there are differences between the individual GBCAs in terms of these parameters.

Gadolinium ion is known to be toxic in

biologic systems, and some of the toxicity is listed here, and I'll just highlight that it's a potent calcium antagonist.

In general, the linear GBCAs are less stable than the macrocyclic GBCAs, but there are two important points here. The first is that the intrinsic stability is more complicated than this simple list, and even the ordering of some of the agents could be debated. The second is that the intrinsic stability does not necessarily reflect comparative toxicity within the complex in vivo environment.

We also heard some discussion on the in vivo gadolinium disassociation kinetics, and we saw this study earlier as well. Basically, each GBCA product was incubated in human serum over 15 days, and a percentage of released gadolinium from the GBCA was measured, as shown in the Y-axis.

We can see the Optimark and Omniscan had about 20 percent disassociation in human serum at day 15, and if we look on the right, the ionic liner agents had about 1 to 2 percent

disassociation. For the macrocyclic agents, disassociation was not demonstrated in this study. And again, this comparative disassociation data may or may not relate to comparative toxicity within the in vivo environment.

The question in terms of gadolinium retention is, does this intrinsic stability correlate with gadolinium disassociation in the setting of retention? And the answer is we only have limited information about this, and I'm going to come back to it later.

Moving on to the nonclinical evidence of toxicity, there has been no histopathologic evidence of toxicity in the animal brain after repeated high doses of GBCAs. So I've highlighted here a Bayer study where the rats received very high doses and the histologic analysis of the brain demonstrated no abnormality.

In addition, there have been no behavioral or neurological abnormalities detected in the completed studies in rats, and highlighted here is the Bracco study where the juvenile rats received

very high doses and the behavioral and neurologic testing was normal. And I'd also like to point out that as part of the NDA review process, all of these products had CNS safety studies with no safety signals demonstrated.

Toxicity has been demonstrated in the skin of animals with normal renal function after Omniscan and Optimark.

Moving on to the clinical evidence of toxicity, in terms of the published human autopsy studies to date, there has been no histologic evidence of toxicity from gadolinium in the human brain. As we just heard, the pharmacovigilance and epidemiology reviews have not defined clinical signs or symptoms related to GBCAs.

We also heard the reports of patients with symptoms, including pain, skin changes, and clouded mentation. Certainly, it's plausible that these symptoms could be due to GBCA administration, and further investigation is needed.

There have also been reports of gadolinium-associated plaques. These are typically

characteristic skin findings seen in late phases of NSF, but there have now been three reported cases where the patients did not have NSF, and one of those three cases did not have renal disease.

When we consider the clinical evidence of toxicity, it's important to bear in mind the context of clinical use, and this has already been stated. But there have been many, many doses of GBCAs administered over several decades, and they provide essential information.

In terms of NSF, it was clear that the susceptible patient population was those with renal disease, but in considering gadolinium retention, we don't have a defined syndrome, so we don't have a defined susceptible patient population.

We can, however, consider populations who may receive a higher lifetime dose such as children and those with chronic conditions. We can consider situations in which patients might have longer exposure times such as renal impairment or in the setting of fetal recirculation. And we also note that there may be an increase of an immunologic

reaction with the retained GBCA in the setting of inflammatory conditions.

With NSF, the FDA was able to determine the comparative risks between the different GBCAs based on these critical data points, but for gadolinium retention, there is no known safety margin. So in making regulatory decisions, we have to consider the comparative exposure to gadolinium caused by each GBCA to evaluate the theoretical risk of the exposure.

So we're going to add to our list comparative exposure to gadolinium from each GBCA, and we are going to consider briefly which agents, where are each of the agents retained, how much, for how long, and in what form.

Before we do that, a few notes. Again, this is a developing science, and these are preliminary studies, and they haven't been reviewed by the FDA. Also, the highlights presented here do not represent definitive assessment of the comparative exposure from each GBCA and are not meant to support cross-product comparisons. Complete

characterization has not been done, and additionally, it would not be unexpected for new data or conflicting data to be presented to us in the future.

I also want to note -- and this is similar to what Dr. Wagner said -- while consideration of the comparative exposure to gadolinium from each GBCA is important, patient factors in addition to renal function are likely to play an important role in elucidating the clinical significance of gadolinium retention.

The first question was which agents enter the brain? Initially, based on imaging, it was thought to just be the linear agents, but it was soon demonstrated that it was all of the agents. Again, this comes back to Dr. McDonald's study in terms of where. By imaging, it was thought initially to occur just in the globus pallidus and the dentate nucleus, but it was subsequently also demonstrated in the human brain in the thalamus and the pons. And here is a Bayer study in the rat brain where gadolinium was detected in all of the

sections of the brain.

If you look at the bar graph on the right, the tall bars in each section represent the higher concentrations seen with the linear agents Omniscan and Magnevist, and the short bars represent the macrocyclic agents ProHance and Gadavist.

Gadolinium is not only retained in the brain, as we know; it's been identified in all tissues tested in the setting of GBCA exposure. For example -- and we recently heard about this from the sponsor -- in 2009, gadolinium was detected in human bone samples up to eight years later. We also know that in 2010, the EMA asked sponsors to conduct a study of bone and skin retention, and this study is ongoing.

Again, I am going to show some of the highlights of the data, but it is not meant to allow for comparison between studies. For example, these are two studies performed in rats, but they had different doses, they were analyzed at different time points, and they're not meant to be compared. But the point is that the linear agents

seem to lead to greater gadolinium retention than the macrocyclic agents.

What I'm doing here is I'm taking that same data from the bar graphs on the last slide and just giving you the numbers so that we can look at the human context. The gadolinium concentrations are shown in nanomoles of gadolinium per gram in brain tissue on the left and in the cerebellum on the right.

In the Bayer study on the left, the rats received 80 times a human equivalent dose total, and in the Guerbet study on the right, they received 20 times the dose.

Here is the human autopsy data where we can see the concentrations found in human brain, and I want to note this was just the information from the dentate nucleus. For the human autopsy studies, the range of subjects are listed here in terms of how much gadolinium was found in the dentate nucleus.

There are a number of confounding factors with human studies. One is the number of GBCA

doses, and the other is the number of days since the last dose. This makes the point that most of the comparative retention data has been done using animal models in order to provide controlled data that is not possible in humans. But we can note that some of the concentrations in the human brain were higher than the concentrations that were measured in rats who were receiving very high doses.

In terms of how much gadolinium retention, this study also demonstrates that the retention in skin and bone is much greater than in brain, and we heard that earlier today. The same graph also demonstrates that the concentrations of gadolinium seen in the context of the linear GBCAs vary quite a bit outside the brain. You can see in the skin, the tall bar represents the linear agent Omniscan, and the short bar represents the linear agent Magnevist.

The next question is for how long is the gadolinium retention? This was a study in rats where after a high dose regimen, skin biopsies were

taken over the course of a year. The study suggests that the gadolinium clearance from the skin after the macrocyclic agents occurred at a much faster rate than for the linear agents.

If we look at the green shapes, we can see that at about day 24, they reach essentially the same concentration as the control animals, whereas if we look at the linears, which are the red, orange, and purple shapes, there seems to be a plateau phase reached at about day 60.

This may have implications for clinical care in the setting of knowledge of the washout for a patient who requires a second dose or a third dose in a short time period.

This is a similar study. This one is in brain instead of skin, and again we saw this, this morning from Bayer. But it demonstrates in the green bars that there was washout of gadolinium from the brain of rats between weeks 5 and 52 and less so for the linear agents in pink and red between weeks 5 and 52.

Back to Dr. McDonald's study, what do we

know about washout characteristics in the brain? In this human autopsy study, the brain gadolinium concentration in humans appears to be cumulative after Omniscan. So the more Omniscan that they received, the higher the gadolinium concentration was found. These were lifetime doses. We don't have this type of information for the other agents or for other body tissues.

What about in children? What do we know about how much and for how long in juvenile models? Again, this is very preliminary, and we're expecting additional juvenile studies. But this represents two different studies. The blue bar is MultiHance, and that was studied by Bracco, and the red bar is Dotarem, and that was studied by Guerbet, and the same protocol was followed for both of the studies.

Juvenile rats received very high doses, and then at day 1 and day 60, the concentrations of gadolinium in these tissues were measured.

I'm just showing here day 60 because at day 1, obviously, the concentrations were much higher.

But the point is here that we see that there is a difference in the amount of bone retention in the juvenile model between the linear agent MultiHance and the macrocyclic agent Dotarem.

The last question is, in what form? Has the GBCA disassociated? This diagram represents a compilation of the two studies we heard about this morning from Bayer and Guerbet where brain tissue from rats was separated into insoluble fraction and soluble fraction, and the soluble fraction was further separated by the molecular weight into two portions.

What's shown in italics here represents a supposition of what this represents, but the definitive characterization hasn't been done, and I'm just showing this because it makes some suggestions.

The insoluble fraction is probably gadolinium salts. The intact GBCA is probably intact GBCA, and the gadolinium bound to protein is what is thought the macromolecule represents. Again, the first form and the last form are

probably disassociated gadolinium.

How does this relate to the stability of the GBCAs? Well, for the most part, the macrocyclic GBCAs, most of the gadolinium was found in what is believed to represent this intact form, whereas for the linear agents, gadolinium was found in all three forms, suggesting that there is more disassociation of the linear GBCAs than the macrocyclic GBCAs in the brain. Again, we don't know the clinical significance of this.

For the regulatory response in 2017, there were no clinical consequences of gadolinium brain retention, and there was no histopathologic abnormality demonstrated in the rats after repeated high dose administration studies. So at this point, the FDA issued an additional drug safety communication stating that no harmful effects had been identified to date, but the review was ongoing and this meeting was planned.

Around the same time, the EMA concluded their review and recommended suspensions and use restrictions for most of the linear agents. We

don't mean to speak for the EMA, but the basis of their opinion seemed to rest on these factors among others, so I'm just going to review them: that there's a theoretical risk associated with gadolinium retention in the brain; that the clinical consequences could take many years to identify; that the concentration of gadolinium in the brain seems to be higher after the linear agents compared to the macrocyclics; gadolinium clearance from the brain occurs at a much faster rate after macrocyclics as compared to linears; and that there is greater disassociation of gadolinium from the linear GBCAs compared to the macrocyclics; and that clinically, the multipurpose GBCAs are interchangeable.

The FDA position is that we agree with their interpretation of the science for the most part in terms of what we know about comparative retention, although we acknowledge that it is very early data, but we have diverged in our regulatory approach.

That brings me to the summary of what we know about gadolinium retention. We know from the

chemical stability that the linear agents are more likely than the macrocyclic agents to release free gadolinium. We know that skin toxicity has been demonstrated in animals, but no toxicity demonstrated in the brain. We know that there is no definitive signs or symptoms or syndrome associated with GBCA retention, but we do know that the symptoms reported could plausibly be due to GBCAs.

In terms of susceptible patient populations, we would want to consider those who will be exposed to higher doses or experience longer exposure times and that there may be potential immunologic predisposing factors.

Finally, in terms of the comparative exposure to retained gadolinium from each GBCA, I want to just reiterate that this is preliminary data that hasn't been reviewed by the FDA, but it seems that gadolinium retention occurs everywhere from all of the agents. But there are differences in the amount, the length of time, and the form between the linear and the macrocyclic agents. We

do not have the data to characterize the individual agents, and it is important to note that without a defined safety margin, the clinical relevance of this comparative retention data remains unknown.

Thank you for your attention. I would like to introduce Dr. Anthony Fotenos, who is going to talk about endpoint sensitivity.

FDA Presentation – Anthony Fotenos

DR. FOTENOS: Good morning. Last speaker before lunch. Perilous. My name is Anthony Fotenos. I am a medical officer in the Division of Medical Imaging Products.

Many of the talks that we have heard this morning have been focused on recently acquired evidence regarding the safety of gadolinium retention. The focus of this talk is oriented more toward longer term research planning.

FDA recognizes that all GBCAs cause some level of gadolinium retention, meaning this is a safety issue that is here to stay even under a hypothetical 100 percent usage of the least retained agents.

We also recognize that the clinical consequences of gadolinium retention may be subtle or rare, that all untoward consequences are worthy of an intense research effort, especially because the spectrum of patients who receive GBCAs for diagnostic purposes is broader than for most therapeutic drugs and may range from critically ill to essentially healthy individuals.

This simple matrix further contextualizes our objective. Imagine you wanted to measure all potential GBCA reactions. You might think of each reactions as falling into one of these four boxes based on whether what you had to measure was well defined, ranging from yes on the top to no on the bottom; and whether when the reaction occurred was predictable, ranging from yes on the left to no on the right.

Essentially, the easiest to measure reactions fall onto the upper left A box, meaning well-defined and predictable, and the most challenging fall in the lower right D box. Box D delineates the focus of today's meeting.

In general, FDA's premarketing requirements for animal and human studies are best designed to catch acute safety issues on the left. NSF and MR signal intensity increases might be thought of as falling into the unpredictably timed but better defined C box. Indeed, these NSF and signal intensity issues came to light in 2006 and 2014, decades after the first-in-human GBCA study in 1983.

We also recognize the diligent efforts of the GBCA manufacturers and other investigators since 2006 to understand NSF and gadolinium brain retention, including the generally negative findings to date in terms of identifying histopathological reactions in animals and human brain autopsy studies. This morning, we also learned about some recently reported epidemiological investigations that have yet to identify any definite new retention-related safety signals.

So perhaps, it is now time to conclude that the relatively easier GBCA safety issues have been

accounted for in boxes A through C, but that begs the question of box D, requiring further clarification of what else we need to assess and when.

In short, an important objective of this talk is to consider some potential new directions, which we will refer to as steady design leads. Our hope is that entering these leads into discussion might help to steer forward-thinking conversation toward approaches to complement and build upon the foundational methods we have relied on historically to advance our understanding of GBCA safety. But first, a talk outline is in order.

We will start with a summary of the current state, and we will transition to our focus on steady design lead generation. We will end by outlining future approaches and general conclusions.

Let's start with a simple framing of our knowledge gap. How are the risks of gadolinium retention best characterized? Based on what we have learned in greater detail this morning, here

is a quick recap of what we know in reference to this question.

First, from FDA's surveillance and epidemiology reviews, we know that there is some clustering of adverse events from over 100 reported in patients with normal renal function, though a causal association to retention is not clearly established. GBCA usage patterns are changing.

Second, from our medical imaging review, we know that gadolinium retention is a class-wide issue, that retention occurs in other tissues more than brain, that it involves linear more than macrocyclic agents, that there's considerable variability in retention among the linear agents, and that Omniscan and to a lesser extent certain other linear agents have caused fibroblastic pathology in high repeat-dose GBCA comparison studies in animals with normal renal function.

Third, we know based on FDA's 2004 guidance on the development of medical imaging drugs that GBCAs are approved based on the assumption of single or infrequent use rather than chronic,

meaning that most repeat-dose studies are limited to animal testing over a time period measured in weeks. We also know that placebo-controlled parallel-arm clinical trials in humans are not required.

Nevertheless, premarket, hundreds of animal and dozens of human studies involving thousands of subjects must be reviewed before FDA will approve any GBCA for marketing. In addition, in the postmarketing setting, millions of patients have benefitted from GBCAs without reported adverse reactions since the first drug in the class was approved in 1988.

Fourth, based on completed and ongoing GBCA animal toxicology studies, we know that investigation of brain for initial GBCA approval was typically limited to acute observations, whereas more recent noncomparative repeat-dose studies in juvenile rats for certain GBCAs have evaluated cognitive, motor, and sensory functions and identified no safety signals.

That's what we know. The next slide is

about ongoing investigations with pending study results.

In the briefing documents and talks this morning, the GBCA manufacturers outlined several ongoing investigations with respect to heightened pharmacovigilance, GBCA-wide toxicokinetic studies in animals that include functional and neurological assessment, and human epidemiologic and database mining efforts. In addition, we are aware of one phase 4 prospective uncontrolled study to explore long-term retention of gadolinium in adult patients scheduled for orthopedic surgery with bone and skin sampling. FDA encourages these investigative efforts and remains eager to review their findings.

That's a summary of what we know and what we are learning. The next slide is about limitations.

Specifically, this table describes some limitations in our current understanding of gadolinium retention in the form of specific and actionable questions. Let's start with potential brain reactions. Have the most sensitive cognitive, psychomotor, and pathological methods

been adapted for studies of brain gadolinium retention?

Turning to potential body reactions, have symptomatic patients received systematic clinical evaluation, including centralized pathological analysis? Has recent progress in understanding gadolinium pathophysiology been translated into more sensitive endpoints compared to originally established criteria for NSF?

To the best of our knowledge, the answer to these questions is no. So now let's turn to how we might chip away at some of these limitations going forward.

Our general approach is to highlight study design leads from where investigators have looked for or found subtle safety signals caused by retention of gadolinium or related metals historically. This slide provides a quick overview of sources. Citations are provided for future reference for those interested in more detail, but suffice it here to say that the leads we will walk through next derive from studies of gadolinium or

related metals following direct exposure in humans or from studies of intravenous GBCA administration in animals.

First, however, an important caveat is in order. The next few slides show some examples of endpoints and design ideas, which we call leads, in reference to the potential adaption for studying gadolinium retention. These might or might not be applicable and are provided not as part of any regulatory recommendation but rather as something to consider.

Brain Study Design Lead 1 is of particular relevance here to us at the FDA. Lanthanum carbonate, trade name Fosrenol, is a therapeutic drug indicated to reduce serum phosphate in patients with end-stage renal disease. It was approved by the FDA in 2004.

Lanthanum and gadolinium come from the same lanthanide row of the periodic table, a row with the uniquely shared tendency for chemical interaction. Nevertheless, lanthanum carbonate and the GBCAs are, of course, very different drugs. A

GBCA is administered intravenously once per MRI. Lanthanum carbonate is taken orally with each meal.

Chemically, the gadolinium GBCA is complex with an organic chelate to maximize elimination. The lanthanum in lanthanum carbonate relies on high levels of fecal excretion to maximize elimination.

Despite these differences, the evaluation of the safety of lanthanum carbonate and the current safety issue of gadolinium retention share an important similarity because trace amounts of lanthanum were found to be absorbed via the gut and retained in the body, meaning FDA confronted many questions similar to those we face today but in a different clinical context.

For example, to win approval, the manufacturer of lanthanum carbonate compared cognitive function over a two-year period in patients randomized to the study drug versus standard therapy. Cognitive function declined in both groups as measured by a composite of five subdomains in the cognitive drug research battery. The results from one subdomain are shown in the

figure.

There were no significant differences in the rate of cognitive decline between Fosrenol and standard therapy, suggesting that adverse reactions caused by potential brain retention of lanthanum are not numerically worse.

I will return to this study design lead at the end of this talk when we cover approaches for evidence generation. It's also noteworthy that the manufacturer of lanthanum carbonate collected and analyzed several hundred bone biopsies as part of its premarketing evaluation and recently reported on a generally reassuring five-year postmarketing observational study of bone health.

Brain Study Design Lead Number 2 highlights a recent methodological advance for estimating cumulative gadolinium concentration in vivo without the need for invasive biopsy. This XRF approach has been helpful in characterizing subtle cognitive and functional neuroimaging consequences in response to retention of other metals because bone concentration may be more sensitive than blood

levels for chronic toxicological investigation.

Now let's turn from brain to body study design leads. We are fortunate to have as our invited speaker today Brent Wagner, an author of one of at least three recent reviews on gadolinium-induced immunological reactions in the body and a leading academic investigator in the field. Without stepping into the details, here are three take-home points.

First, gadolinium-induced immunological reactions are consistently phagocyte mediated and occasionally, perhaps as a downstream second hit, fibroblastic. There is definite variability between individuals in terms of immunological susceptibility.

Second, progress has been made since our NSF advisory committee meeting in 2009, both in understanding and in investigational treatments of several fibroblastic diseases, including NSF.

Third, we are optimistic that this progress can also be translated into more sensitive probes of potential adverse reactions in patients with

normal renal function. This leads into a discussion of our last design lead.

This one is framed in the form of a question since we have unfortunately not yet identified a study that aims to address it. The question is, can abnormalities established for immunological measurements in animal studies be translated into more sensitive probes for evaluations of potential body reactions in patients with normal renal function?

We offer this tentative list of candidate markers selected from published studies. A preliminary understanding is that the listed measurements tended to rank among the most sensitive in dose-response terms for phagocyte-mediated GBCA reactions compared to a multitude of other markers that have been explored.

Interestingly, these quantitative pathologies, cytokine, and extracellular protein measurements have generally been found to react to all tested GBCAs, including the least retained macrocyclics. This again highlights FDA's finding

that gadolinium retention is a GBCA-wide issue in which no agent stands outside of existing knowledge gaps. Even straightforward questions remain open such as the time course of these immunological reactions and their inter-individual variability.

As we wrap up, let's return to the question with which we started. How are the risks of gadolinium retention best characterized? Again, in the hope that this quick tour through current state and study design leads might help with study planning, the next slide provides an overview of approaches to evidence generation going forward.

In this table, we divide into descriptive versus analytical bins 9 examples of study designs that are ongoing, in the feasibility stage, or that we recommend be considered. The point isn't to step through this busy table cell by cell, but rather to highlight the deliberate step-by-step approach that the scientific community is following to understand the safety implications of gadolinium retention.

Ongoing descriptive approaches have

generally not identified new safety signals, though registry studies, particularly of symptomatic patients, should be considered for the potential to build on this foundation.

A central theme of this talk has been on the need to complement descriptive with more sensitive analytical approaches. This morning, we have learned about ongoing administrative, database, immunologic, observational, and prospective uncontrolled examples that are in the process of aligning with current needs.

FDA is also encouraged that some GBCA sponsors have indicated they are entering into the feasibility stage of planning prospectively controlled parallel-arm studies. We further encourage stakeholders to build on current momentum, including the lanthanum carbonate precedent introduced earlier, by also considering randomized and placebo-controlled prospective approaches.

Complementing descriptive with more sensitive analytical approaches raises several

considerations. For example, as part of further discussion at this meeting and of our questions to the committee, we will discuss registries and pharmacovigilance. Is there an additional role for prospectively controlled clinical studies? How might symptomatic patients be systemically evaluated and compared to patients studied prospectively?

How should prospective studies be powered, and how might prospective study protocols proposed by different GBCA manufacturers be integrated? FDA needs your feedback on this integrated approach to safety evidence generation.

Before concluding, however, we offer some general points for consideration regarding good gadolinium retention study design. With respect to in vitro studies, we recommend that investigators compare multiple GBCAs' concentrations bracketing in vivo exposure and exposure durations and also account for potential osmolarity effects when designing positive and negative controls.

With respect to animal studies, we recommend

that investigators aim to identify safety signals by prioritizing questions least amenable to human study such as the effects of retention on early neuro development; administer GBCA doses that span the full range of the dose toxicity curve from no to maximally tolerated effect; include positive and negative comparator controls; select maximally sensitive endpoints; extend dosing over a period of months for repeat dose studies; and compare endpoints both before and after drug-free washout periods and do not exclude sensitive species.

In particular, we note that the vast majority of safety research since the discovery of gadolinium-induced NSF in 2006 hinges on studies of rats and mice, suggesting a potential for overdependence, particularly if neurological GBCA reactions in these species extrapolate poorly to humans.

Moving from animal to human studies, we recognize that the most pressing knowledge gap requires learning how to characterize the risks of gadolinium retention. A strong argument can be

made that the issues of greatest concern cluster around subtle brain and pain issues that are uniquely human and therefore best addressed via studies in humans.

These should include neurological endpoints sufficiently sensitive to detect subclinical adverse reactions caused by retention of metals with known toxicity, endpoints more sensitive than NSF for potential body reactions, and maximum control over sources of confounding and bias.

Finally, FDA encourages all stakeholders to meet with us early and often for protocol discussions when GBCA safety studies are planned.

In conclusion, gadolinium retention safety is a priority for the MRI community and most importantly, for many patients in need of diagnostic evaluation. The focus of this presentation has been on gaps that remain between what we would like to know and do and between what experimental designs we might adapt and have.

We hope our discussion of study design leads might serve to point investigators in helpful

directions as their considerable progress accelerates. Regulators and manufacturers are aligned on understanding of available data, but consensus is lacking on implications for risk.

FDA awaits results from ongoing studies by manufacturers and the academic community, and ongoing and additional sensitive safety studies have potential to build on mostly reassuring evidence reviewed to date in order to shed more light on this important public health issue.

Finally, before I return to my seat and respond to any clarifying questions along with my FDA presenter colleagues, I have been asked to provide a summary of our questions for the advisory committee.

The committee chair, Dr. Herscovitch, will read FDA's formal questions into the record later this afternoon, but in order for everyone to have a bit more to chew on during lunch, here is a quick preview.

Question 1. How do you characterize the risks of gadolinium retention? In other words, FDA

has determined that benefit-risk is favorable for all approved GBCAs, but we have a new finding of gadolinium retention in general, and in the brain in particular, in patients with normal renal function associated with an unknown risk.

How is this unknown risk related to the known risk of gadolinium retention in certain patients with renal failure?

Question 2. Is there a causal relationship between retention and symptoms in patients with normal renal function?

Question 3. What investigations do you recommend to address knowledge gaps?

Question 4. FDA plans to address the finding of gadolinium retention in patients with normal renal function through labeling revisions. Is this plan premature, just right, or not enough? Thank you for your attention.

Clarifying Questions to Presenters

DR. HERSCOVITCH: I would like to thank the FDA speakers.

Now I'll ask the panel if there are any

clarifying questions for the FDA presenters. And we are running somewhat late, so please keep the questions as well as the answers as brief as possible, and I would like to just go around the table this way to seek questions from the panel.

Dr. Frank, do you have a question?

DR. LATOUR: Larry Latour, NINDS.

DR. HERSCOVITCH: Sorry. We'll start in order. Dr. Frank?

DR. FRANK: Dr. Bird characterized high-risk patients in the categories of pregnancy, breast cancer, and MS. I wonder how did she identify those patients as being at high risk.

DR. BIRD: I think a better clarification would have been highly exposed. So we know that certain populations require repeated scans over time, and these highly exposed populations may be the best avenue to study in the future.

DR. FRANK: Thank you.

DR. HERSCOVITCH: Moving around, please.

DR. HENNESSY: Sean Hennessy, I have a question for Dr. Croteau. I hope I'm pronouncing

that correctly.

Slide 13 shows different symptoms associated with gadolinium in patients without renal impairment, and I'm wondering if we know whether this distribution of symptoms would be similar if we were to look in patients with renal insufficiency. In other words, is it just quantitatively different in patients with and without renal insufficiency, or are the symptoms qualitatively different?

DR. CROTEAU: We haven't looked at the patients with renal insufficiency. The review excludes those patients to eliminate the background related to NSF. So that's something we could look into, but I don't have an answer for that.

DR. HERSCOVITCH: Dr. Latour?

DR. LATOUR: Larry Latour, NINDS. This is for Dr. Bleich.

It seems that there is a consensus that there is gadolinium accumulating. Is there a consensus on whether or not it's chelated and where in the brain, in which cells the gadolinium is?

DR. BLEICH: I wouldn't say there is consensus. There was preliminary data about disassociation in the brain that Bayer and Guerbet presented.

In terms of was it in the cells or not, I think the McDonald study analyzed that, and I think two patients, it was found within the glial cells, right? But for the most part, it's not. In fact, the entry into the brain may not be through the blood-brain barrier. It may be through the CSF.

Does that answer your question?

DR. LATOUR: Yes.

DR. HERSCOVITCH: Please.

DR. FURIE: Karen Furie from Brown. This is also for Dr. Bleich.

None of the models that have been proposed have a disturbed blood-brain barrier, and I wonder whether you would comment as to whether that would be an important element to consider.

DR. BLEICH: Right. As a radiologist, the brain doesn't enhance unless it has a tumor or another abnormality, and then it only enhances

right there. So it doesn't cross the blood-brain barrier in the sense of enhancing the way the liver or the spleen does.

Remind me of the end of your question.

DR. FURIE: Just whether studying this in the setting of an impaired blood-brain barrier might affect the penetration and doses in the brain and affect the rates of retention or potentially the subsequent complications.

DR. BLEICH: Yes, I think that for the human autopsy study, many of the patients had brain diseases, and that could be confounding because the blood-brain barrier is disrupted, whereas in the animal studies, they did not.

DR. HERSCOVITCH: Any other questions here? Dr. Vaughan?

DR. VAUGHAN: Bill Vaughan. To Dr. Bird, on the Ray study out of Canada, you talked about mortality in the fetuses, but it also talked about a bunch of morbidity issues that I think are going to sound a lot like some of the patients talking about.

Can you talk about whether that study is any good on symptoms other than death?

DR. BIRD: So the Ray, et al. study also examined other infant outcomes that appeared after birth. The coding uses for those outcomes, the rheumatologic outcomes, the other exploratory outcomes they had, included a very wide array of conditions. For example, a simple rash was in there, so it was difficult to evaluate exa1)ctly what they meant.

It's possible that there are outcomes that are picked up with this general coding, but we focused mostly on the stillbirth and the neonatal death because they were harder outcomes that we could understand what they meant.

DR. VAUGHAN: Thank you.

DR. HERSCOVITCH: Moving on, questions from the panel. Dr. Jacobs? Dr. Applegate?

DR. APPLEGATE: Yes. I wondered from the last presenter in terms of study design and vulnerable populations in trying to pick up better signal about the systemic effects, if there had

been consideration of looking at these high dose gadolinium populations to include children with brain cancer.

I just want to mention that the most common solid tumor in childhood is brain tumor, and some of these children are known to get 40 head MRs with gadolinium for the course of their workups and management. And this does not include the studies for other reasons to get MR with gadolinium or without to manage complications from that. That's just during their childhood.

They will go on, survive. Eighty percent of childhood cancer is survivable, so they will go on and have gadolinium MR for many other reasons during their lifetime. They're at risk of secondary tumors. They're at risk of other diseases because of their treatment and genetic predispositions.

I just want to bring this up as a potential population to study with urine sample, with skin biopsy as a rich sample to look at. They're all often in trials with COG.

Another consideration that I think no one has brought --

DR. HERSCOVITCH: May I just say, do you have a question because we'll have ample time to discuss these issues later.

DR. APPLEGATE: It's about study design and potential populations to look at.

DR. FOTENOS: I would just comment. Again, I think there's sort of a basic dichotomy here of brain versus body --

DR. APPLEGATE: It wasn't about brain. It was about body systems.

DR. FOTENOS: Right, and certainly, a clear place to start when looking at causality in symptomatic patients is with a symptomatic patient. That's an obvious target.

Then I agree that high exposure groups prospectively in better controlled ways could add to that, although we have to keep in mind the possibility that these body reactions are extremely rare, so you may need a very large population with which to study.

On the brain side, I think there is a tension between a central message we're trying to send with regard to increasing the sensitivity of the endpoints and then the prospect of studying populations with a lot of comorbidities and confound. So if you wanted to do a brain outcomes study in that population, there would be a lot of trouble disentangling.

For example, Bayer this morning referenced a Forslin study, which actually does have a positive brain study, and it wasn't just based on comparison to controlled populations. It was based on adjusting for the severity of multiple sclerosis in an 18-year-long longitudinal study with prospectively defined endpoints.

But as you noticed, we more or less ignore that study when we talk about there being no positive brain outcomes because even with this attempt at statistical unconfounding and adjustment, it is always lurking there in the back as an alternative explanation for the findings.

DR. TOLEDANO: Dr. Toledano. Thank you.

Again, a question for Dr. Bird on the Ray 2016 study, your slide 27. When I look at this fourth bullet, the rate of stillbirth or neonatal death and I see 7 outcomes in 397 women who had contrast MRI and the control is listed as pregnant women who had no MRI whatsoever, how can I separate out the confounding of the indication for that MRI in the first place?

DR. BIRD: I definitely agree there are many limitations in this study. I think that a well-done study would require a MRI without contrast comparator. It would require an in-depth look into the indications themselves.

I think a lot of this information could have been done and a lot of the coding is available to do a better study that takes these into considerations. Without this, it's difficult to interpret because there are so few exposed outcomes.

DR. TOLEDANO: Thank you.

DR. BRENT: Jeffrey Brent. Question for Dr. Bleich and Dr. Fotenos. We're interested here

in looking at the consequences, if any, of gadolinium retention, and I think we could potentially run into a problem if we confuse gadolinium dose with gadolinium retention because they can be very different things. We're sort of taking dose, i.e., multiple MRIs, as a surrogate for retention.

I understand that the typical biomarkers for retention are not very good, like urine or hair tests, ones that were mentioned in the FAERS presentation. Can you think of any reasonable biomarkers for retention that can be used to define the population where there has actually been retention as opposed to just people who have multiple MRIs?

DR. BLEICH: Well, I think one of the first points is that we don't know if only certain populations are retaining gadolinium or if this is all part of the normal pharmacokinetics. So the first question might be to figure out where it is when across a population of normal and unhealthy.

In terms of biomarkers, I know that

Dr. Fotenos talked about being able to analyze the bone concentration not invasively, and that might be useful.

DR. FOTENOS: I would push back a little bit, too, on the idea that urine is not in some ways a reasonable measure of retention in the sense that a very simple way to assess retention, it's sort of the ideal outcome for any imaging drug would be a mass balance study over five days in which the excretion -- and there is only a few routes. There's urine, feces. For most gadolinium-base contrasts, it's almost all urine. The ideal outcome would be the mass balance study, which showed 100 percent elimination at the end of the five days.

So to the extent that that ideal is not found, it clearly is a metric. The fact that you have gadolinium in your urine at a year or two is probably a sign of retention. There are important questions about patients. Symptomatic patients, for example, use reference ranges, and those reference ranges are obtained in patients who never

were exposed to a GBCA. So are these retention levels higher in the symptomatic patients or not?

Those are important unanswered questions, but I do think we can recognize that significant amounts of gadolinium in your urine at a year or two out of a study is evidence for retention.

DR. HERSCOVITCH: Thank you.

The two members participating by telephone, do either of you have any questions for the FDA presenters?

DR. WEISMAN: Yes, I do. It's Michael Weisman. Can you hear me?

DR. HERSCOVITCH: Yes, we can. Thank you.

DR. WEISMAN: If we know that renal failure is a major risk factor for problems with gadolinium, we already know that, and we know that in 2006, there was a huge change in recognition of indications for gadolinium, is there any other way you can measure the more subtle effects of renal function in administrative databases or other databases on potential toxicity of these agents that would give you an opportunity to look within

what are considered to be the normal ranges of renal function?

I'd like the FDA to be able to address that, especially those individuals that are interested or knowledgeable about these kinds of approaches.

DR. BIRD: First, the majority of administrative databases don't have a good capture of chronic kidney disease or renal function. Some do. There are electronic medical records that could be leveraged, and this would probably be needed to look into it a little further.

I think a bigger challenge as well is identifying what outcomes to look at. Without an outcome to study and to assess whether we can completely and accurately identify it, it's going to be very hard to conduct a study in any administrative database.

DR. WILLIAMS: Gene Williams, FDA, clinical pharmacology. I don't have a lot to add to what Dr. Bird said other than to say that the implication that if you studied or if you had information on patients with varying degrees of

renal impairment and you could tease out the effect of the renal impairment itself, you might expect it to be a continuum. The idea forwarded by the advisory committee member from a clinical pharmacology standpoint, I think is a reasonable idea.

DR. WEISMAN: But the argument that I heard was that your clinical endpoints are not well defined. What ideas do you have to further define these clinical endpoints?

DR. FOTENOS: Two hopefully major themes that we're trying to communicate is that on the neurological front that we use neuropsychiatric psychometric testing, the same sort of endpoints that are used to detect subclinical toxicity of known neurotoxicants. Then on the body front, that the cytokine and other sort of immunological reactions that have been well-characterized in animals be adapted for human testing.

DR. MARZELLA: I think from what has been said, it's clear that we are still early in the hypothesis generating stage, and so the FDA has

been somewhat reluctant to impose a specific line of investigation. So we actually welcome the various approaches that the industry and the academicians have taken because we're still basically, I think, in the hypothesis generating stage.

Some refinements, I think, are important. Increasing efficiency through standardization of protocols, for instance, would be a useful approach. I think we have suggested perhaps the idea of examining the potential for subclinical neurological functional manifestations that potentially could be done, but we're still in the early stage. We're still going to have a case definition.

DR. BIRD: I think a first step is focus groups and clinical examination of highly exposed patients, and we may also consider leveraging pre-2006 data on patients with end-stage renal disease who receive gadolinium from what data we can find.

DR. HERSCOVITCH: Dr. Bolch, on the phone,

do you have any questions?

DR. BOLCH: No, I do not.

DR. HERSCOVITCH: Thank you.

Well, then this part of our meeting has concluded, and I would like to thank everyone for their participation. It's now time to break for lunch. We will abbreviate our lunch to 45 minutes, so we will reconvene here at 12:30. Please take any personal belongings with you.

Committee members, please refrain from any discussion of the topic with anybody during lunch, and committee members, we have lunch out this way and to the left. Thank you all.

(Whereupon, at 11:46 a.m., a lunch recess was taken.)

A F T E R N O O N S E S S I O N

(12:29 p.m.)

Open Public Hearing

DR. HERSCOVITCH: We're back on the record. Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision-making. To ensure such transparency at the open public hearing session of this advisory committee, the FDA believes that it is important to understand the context of an individual's presentation.

Because of this, the FDA encourages you, the open public hearing speakers, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with any industry group; its products; and if known, its direct competitors.

For example, this financial information may include industry's payment of your travel, lodging, or other expenses in connection with your attendance at this meeting. Likewise, the FDA encourages you at the beginning of your statement

to advise the committee if you do not have any such financial relationships.

If you choose not to address this issue of financial relationships at the beginning of your statement, it will not, however, preclude you from speaking.

The FDA and members of MIDAC really place great importance on the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of the issues we are discussing.

That said, in many instances and for many topics, there will, of course, be a variety of opinions. One of our goals today is for this open public hearing to be conducted in a fair and open way where every participant is listened to carefully and is treated with dignity, courtesy, and respect. Therefore, please speak only when recognized by me, the chairperson.

Thank you for your cooperation, and again, another reminder that the open public hearing speakers have been given five minutes. I

understand there's a warning light. Please keep to this five-minute limit so that we have time to hear from everybody.

Will speaker number 1 step up to the podium and introduce yourself, and please state your name and any organization that you are presenting for the record. It will just take a minute for the visual to come up, so please bear with us just for a minute.

We may have a little computer glitch, so please give us a couple of minutes. It won't come off your time.

(Pause.)

DR. HERSCOVITCH: Fine. Thank you very much for fixing that technical glitch, and we will now hear from open public hearing speaker number 1. Please identify yourself and continue.

DR. DAVENPORT: Thank you very much for the opportunity to speak. I have no industry relationships with any of the sponsors.

My name is Matt Davenport. I am an associate professor of radiology and neurology,

director of body MR, associate chair for quality at the University of Michigan. I also chair the American College of Radiology's committee on drugs and contrast media, which is responsible for authoring the widely used and referenced manual on contrast media.

I'm here on behalf of the American College of Radiology representing both ACR and the American Society of Neuroradiology regarding this important issue of gadolinium retention. I would like to take this time to read some excerpts from some written statements by the ACR and the ASNR on this topic.

"Recently, residual gadolinium has been found within the brain tissue of patients who received multiple doses of gadolinium over their lifetimes. For reasons that remain unclear, gadolinium deposition appears to occur preferentially in certain specific areas of the brain even in the absence of clinically evident disease and in the setting of an intact blood-brain barrier.

"Such deposition is not expected and led the FDA to publish a safety alert in July of 2015 indicating they were actively investigating the risk and clinical significance of these gadolinium deposits. To date, no adverse health effects have been uncovered, but the radiology community has initiated a rigorous investigation.

"Gadolinium deposition in the brain may be dose dependent and can occur in patients with no clinical evidence of kidney or liver disease. Fortunately, there have been no reports to date in the scientific literature to suggest these deposits are associated with histologic changes that would suggest neurotoxicity even among gadolinium contrast agents with the highest rates of deposition.

"Although there are no known adverse clinical consequences associated with gadolinium deposition in the brain, additional research is warranted to elucidate the mechanisms of deposition, the chelation state of these deposits, the relationship of gadolinium stability and

binding affinity, the theoretical toxic potential, which may be different for different agents.

"Until we fully understand the mechanisms involved and their clinical consequences, the safety and tissue deposition potential of all agents must be carefully evaluated. Gadolinium contrast agents provide crucial lifesaving medical information.

"Each time a contrast-enhanced MR study is considered, it would be prudent to consider the clinical benefit of the diagnostic information or treatment result that MRI may provide against the unknown potential risk of gadolinium deposition in the brain for each individual patient.

"Particular attention should be paid to pediatric and other patients who may receive many gadolinium-enhanced MRI studies over the course of their lifetimes. If the decision for an individual patient is made to use a contrast-enhanced study, multiple factors need to be considered when selecting an agent, including diagnostic efficacy, relaxivity, rate of adverse reactions, dosing and

concentration, and a propensity to deposit in more sensitive organs such as the brain.

"In March of this year, the pharmacovigilance risk assessment committee of the European Medicines Agency formally submitted its recommendation to suspend use of some linear contrast agents due to potential risk of gadolinium accumulation within humans.

"As an organization committed to the highest standards in patient care and safety, the ACR closely follows this evolving and controversial topic. After extensive review of their position and voluminous other materials, the ACR disagrees with this recommendation.

"Although intracranial gadolinium deposition following intravenous administration has only recently been reported, it has been known for over 10 years that some gadolinium chelates are not completely stable in vivo. Fortunately, there is indisputable evidence that the amount of gadolinium deposited in tissues after a single dose is very small and is detectable using only very sensitive

medical and scientific instrumentation.

"Further, although it appears to be dose dependent, there remains no evidence of cellular toxicity. However, given the risk-benefit assessment on a per patient population basis, all of these issues, including deposition, acute reactions, relaxivity, and other pharmacologic properties should be considered.

"The radiology community in general and our organizations in particular will continue to actively pursue investigations and monitor this issue.

"For patients who believe that they may have been affected and for current and future patients who may be affected in the future, we have to continue studying this important issue." Thank you.

DR. HERSCOVITCH: Thank you very much.

Will speakers number 2 please come to the podium?

MS. WILLIAMS: I'm Sharon Williams, and this is Hubbs Grimm. We are the coauthors of "The

Lighthouse Project," at gadoliniumtoxicity.com. Our support group is the source for the urine testing data that Hubbs will present today. We will cover the six points shown on the slide and explain our rationale for why the FDA needs to take action.

What does the medical literature tell us about gadolinium? The literature makes it clear that gadolinium is toxic, and it adversely affects all body systems. Note the dates of the references. Except for the 2016 paper by Ariyani, all were published before 2012.

I wrote to the FDA in 2012, and I cited those papers and many others as evidence of a potentially serious problem related to gadolinium retention. That problem still exists.

Most risk factors for gadolinium retention could affect anyone. Having an altered blood-brain barrier is a risk factor that seems to be overlooked. If you have a tumor or lesion that disrupts the blood-brain barrier, product labeling indicates that the GBCA will be deposited in the

tissue where it will accumulate.

Recent findings of gadolinium deposition in the brain appear to confirm that, but even without a tumor or lesion, there are many ways that the BBB might be crossed or temporarily altered, including by MRI itself. Diffusion into the brain can also occur. However, more gadolinium has been found in bone and other tissue than in the brain.

If everyone is retaining gadolinium, NSF-like symptoms should be expected even in people with normal renal function. The more you retain, the worse your symptoms could be.

Gadolinium toxicity is a disease of degrees with NSF being the worst manifestation of it. People in our support group are experiencing the symptoms shown here.

It makes no sense to think that there are only two options, NSF or nothing at all.

MR. GRIMM: You've seen our evidence of gadolinium deposition from our urine testing database of 70 cases and 120 test results in the comments we submitted, so I am just going to hit

the highlights.

There are five numbers here that are very important. These are 24-hour urine tests taken after a gadolinium contrast. The lowest result in the first month was 16 micrograms of gadolinium per 24 hours. None of the 58 cases with results in the first month was within the Mayo reference range.

There are 8 documented cases of measurable gadolinium in years 4 through 10. Only 4 cases out of 70 ever got to undetectable gadolinium, and provoked results are typically 20 times higher than the unprovoked results, so the gadolinium has plenty of time to disassociate.

I want to talk a bit about how the results are so consistent. We've been able to develop trend lines for the result as a function of the time since last contrast, and in this case, we have a person who received a macrocyclic agent and 10 days later received a linear agent. We took the two trend lines, we added them together, we get the green line, and you can see that the patient's trend line is very close to that trend line that we

computed.

Here is a second case that is a linear agent. Again, they are right on the line. Here is a macrocyclic agent where the person did 4 urine tests. You can see that the black line and the green line are very close together.

This is a confounded cases where the person had three contrast MRIs, and again, their number is right close to the line for anyone with 2 to 4 contrasts.

The underreporting of symptoms is simply that the doctors tell patients, your symptoms could not be caused by contrast because you have good kidney function.

Lastly, I want to talk -- and I am going to be out of time.

MS. WILLIAMS: Sorry. This is a lot to cover in five minutes' time.

Our recommendations to the FDA are to investigate suspected cases of gadolinium toxicity, fund urine testing studies for gadolinium, inform clinicians that all patients retain gadolinium,

develop a patient-focused fact sheet about gadolinium retention to allow for fully informed consent, and follow the EMA's lead regarding the use of the linear agents. Thank you.

DR. HERSCOVITCH: Thank you for your comments. Will speaker number 3 please come up to the podium?

DR. LENKINSKI: Hi. I'm Bob Lenkinski. I'm the vice chair of research for radiology at the Department of Radiology at UT South Western Medical Center. I'm a lanthanide chemist by training. I have three financial disclosures. I have participated in key opinion leaders forums for both Bayer and Guerbet, and I'm currently participating in a continuing medical education series of lectures lecturing on this topic run by ICPME.

What I'd like to do in my five minutes is highlight how some of the chemical properties of these agents and the data that's been collected that's been gone over here in animal models might inform us about not only gadolinium deposition retention in the human brain but what kind of

studies we should plan going forward to help us understand exactly the mechanism or mechanisms that might be going on.

My goals are actually to explain to you why the relative rates of gadolinium disassociation are critically important. We have heard about thermodynamic stability and kinetic stability. I'd like to connect the dots about kinetic stability, and can these differences in disassociation rates explain differential gadolinium deposition in the brain.

Lastly, if I have time, I want to talk a little bit about T1 hyperintensity because as it exists today, it's our only surrogate for measuring gadolinium deposition in the brain short of taking biopsy, and only the noninvasive surrogate that we can run in people.

What I am going to talk about was covered in two publications in the post-NSF or during NSF that actually showed up in some relatively prominent journals and seemed to be ignored in the discussions of gadolinium retention in the brain.

Three lanthanide chemists, Dean Sherry; Pete Caravan, who is here; and myself wrote this primer on gadolinium chemistry for the Journal on Magnetic Resonance Imaging, and I'd like to hit the highlights of those.

Here are the two chelates that we have heard about, linear and macrocyclic. The major difference between the two is the flexibility of the chelator. The linear chelates are very flexible. The macrocyclics are very rigid.

Based on several decades of work in the inorganic chemistry literature, we've learned that the flexibility of the chelate has a direct influence on the rate of disassociation. The more rigid the chelate is, the more slowly it disassociates, and this factor may account for the intralinear differences and the intramacromolecular differences.

You also have here the relative rates of disassociation at or near a neutral pH. The linears are rapid. They go between minutes and hours. The macrocyclics are very slow, days. They

are so slow you basically can't measure them easily at neutral pH.

Because of this relatively slow disassociation and the mechanism of how these chelates disassociate, the macrocyclics are not prone to transmetalation. It's very hard to replace them with zinc, copper, or other metals. On the other hand, the more flexible chelates like the linears are prone to transmetalation, and this has been measured in vivo.

The reason this is important is because the thermodynamic stability tells us what happens when we're at equilibrium. We're not at equilibrium after the chelates are actually injected. It's being diluted. It's being cleared. It's being taken up.

If, for example, phosphate ions are present -- gadolinium phosphate is highly insoluble. It will precipitate. This creates an unequal equilibrium stress. The system will try to re-equilibrate, obeying La Chatelier's principle, which is a fundamental principle in chemistry. The

linear chelates will respond rapidly. The macrocyclic chelates respond very, very slowly. So even though they're not at equilibrium, the macrocyclic chelates are not very sensitive to the environment that they find in the body.

I'd like to shift gears. When I made this slide, there were 6 rat studies and 2 mouse studies. You've heard most of the data from them today from the people who ran them. Most of these studies were ran by the people who manufactured them. But the one thing I want to tell you is that these studies are not standardized, so they're not standardized in terms of dose, frequency, and time after sacrificing the animals, and that leads to a lot of ambiguity in the results.

I just want to point out in this particular paper that was referenced before, if you look at the table, you'll see that not only is the total gadolinium concentration for the macrocyclics in this rat study lower than the linears 24 days post-injection, but there's a much higher insoluble fraction and a much more higher concentration of

the macromolecular complex.

I'm going to stop here and just wind up by saying we need to standardize these animal experiments so we remove the ambiguity, and we have to begin to understand what influence this may have in humans where doing, as someone pointed out, prospective, rigorous studies are very difficult. Thank you.

DR. HERSCOVITCH: Thank you for your comments. Will speaker number 4 please come up?

DR. ALMASHAT: Thank you. My name is Sammy Almashat. I'm a physician and researcher with Public Citizen's health research group. We have no financial conflicts of interest.

This is somewhat of a unique FDA advisory committee meeting given that the major questions are not being disputed at this committee meeting. I think it's safe to say that most people in this committee would concede that linear GBCAs are more likely and potentially far more likely to be retained in certain areas of the brain than macrocyclic agents. And this is, of course, what

the European Medicines Agency concluded.

Everyone would also agree that the consequences of that retention are unknown, and the committee meeting today will not resolve the question of what are the long-term harms of the retention. And I think most people would agree that the answer to that question will not be known for at least a few years.

The question for a regulatory agency is what do you do in the face of uncertain evidence regarding harm of a regulated product? We think that this can be answered in two ways or through two questions.

One question is, are there unique benefits of the products that are of most concern in today's meeting? Are there unique benefits of intravenous linear contrast agents over macrocyclic agents?

The second question is, if there are no unique benefits to certain products and they do have uncertain harms compared to other agents that are just as effective, is it feasible to withdraw those agents from the market, at least on a

provisional basis, until more is learned about their potential harms? And I'll go through these two questions in the presentation.

The European Medicines Agency concluded, as was pointed out, that in the face of uncertain evidence and a lack of any unique benefit of most linear products, the European Medicines Agency has withdrawn these products from the market. The FDA, in the face of this same evidence and drawing the same conclusions about the evidence, decided to continue to expose patients to linear agents until the question is resolved.

The EMA asked the manufacturers here to provide evidence of whether their products had particular clinical advantages relative to other products in the class. The EMA concluded, based on that evidence provided by the manufacturers, that with certain exceptions, in certain organs, and in certain regions of the body, there are no unique benefits to three intravenous linear products, and those products should therefore be suspended.

The EMA left the door open to the companies

to come back with evidence that their products do provide a unique benefit for certain patients or for certain uses. We think this approach is superior to the approach of looking at each product in isolation to determine its risk-benefit profile.

When any physician talks to a patient or any patient wants to know what product they will be given, they likely -- and we think the ethical approach is to inform them of the risk-benefit of all of the products within a certain class that have similar efficacy. We believe that if patients are informed of the evidence that is presented today, virtually all patients would prefer a macrocyclic product over a linear product, and I think all of us would, too.

The NIH reached a similar cautionary conclusion that the EMA did a few months ago in stating that "although further investigation is warranted as to the consequences of retention, it appears prudent at this time to revisit institutional protocols for GBCA administration until additional information is obtained." The NIH

also recommended that macrocyclic products be considered first-line agents for all procedures unless there is a contraindication to a macrocyclic product.

If linear products should be withdrawn as the EMA concluded, can they be withdrawn? Is it feasible to withdraw linear products without disrupting the supply of gadolinium-based contrast agents?

The trend lines are clear, that macrocyclic products are rapidly outpacing linear products, especially since 2013, likely due both the concerns on the part of radiologists that linear products could pose a long-term danger to patients and the fact that certain companies are now investing a lot more in macrocyclic products. The trend lines in pediatric patients are even more striking.

We think that a phased withdrawal of linear products is feasible, and we believe that the precautionary principle should be applied in the face of uncertain evidence and that the FDA should adopt the approach of the EMA. Thanks.

DR. HERSCOVITCH: Thank you very much. Will speaker number 5 please come up?

MS. GERRITY: Hi. My name is Judy Gerrity, and I am here with my husband Mike and my daughter Kayla. Our story began when my husband went in for a prophylactic MRI/MRA. This was to rule out familial arteriovenous malformations. What has followed has ruined our lives.

Within days of his diagnostic test, he presented with many symptoms that would continue to get worse. He developed bulbar symptoms, a severe speech ataxia, tremors, and seizures. He went from being an intelligent businessman to a shell of his former self.

We sought help from many types of doctors and specialists. He was diagnosed multiple times, and all of the diagnoses were eventually ruled out. At that point, we had to think outside the box. We sought out doctors who did testing that insurance did not cover.

That was when we decided to have a provoked heavy metal test done. When we did this test, we

thought his neurological problems could have been environmentally triggered. This test was performed a year after his last set of MRIs with contrast.

This is an important part of Mike's story because the provocation agent was EDTA rather than the more effective chelator known as DTPA. EDTA has a much weaker bond to gadolinium. Therefore, its affinity to bind with gadolinium, although original chelator in the contrast agent, would have been impossible unless the gadolinium had disassociated and was it in its free state. The only way for the EDTA to latch onto the gadolinium was if it were in free raw state.

Let's face it. We all know that you can't pull something out of the body that does not exist in the body. The measurement you get from the heavy metal test is not the total amount the patient retained. It is only relevant to what you are able to pull out of the body in a two-hour EDTA chelation treatment and excrete out of the body over the next eight hours. The only way to know the total retained would be upon autopsy.

Free gadolinium is proven to be neurotoxic, hepatotoxic, and cytotoxic. His results revealed a 17, which indicated a large amount of free gadolinium had remained in his body a year post-MRI.

It took us several more years to realize exactly the part this elevated toxin had played in the decline of his overall health and symptoms. After much research, I recently discovered scientific data that revealed animals presented with the same symptoms as my husband after being injected with gadolinium. They presented with Parkinson-like symptoms, tremors, cerebellar atrophy, and seizures.

He was previously an athletic man in his 50s with a picture perfect health his whole life. We own and operate several businesses in the Kansas City area, and his day-to-day life was filled with many executive duties. He also enjoyed an active social life and was involved in many sport activities with family and friends.

Today, he resides full-time in a wheelchair

with tremors and speech issues. I have become his full-time caregiver. He has had many falls in the past years, and we've had to make our house handicap accessible as his condition declined.

The impact that this has had on our lives and our marriage is one that most marriages could not endure. We're left with the constant stress and anxiety of not knowing what our future holds. We've spent hundreds of thousands of dollars trying to figure this out and the money we were saving for retirement.

We're small business owners, and so we pay amongst the higher premiums in the country, and that's because small businesses do not have the luxury of spreading the risk like large companies. I could accept some of this if the insurance industry recognized his condition. However, they do not. They pay to put the toxin in, but they do not pay to take the toxin out or any modalities that have proven to help patients reverse their neurological symptoms.

That being said, you have the power to save

lives and many victims. Science has proven that DTPA works much more effectively at removing the gadolinium from the body than EDTA. DTPA is already FDA approved for plutonium and americium. If it remains in an off-label status, doctors are going to be reluctant to administer it. We need now. We do not need it five years from now.

I want to stress the urgency of this matter because free gadolinium left in the body will lead to mitochondrial dysfunction, cytokine damage, calcification of the vertebral arteries, and it also blocks calcium channels. These toxicity issues are progressing.

Please do the right thing by fast tracking the FDA approval for the use of DTPA, and if you're not willing to remove these agents from the markets, at least consider making it part of the mandatory part of the MRI protocol to chelate post-tests. It truly is our own hope.

Let's face it. No aspect of this issue is transparent. Patients are highly unlikely to figure this out on their own. Let's face it. It

is your duty to make sure every patient injected is safe. Thank you for your time.

DR. HERSCOVITCH: Thank you very much for your comments. We will now move on to speaker number 6, please.

DR. MORRIS: Hi. Thank you. My name is Elizabeth Morris, and I am the past president of the Society of Breast Imaging. I am also the head of breast imaging at Memorial Sloan Kettering. We screen many women for breast cancer with MR.

I have slides, as I am a radiologist, and I just want to show you that we are limited in picking up breast cancer in high-risk women, particularly young women with high density.

This is a normal mammogram. There's absolutely nothing going on in the breast. Gadolinium is absolutely essential in some women for breast cancer screening. It can pick up cancers that are not seen.

People often say, well, why can't you do an MR without gadolinium. It doesn't work. You have to have the vascularity. You can see a very large

cancer on the post-gadolinium image that you can't see on the pre.

Many of our women come every year for a screening. This is a 35-year-old woman who had been coming to us since she was 30. You can see her breasts. There is absolutely nothing on her mammogram, and you can see in her left breast an obvious cancer picked up on the MR that was not seen mammographically.

We have been very concerned about the issue of gadolinium as many of these women have been screened year after year, many of them for many years. I'm showing you, here are some small cancers that were only picked up on MRI.

There are multiple societies that recommend annual MR screening. The American Cancer Society is one such society, but there is NICE in the U.K. and many other countries around the world have recommendations.

I am very concerned when I travel the world and I hear about concerns with gadolinium that many people are choosing to not recommend this

lifesaving test.

This is a woman who's had 10 years of MR screening, and we were able to pick up a very small 3-millimeter cancer on MR that you can see there. As we all know, picking up early detection can save lives. That was a 3-millimeter cancer that gadolinium can detect.

From my point of view as from the society point of view and also taking care of many of these high-risk patients, gadolinium is an absolute necessity. We have performed closed to 100,000 examinations. Anecdotally, we do not have any reports of any adverse effects, but we tried to study whether or not there was gadolinium deposition in our high-risk screening population. But unfortunately, many of these patients do not undergo -- they're healthy, and they don't undergo brain MR.

I would support prospective trials looking at this. I think it's essential. Thank you.

DR. HERSCOVITCH: Thank you very much. We will now move on to speaker number 7, please.

MS. COMBS: Hi. My name is Lori Combs. I am here to share my 12-year gadolinium journey. I am a patient with no financial interest.

I believe the supposed lack of known clinical symptoms is a misrepresentation. You see, I am one of those elusive humans, one who has normal renal function, yet has retained gadolinium from a single dose of Bayer's Magnevist for over a decade. I've been exhibiting and reporting clinical symptoms the entire time.

My one and only contrast MRI was done in January of 2006 after a minor accident. Prior to the injection, I was in the prime of health. It's important to note those initial scans were normal. I had no underlying conditions.

Symptoms have been reported, and patients have spoken. How do I know? Because I've personally been reporting my symptoms since 2006 to the FDA, to Bayer, and to multiple researchers, and every single one of you has refused to listen. None have offered to help me.

But I'm not the only one reporting. As of

August 2016, per FOIA, there were over 33,000 -- not the N equals 132 number from earlier today -- adverse events reports submitted to the FDA regarding Magnevist alone. But industry stance seems to be that this number is statistically insignificant. So it's no longer acceptable to me and to many here, I would believe, to allow the manufacturers and others to continue to dismiss these reports of the adverse clinical effects and start over.

I will share my personal clinical symptoms again today. My initial severe adverse reaction consisted of seizures, a near death experience, temporary paralysis, intense burning, swelling, redness, blisters, tremors, twitching, weakness, and pain, all which occurred within the first hours and weeks of the injection.

In the months and years since, I have experienced the following idiopathic conditions -- and this is not an all-inclusive list -- peripheral polyneuropathy, benign fasciculation syndrome, muscle weakness and severe

cramping, lymphadenopathy, cognitive dysfunction, brain lesions. I now have seven. A chronic neurodegenerative disease; chronic pain, including deep bone and rib pain making it difficult to breath; anemia; edema; a loss of my peripheral vision; thyroid nodules, which continue to multiply and grow; reactive gastropathy; internal bleeding; stomach polyps, adhesions, obstructions; intestinal tethering; and multiple episodes of ileus; calcification in various parts of my body, including my spine; a thickened uterus; skin tightening and disturbances in sensation; hyperpigmentation and rashes; cervical, thoracic, and lumbar spine disease at multiple levels; hypertension; hypotension; hyperlipidemia.

The list goes on and on. As these symptoms occurred and progressed, I was referred to multiple specialists at top hospitals to rule out things such as MS, ALS, Lyme, lupus, infectious and autoimmune diseases. Yet, none of these specialists ever agreed to test me for gadolinium. Why? Because the FDA advises there are no known

clinical symptoms. So instead, I'd be told to watch and wait, to come back if symptoms get worse, which they inevitably did.

My health issues have now been deemed complex and systemic. It wasn't until June of 2016 that a simple urine test confirmed I had in fact retained gadolinium, and I have been suffering from poisoning all along. I also learned there's no FDA-approved treatment to remove this gadolinium once retained, which hasn't been talked about at all this morning.

So now what do I do? Doctors don't know what to do with me or how to treat me. Perhaps if the FDA would have seriously acknowledged my reports sooner, I would not have become so ill that I have now been deemed disabled.

Another question, NSF has been talked about all morning. Why is it so difficult to consider that if retained gadolinium can cause NSF in renal patients that it would not wreak a similar havoc in non-renal patients?

Research and basic chemistry tells us that

heavy metals cause toxic effects in humans. Gadolinium is a toxic heavy metal. It shouldn't be so difficult to fathom, especially amongst this prestigious team, that if it remains in the human body, it will cause symptoms. NSF is proof that it does, and I am proof that it does.

If you still believe more clinical evidence is needed, spare the animals. Study me and others like me, not at autopsy, but while we are still alive and can speak to our symptoms.

In closing, I ask the committee to challenge the FDA to suspend the use until these questions can be answered. I'm out of time.

DR. HERSCOVITCH: Thank you for your comments. We will now move on to speaker number 8, please.

DR. REEDER: Thank you very much. My name is Scott Reeder. I am a professor of radiology at the University of Wisconsin. I am here to represent the International Society for Magnetic Resonance in Medicine as well as the Society for Computed Body Tomography and Magnetic Resonance.

I do not have any direct disclosures, although my institution does receive research support from GE Healthcare and from Bracco Diagnostics.

I am here today to express concern from the ISMRM and the SCBTMR regarding potential overreaction to the phenomenon of gadolinium deposition. I am also here to ensure that the lifesaving benefits of gadolinium-based contrast agents are fairly represented.

We have heard a great deal today about the current state of knowledge of gadolinium deposition as well as the concerns that arise from this important observation. While the ISMRM and SCBT share these concerns, it is important to examine the gadolinium deposition phenomenon in the context of the indispensable clinical benefits of gadolinium for diagnosing and treating patients with a wide variety of diseases, as well as the overall outstanding safety record of these agents.

I also wish to express our concerns over recent actions taken in Europe to discontinue

specific gadolinium agents based on incomplete data and a lack of any data showing any risk of harm to patients.

I would strongly encourage you to read the recent ISMRM white paper that was published in Lancet Neurology this past July. This paper provides a comprehensive review of all of the available evidence on gadolinium deposition and also provides seven specific recommendations. Briefly, the ISMRM white paper, and I paraphrase, recommends caution in the use of any medical compound, including gadolinium-based contrast agents.

Per standard practice, the use of gadolinium agents should be avoided when not necessary. The evidence on gadolinium deposition emphasizes but does not alter this practice, and gadolinium contrast agents should not be withheld from patients with a clinical indication for a gadolinium-enhanced MRI.

In addition, the ISMRM white paper also notes that some commercially available macrocyclic

agents appear to deposit less gadolinium than some linear agents, although the evidence is overwhelming, as we've heard today, that macrocyclic agents also deposit gadolinium. These data strongly suggest that differences in deposition are agent specific and not class specific. For this reason, the data do not support the exclusion of any agent in general, but linear agents in particular.

Perhaps more importantly, however, other than some important anecdotal reports, there are no data demonstrating any biological or clinical adverse outcomes. While rigorous studies in animals and the recent autopsy studies that we heard earlier today by Dr. McDonald demonstrate the presence of gadolinium in the brain, these studies also demonstrate an absence of any cellular damage. Tiny amounts of gadolinium are there, but there is no harm as seen on autopsy.

Finally, it is important to stress that all gadolinium agents are not the same. There are tremendous differences in the pharmacokinetics and

risk profiles of these agents. For example, overwhelming evidence demonstrates the clinical superiority of high relaxivity agents. One important example in breast imaging is from the DETECT trial that used gadobenate dimeglumine, and it was shown to detect 12 percent more invasive breast cancer than conventional extracellular agents with no increase in the false positive rate. And I would note that gadobenate is a linear agent.

Agents such as gadoxetate disodium have unique pharmacokinetic properties such as uptake in the liver, and this leads to improved detection of metastatic cancer as well as hepatocellular carcinoma. And I would note that gadoxetate is also a linear agent.

There are also significant differences in the safety profile for different agents. Significant acute adverse events resulting from gadolinium administration occur approximately on a rate of 1 in 1,000 to 1 in 10,000 and can be life threatening or even fatal. But despite this, overall, gadolinium is considered to be extremely

safe, and these allergic reactions, however, are by far the most serious risk that we consider every time we administer gadolinium. Based on the current knowledge, gadolinium deposition in the brain does not change this risk-benefit equation in any meaningful way.

In summary, gadolinium deposition is an important issue and requires further research. However, based on our current knowledge, gadolinium deposition is effectively an imaging phenomena without any paired adverse or biological clinical outcomes.

At the same time, there are enormous proven benefits of gadolinium. The variety of gadolinium agents that are available also provides an armamentarium of indispensable tools for early detection, staging, and treatment monitoring of diseases such as cancer and cardiovascular disease.

It is our mission in the medical community to provide the best and safest possible medical care to our patients. Continued availability of these agents is of vital importance to the health

of millions of Americans. Thank you very much for your time.

DR. HERSCOVITCH: Thank you for your comments. Will speaker number 9 please come up to the podium?

DR. KANAL: Thank you. My name is Emanuel Kanal. I'm at the University of Pittsburgh Medical Center, director of magnetic resonance services. I presently consult for Bracco Diagnostics and Guerbet Corporation, and in the past, I have consulted for Bayer, for General Electric, and for Mallinckrodt on gadolinium contrast agents.

Today, I'm here completely on my own recognizance. I'm not accepting any funding from anyone, and I'm here on my own expense.

I am a past chair of the American College of Radiology safety committee for magnetic resonance and that of the American Society of Neuroradiology as well. I'd like to thank you for the opportunity that you're providing to address you today, and I would like to give you three messages, if possible, if no particular order.

The first is that we're constantly referring, including here today, how macrocyclics behave and how linear agents behave always in the plural as if the agents within each class are interchangeable with each other in regard to gadolinium retention. Peer-reviewed publications of these single study agents have been done, and yet conclude or predict how all agents of that class would therefore behave.

As noted by the American College of Radiology, Europe has already issued recommendations equally for all liner agents despite significant demonstrated and reproducible differences in their diagnostic efficacies and reports of possible differences in their adverse event rates as well.

They also advocate continuing to use, quote, "macrocyclic agents" despite several peer-reviewed studies that have suggested still unexplained differences in gadolinium retention behavior amongst the various macrocyclic agents as well.

The disassociation or transmetalation theory

might predict similar gadolinium retention among the various agents of each class. However, the peer-reviewed literature has repeatedly demonstrated that there is significant differences in the amount or rate of retained gadolinium in humans and/or animals among the various linear agents and amongst the various macrocyclic agents.

I respectfully request that the FDA consider resisting the urge to generalize by class and that instead, each and every gadolinium-based contrast agent be evaluated individually based on actual data and not mere class-based predictions or generalizations.

Number two, as you've just heard, society cannot afford to ignore efficacy when assessing gadolinium contrast agents' safety. Significant differences exist in the R1 and R2 relaxivities of the various neuroradiologic gadolinium agents in use today.

The physiology and physics of human vision are such that the relative relaxivity values may play a minor or insignificant role for larger

lesions, but for small or very small lesions or for lesions with poor or subtle enhancements, these known relaxivity differences can make the difference between lesion detection and lack of detection, between diagnosis and missed diagnosis.

To a diagnostic radiologist, and I might say especially to the patient, the potential for missing a diagnosis is a patient safety issue, and everyone should approach it as such and not let it hide under the word "efficacy."

Finally, I believe that the single most important question that has yet to be answered regarding residual gadolinium is, of course, whether or not it's associated with patient injury or harm. No formal studies may have documented any harmful effects of such retention to date, but we have just now begun to formally study this issue. And of course, the absence of known injury should not be misinterpreted as demonstration of safety.

Despite having extensively investigated this issue of retained gadolinium, I personally remain quite impressed with how little we actually know

about this issue today, and for now, we seem to have more questions than answers. So much controversy exists in the published literature on this topic with numerous manuscripts reporting findings that refute the conclusions of many others.

There are individuals who are confident, as you heard today, that retained gadolinium is harmful and who may even wish to see these agents removed from human diagnostic use. Others are far more fearful of the harm that may befall to society if we do not use gadolinium agents when they are clinically indicated.

There is no shortage of very strong opinions and very powerful emotions by so many regarding this topic. Society requires objective large scale studies to assess potential harm, but at this stage, we've not even agreed on what population to study or what specific adverse events we should be evaluating.

To this end, over the past few years, I've had numerous discussions and discourses with the

leadership and several members of the group who call themselves The Lighthouse Project from whom you've heard today. They seem to share a common belief of having been harmed in some way by the administration of a gadolinium-based agent.

It's my opinion that this lay group has produced some data that at the very least raises several unanswered and somewhat troubling questions. While objective adverse events may not be readily evident for many in this group, virtually all members of this group seem to report a temporal relationship between having received a gadolinium agent and the onset of perceived symptoms and adverse events.

While a temporal association does not, of course, prove causation, it certainly provides for a plausible etiologic hypothesis worthy of further investigation.

In closure, I'd like to therefore formally recommend that in addition to what other studies you may have already planned in this regard, the FDA encourage and/or support formal investigation

of this population, the very population that claims that they have been harmed by these agents. Consider convening a subcommittee to advise what specific surveys or tests or studies should be performed on volunteers recruited from this specific group of patients to further assess the safety of these agents. Thank you very much.

DR. HERSCOVITCH: Thank you. Next, we'll hear from speaker number 10, please.

MS. WINGREN: My name is Ann Wingren. I don't have any financial benefit from being here. I am a patient advocate.

Gadolinium was first tied to NFD and then NSF. That is not where the disease ends. It does not just cause external skin changes. It can lead to cognitive impairment, healing problems, fall risk, decreased lung and heart functions, and inability to swallow. This list just scratches the surface of some of the repercussions. More and more we need to call it as what it is, gadolinium toxicity.

In 2005, a patient with acidosis due to

bowel surgery and had a DVT as a result of birth control medication was on supplemental iron for anemia. Following an MRI to evaluate the DVT, she developed what came to be called the classic symptoms of nephrogenic systemic fibrosis.

These studies by the dermatologists who saw her and had attended one of the early NFD symposiums thought -- not truly knowing that it was, nor having learned the full risk, in an ironic twist, she underwent additional MRIs, including one less than 30 days before the black box warning. Her primary doctor tested her three times for Lyme disease. The doctor that she was referred to at the time dismissed the symptoms as eosinophilic fasciitis.

Fast forward two years and this patient's acidosis became critical. It contributed to the exacerbated slowly progressing kidney disease she was born with. This whole time, the burning pain, rash, and constrictors progressed. By the time she went to the NSF specialist of the time, she required a cane and a wheelchair.

Many around her wondered what the next turn would be. Now in dialysis, she met the renal requirement of NSF, and about that same time, the doctor she was seeing also noticed she had been referred by a sharp-eyed educated dermatologist and nephrologist.

The second look took a punch biopsy with a clinic evaluation, [indiscernible] scale measurements, and lollypop pathology, diagnosis of nephrogenic systemic fibrosis was made. But is it NSF? Is that all it is?

As you may have guessed, I am that patient. Luckily and literally, I stand before you 12 years post-exposure. So I ask the committee and those in this room who are involved in gadolinium use, research, guidelines that same question. Is it just NSF, or are there more to the story of gadolinium? The disease of degrees many patients experience and the medical community is beginning to acknowledge in earnest.

When I told my son I was speaking to you, he said to me, "Is it really a kidney thing? Why

don't all kidney patients get it, and why did you get it?" I also ask you to consider these points, and if it is only NSF, why am I back standing with others no longer here?

At the medical center I was followed at, there were eight other patients that were diagnosed. Yes, eight at one center. Is it as rare as we want to believe, or is it, in fact, very under diagnosed as we suspect? The eight other patients were on dialysis at the time the disease initiated. There is now only one other patient besides me, and he is confined to a wheelchair.

That is me. Onset, showing the marbling. The middle one was actually in The New England Journal of Medicine, and the now was literally taken a couple of months ago.

You may not have heard of one of the patients that was here in 2009, Celeste Castillo Lee. She's no longer here. I'm here trying to continue this and hoping that 8 years, 10 years from now, I won't be one of the statistics that are written about in obituaries.

My goal is to ask you to step back, look back, then look ahead, and do your own nonpolitical analysis of the evidence provided to you. What I am going to say next is not popular with my peers, but is one to demonstrate that I do understand the decisions you make and many of the hard -- that you're in the hands of us.

I'm not advocating banning GBCAs. I have acknowledged that while gadolinium almost killed me, it may have also been part of what saved me as a result of the severity of the DVT I had. It went from my calf to my abdomen, so yes, I needed an MRI. But later, I had CAT scan that showed my brain was shrinking. Scared, went for an MRI without contrast. Did not need contrast to find out that the CAT scan had been done wrong.

I do have to end. There were other things I wanted to say. My apologies and thank you.

DR. HERSCOVITCH: Thank you very much for your comments. We will now move to speaker 11, please.

DR. PRYBYLSKI: Afternoon. John Prybylski.

I am a pharmacist and a post doc at UNC Eshelman School of Pharmacy. So I am here to present some recent results that we think are important in conversations of policy relating to GBCAs, and a lot of the conversation here and when this topic comes up does an inaccurate dichotomization of high-risk linear agents and low-risk macrocyclic agents.

To address this, I have up here essentially the sum total of data that directly compares the deposition in bone and whole brain for linear and macrocyclic agents. As we can see, there is about 10-fold more gadolinium per surface adjusted dose in linear agents compared to macrocyclic agents, but here, we're talking about a scale of nanomoles per gram tissue. So we're talking about less than a part per million.

Looking at relative differences sort of artificially inflates the clinical significance, and in this case, we have to also keep in mind that less is not the same as zero.

To try to consider these long-term kinetics,

we have been working on a model that considers the complex biokinetics of gadolinium along with the relatively simple pharmacokinetics of GBCA and GBCA ligand and try to connect them with the hypothesis that all GBCAs have the potential to release gadolinium in the body.

What we found when we fit that model to the available data was a concordance of 86 percent, which is pretty good for a nearly purely mechanistic model, and in our minds supports the conclusion that at least part of the deposition is caused by gadolinium release.

It's also important to note at this point that there is questionable validity to the assertion, at the low concentrations we're talking about, that soluble small molecule complexes that contain gadolinium are intact GBCA, just a side note, which leads me to a few questions that the literature raises that we should consider today that we don't necessarily have the answers to.

Are we trying to eliminate hyperintensity or are we trying to eliminate deposition? Because

there is a fair amount of evidence that we have discussed that hyperintensity does occur less with macrocyclic agents, if at all, although that's up for debate in pediatric patients. And if we are targeting hyperintensity, what is our magnitude of benefit? Are we simply eliminating an imaging phenomenon that's not necessarily linked with any sort of symptoms?

Then if we're going to go for deposition and if there's evidence to suggest the deposition is harmful, which I think there are many in this room who would attest that it is harmful, is it a continuous dose-response curve? Is less deposition associated with less harm, or are there just some patients who when they have deposition, which may be associated with all agents, they will experience these symptoms?

On a related note, we also have to consider to balance the equation the acute adverse event rate, which we learned fairly recently happens more in macrocyclic agents than in traditional linear agents like gadodiamide or gadopentatate. Are we

intentionally wanting to expose patients more to demonstrably more harmful macrocyclic agents in an attempt to limit a potentially benign outcome like hyperintensity or to modestly decrease deposition?

In my mind, I wouldn't feel comfortable implementing that in a small practice, let alone across the nation. So thank you, everybody, for your time.

DR. HERSCOVITCH: Thank you very much. We will now skip to speaker number 13, please.

DR. ENTERLINE: Good afternoon. My name is Dave Enterline. I'm a neuroradiologist at Duke University, and I thank the panel for convening this very important process. I have no financial support, and I'm speaking on my own behalf.

At our institution, we see approximately 37,000 contrasted exams every year, and we use a variety of different agents, 6 of the 8 that are currently available. Of note, none of the patients have reported unusual symptoms such as we've heard here, but I think it is something that certainly requires a lot more study over time.

A couple points that I'd like to make. "Gadolinium agents are lifesaving medications used to make critical medical decisions." This is from the ACR statement. The important thing is that all approved agents are efficacious with excellent safety profiles, which doesn't mean that they have no risks associated with them.

There are no neurological adverse events associated with retention, and we see numerous things as neuroradiologists, whether it's calcium, iron, manganese commonly in similar locations in patients receiving MRIs and CT scans.

It is important that we look predominantly at additional data. Animal data and pathology will be particularly valuable as well as patient studies in looking at symptoms. My opinion is that the recent statement by the FDA drug safety group done in May of 2017 was very much on target, and that corresponds well to the major radiology societies' statements as well.

Another point I'd like to make is that the different agents have very different properties,

and we've talked a lot today about macrocyclic versus linear. But there are many other ways of looking at these different agents, including cost, and really to adequately look at safety, you also have to look at the benefits.

One of the things that we found particularly useful in our practice for neuroimaging and MRA is to look at agents with higher relaxivity. The support for this comes from multiple intra-individual crossover studies as well as our clinical experience.

I agree with the point made earlier that the accurate detection and definition of disease is essential for important clinical treatment judgments and to balance safety and efficacy.

There are a couple images I'd like to share just to show relative merits. Here is an example from a study by Seidl showing a nodular area of enhancement, recurrence of a frontal glioma that is not visualized by one of the macrocyclic agents, and a different study by Vaneckova also demonstrating not being able to see a recurrent

lesion that is present at an equal dose of a different agent. So there are differences in how these agents respond.

There are also other needs for multiple gadolinium agents. We frequently will change classes of medications if a patient has prior adverse events, and of course, before we administer any agent, we're going to make sure that they really have a true indication, and I think that's a very important feature.

We perform a lot of multicenter trials, and all of these specify a specific agent. This is done so that there's not differential enhancement with many of these different agents, which do occur.

Finally, in looking at the emerging field of immunotherapy, where frequently these agents are injected with very dilute gadolinium in the brain area, this mimics somewhat the CSF pathway, which has been described. The retention models for the brain itself, while no clinical effects are there, have been visually kind of confirmed by Onyer's

group, but the toxicity of macrocyclics in higher in the spinal fluid compared to linear agents. I thank you very much for your attention.

DR. HERSCOVITCH: Thank you for your comments. Will speaker number 14 please come up?

MS. BUNNING: My name is Sue Bunning. I am here today on behalf of the Medical Imaging and Technology Alliance or MITA. We appreciate the opportunity to be part of this productive discussion on the benefits and risks associated with gadolinium-based contrast agents. We would like to thank the FDA and all of today's participants who have contributed their knowledge and input to ensure a balanced dialogue.

We would also like to recognize our member companies for their commitment to patient safety. As you have seen in their presentations today, GBCA manufacturers, many of whom who are also device manufacturers, put patient safety at the forefront and have worked diligently to ensure the patients' interests and always top of mind through a rigorous pharmacovigilance and ongoing research to gain

insight into GBCAs and their safety profile.

MITA is an industry trade group whose manufacturers include not only those which develop and provide MRI systems but also those that manufacture accessory devices, including the power injectors which deliver contrast agents. Also among our member firms are most of the GBCA manufacturers.

Our members have a vested interest to ensure that patients are receiving the highest quality imaging possible. As a representative of these manufacturers, MITA is here today to reinforce the importance of GBCAs to the medical imaging community.

Roughly 13 million MR procedures each month depend on a GBCA to provide radiologists with the image needed to provide diagnosis and disease monitoring updates that inform treatment decisions. MITA is committed to driving effective patient care through screening and diagnosis and treatment.

These goals can be achieved through reducing barriers, sharing best practices, and establishing

standards. In addition to the guidance published thus far by the FDA, our clinical counterparts, the American College of Radiology and the International Society for Magnetic Resonance in Medicine, have published guidance regarding the use of GBCAs. We support the guidance of the FDA, ACR, and ISMRM.

A large part of our mission is to ensure effective patient care, which includes ensuring that imaging services aren't compromised. Without the use of GBCAs, we would be compromising the ability to give radiologists and healthcare professionals those important patient insights.

Our goal is to advocate that medical professionals have the tools and resources to fulfill their patients' needs. Members of our medical community also want to know that they are using the best diagnostic tools available while performing the diagnostic procedure efficiently.

GBCAs helped to limit the number of times a procedure must be performed by providing the clearest image the first time. The role and need for GBCAs in quality medical imaging is clear, but

there are also important factors such as clinical research and the benefit-risk profile of GBCAs.

Since their introduction almost 30 years ago and after more than 450 million administrations worldwide, gadolinium-based contrast agents have been established as a crucial element in transforming MRI into a high performance diagnostic test with beneficial and even lifesaving diagnostic capabilities. GBCAs are crucial in addressing certain diagnostic questions that often cannot be accurately answered without the higher quality imaging produced with the use of the contrast agents.

In conclusion, today's meeting provides an important forum to discuss the existing knowledge base of GBCAs and to identify the current gaps in information. Although no clinical relevance of gadolinium presence in the brain has been detected to date, our member companies, and more broadly, the medical community, are thoroughly investigating the possibility of any clinical relevance to further guide research.

We encourage an open and collaborative dialogue with the FDA and industry regarding additional studies and scientific-based data that should be gathered to help provide guidance to ensure safe and effective use of products. Thank you very much.

DR. HERSCOVITCH: Thank you. We will now hear from speaker number 15, please.

MR. ULLESEIT: Good afternoon. My name is Curtis Ulleseit. I am independent researcher in gadolinium-based contrast safety. In order to understand the complexity of gadolinium-based contrast agents and the toxicity involved, we must have a basic understanding of the chemistry.

Free gadolinium is toxic. Gadolinium is a potent calcium blocker. Many side effects of calcium blocking due to gadolinium exposure appear to be essentially the same as the side effects of hypocalcemia or low free calcium levels, and these effects appear to be mainly functional disturbances.

The higher the dose of free gadolinium, the

more severe functional disturbances there will be. Gadolinium poisoning in patients is most likely grossly underreported due to lack of awareness of gadolinium toxic effects and testing.

There's an important paper by Frenzel and party in December of 2008 issue of Investigative Radiology in volume 43, number 12, and table 3. Linear GBCAs take 5 to 7 days to disassociate in number blood pH of 7.4. However, in acidic conditions, all of the listed GBCAs disassociate in less than 5 seconds.

This shows that the linear GBCAs can disassociate before they can be fully eliminated from the body in acidic conditions. This can quickly lead to gadolinium poisoning in a dose-dependent manner.

In comparison, the macrocyclic GBCAs take over 30 years to disassociate in a normal pH of 7.4. And even in extremely acidic conditions, the macrocyclic agent known as Dotarem takes 26 hours to even begin to disassociate. In comparison to the linear agents, the macrocyclic agents allow

much more time for the contrast to be fully eliminated before disassociation can begin. This provides a much needed buffer to account for unknown conditions in the patients such as dehydration and acidosis.

Frenzel's paper also includes table 4 and 5, the linear agent known as Omniscan, which appears to have the weakest chemical bonds out of all the linear agents. In a test in human blood samples, Omniscan showed that it released less than 1 percent in the first 24 hours at a normal pH of 7.4. However, after extra phosphorous was added, Omniscan released over 20 percent of its toxic free gadolinium in the first 24 hours.

In the tables, this is compared to a linear agent known as Magnevist, which appeared to have a relatively stronger bond than Omniscan but is still dangerous because it still releases about 2 percent within the first 24 hours but far less than Omniscan. However, all the macrocyclic agents tested appeared to not have released any free gadolinium even after 15 days in human blood with

extra phosphorous added, providing a superior chemical stability of macrocyclic GBCAs.

It appears that the patients with normal renal function, concentrations of contrast are still high but decrease quickly during the first 24 hours after the GBCA injection. It is likely that the first 24 hours is the most critical to ensure that the GBCA is not capable of disassociating to any degree, especially in acidic conditions. It appears that the macrocyclic agents appear to provide extra cushion time for these conditions. However, the linear agents do not.

It was reported by Dr. Kay that the average dose of GBCA that is injected into patients for a standard MRI is about 1.5 grams of elemental free gadolinium. In the table, it is shown that Omniscan at 20 percent release of free gadolinium in the first 24 hours of 1.5 grams would account to be about 300 milligrams of toxic free gadolinium in the patient.

Omniscan, which has the weakest chemical bonds, was reported to have caused 85 percent of

all NSF cases in the world. Based on these numbers found in Frenzel's tables, one can begin to speculate why. And keep in mind, Omniscan only had a small fraction of the market share at the time.

It does not take a chemist to figure out what happens when you pour acid on something. It begins to break apart much faster. Case report, in 2006, a paper by Grobner and party reported nine patients with kidney failure were monitored before and after injections of linear GBCA Magnevist injections. Five of the patients had acidosis at the time of Magnevist injection. The other four patients did not.

Strikingly, all five of the patients who had acidosis during their injections of Magnevist developed NSF. The four patients without acidosis did not develop NSF.

However, regardless of the kidney function, it is known that various factors in the human body can lead to acidic conditions as well as excessive competing molecules that can increase the disassociation rate of linear contrast agents.

These factors include medical conditions, medicines, medications, diets, supplements, and even rigorous exercise, which can cause lactic acidosis.

How do we screen patients for gadolinium poisoning? According to Mayo Clinic, elevated gadolinium levels in blood or urine after 96 hours is abnormal in patients with healthy kidneys. Since disassociated free gadolinium has a significantly longer residence time in the blood plasma, around 30 days, versus only 48 hours for intact GBCAs, any elevated gadolinium levels after 96 hours post-GBCA most likely indicate the presence of disassociated gadolinium. However, intravenously injected EDTA or DTPA are chelators that can be used to confirm the presence of free gadolinium.

It is currently unknown what percentage of patients with healthy kidneys are suffering from gadolinium poisoning after receiving linear-based GBCAs. There are many case studies in the past --

DR. HERSCOVITCH: Excuse me. I apologize

for interrupting. Could you please conclude? Your time is up. Please conclude.

DR. ULLESEIT: Sure. In summary, we have a call of action here. Based on the weak unstable chemical bonds found in linear GBCAs and their propensity to release toxic free gadolinium, FDA should put the safety of patients at the forefront. Continuing to use linear GBCAs is chemically unsafe. The FDA should follow the recommendations and actions of the EMA, which is to remove the chemically unstable linear GBCAs from the market immediately. Thank you.

DR. HERSCOVITCH: Thank you. Can I ask speaker number 16 to please come forward?

MR. WALBURG: Good afternoon, committee and industry. My name is Todd Walburg, and I am here to read the joint statement of Gena Norris and her husband Chuck Norris, the actor. Gena is one of thousands of patients who have been suffering under gadolinium deposition disease, and this is their story.

"My name is Gena Norris, and I am a survivor

of free gadolinium poisoning. My husband Chuck has stood by my side and witnessed firsthand this horrible ordeal that I have been through and continue to deal with on a daily basis.

"We both planned to personally attend this hearing to tell our story about how gadolinium almost killed me and to explain the enormous cost and difficulty of the treatment for this disease. Unfortunately, we had to change our travel plans because we are currently at home in Texas dealing with the aftermath of Hurricane Harvey.

"Before this all started, I was a strong healthy athletic woman living a wonderful life with my family. Then my symptoms began right after I undergo three MRIs with contrast during an 8-day period. On all three occasions, I was injected with MultiHance, a linear agent. My doctor had ordered the MRIs of my brain, spine, and both hands to check for a fairly routine medical condition.

"When I arrived at the radiology center, I am given paperwork, but there is no black box warning on the forms. There is only a mention

about people with kidney problems being at risk for side effects, which did not apply to me.

"I asked how safe the injection compound was, and their reply was something like very safe. Just drink lots of water, and it will be out of your system in a few hours.

"Around three days later in the middle of the night, I had such a strong burning pain in my abdominal area that my husband has to rush me to the emergency room. They began treating me with an IV, and the IV did seem to help, but it was short-lived, and the ER visits continued night after night as the burning sensation spread throughout my body.

"On the night of my third visit to the ER, I am feeling as if my whole lymphatic system has shifted into overdrive and millions of tiny ants or particles have just been dispersed throughout my body. A few days later, I wake up in the middle of the night with more burning pain, and my husband rushes me to the ER for the fourth time where they admit me to the hospital for three days.

"I continue to decline. I am later rushed back to the ER for the sixth time by my husband. I am violently shaking with tremors all over my body. I feel confused as if my brain has suffered some type of concussion. I beg for help from the treating doctor, but nothing helps. I wake up around three hours later, and I'm being sent home.

"Once home, I rapidly decline, up and down all night with burning throughout my body. It feels like acid is being poured on every single organ, cell, and tissue. Life Flight is called, and I am helicoptered back to Memorial Hospital in Houston for more tests and a 6-day stay.

"A neurologist there suspects that I have ALS, but that's ruled out. Then I'm home again, continuing to decline with no real answers. I'm fatigued, hypoglycemic, hypermetabolic with muscle wasting. I have lumps growing in my lymph areas and some in my groin, which are three more inches in size. My brain continues to decline. My body is having tremors. I have abnormally low body temperature. I'm unable to exercise, in bed most

of the time, can't sleep, and have to eat every two hours because of massive weight loss.

"After several more stays in the hospital bed and never having seen a toxicologist, I hear that small voice inside my head telling me that my body is dying. My husband Chuck takes one look at me and knows that he is going to lose his wife if he doesn't do something immediately.

"He calls a doctor we know in Reno, Nevada and describes the symptoms. The doctor tells my husband that we need to get to Reno right away. It's critical, so my husband charters a jet with a bed and a paramedic on board, and we fly to Reno.

"I stay in Reno for daily IVs and treatment for the next several months. I was started on a provoked low dose chelator, and they continued chelation treatments throughout my stay.

"My husband read 17 books during this time and never left my side. We were there with our 11-year-old twins for most of the time, and they were traumatized, as you can imagine.

"In Reno, I'm close to dying. My central

nervous system has been badly affected, and I cannot tell the difference between the sensation for urination or a bowel movement. I have bad tremors, muscle cramps, numbness, tingling, buzzing, joint aches, and low body temperature. I have lost a tremendous amount of weight, and my hair is falling out. I have lumps and rash all over my body. My muscles are weak, and my left arm is drawn up.

"The doctors get me on a low dose chelator, and during my stay, I have over 40 IVs of chelation. Finally, I'm transferred back to Texas for treatment, and I begin hyperbaric therapy. I have done approximately 120 hyperbaric dives to help heal my brain. We had to hire a nurse for my ongoing care, and we have installed a hospital grade hyperbaric unit at our home.

"When the symptoms don't resolve, we get desperate and seek out stem cell therapy. We travel to China and stay for a month at a hospital there. Eventually, I learn that my gadolinium levels were off the charts. I find out that my

kidneys have been severely damaged, and I have moderate osteoporosis.

"Today, I still have many symptoms, and I stick to a pretty strict protocol to try to have some quality of life. My husband has literally taken me around the world for treatment and spent millions of dollars to save my life, but we had to go outside of mainstream medicine to accomplish this."

DR. HERSCOVITCH: I'm sorry. Could you please conclude?

MR. WALBURG: "My heart breaks for those who don't have the financial means or the knowledge of where to go to seek treatment they need to save their lives. We will continue to use our platform to raise awareness about the dangers of gadolinium.

"We have spent thousands of dollars of our own money to help several women and men that may have died if we did not reach out and help them with proper medical interventions. Helping others is probably why I did not die. I believe that God kept me there for this purpose.

"In closing, we would like to thank you for taking the time to hear our story. We trust that you will do the right thing. Sincerely, Gena and Chuck Norris."

DR. HERSCOVITCH: Thank you. Will speaker number 17 please come up to the podium?

DR. SEMELKA: Hello. My name is Dr. Richard Semelka, and a number of my papers have been cited through the course of this morning from our work at the University of North Carolina, so I thought it might be good to also hear me directly.

Listening to the patients that we've heard today reminds me of the words of Sir William Osler, who admonished us, "Doctors, listen to your patients. They're telling you their diagnosis."

Actually giving gadolinium is an unusual form of medical and drug administration because we as radiologists, we order the giving of the drug, the drug is given, and then the patient leaves, and that's it. That's basically all of our contact with patients.

I must admit, I've written five papers

myself on NSF. I didn't actually see a patient with NSF until some time after I wrote these major papers. We don't really have contact with patients, so the honest truth is we don't know what happens to them. And to be honest, that makes me worried about everything else we do.

My goal is not to cause any concern about gadolinium. I'm worried about everything we do. I'm worried about iodine contrast, certainly very worried about medical radiation.

One of the things I think we also learned from this is something that I've described in some of my papers, is to revisit NSF. When we look at the literature, only 5 percent of patients in stage 5 renal failure who've received Omniscan developed this condition, only 5 percent.

Well, what does that tell us? Well, it tells us what I'm going to make as my conclusion now just because I may run out of time, and that is that NSF is probably very closely related to what we call gadolinium deposition disease. My opinion is it is a genetic disease of the immune system

that, as you saw from the presenters here, the predominant patient population is Caucasian women. We have to borrow from other forms of medical knowledge. It reminds me of the condition of genetic hemochromatosis.

So the two things I'm very keen on is identifying the patients at risk -- and maybe someday we can do a blood sample that they can come into the hospital; we test them; we see that they have this genetic profile; they can't get gadolinium; and by the way, they can't get these other things, and maybe they're also at risk of severe anaphylactoid reaction to contrast agents.

But the other thing we can't ignore, and these patients called out for it, is to treat them. So that's something that I've focused on because I've already accepted and have actually published quite a bit on the subject of what we call gadolinium storage condition, which is the deposition of the simple presence of gadolinium in the brain after multiple administrations of gadolinium.

I'm focused on treatment. These people are sick. We've got to do something for them. So it's very clear that chelation works, and as some of the people have referenced here, DTPA is a much better chelator than what patients have been relegated to, which is EDTA.

Why have they been relegated to it? It is because we in the mainstream medical community have not acknowledged their disease. To be honest, for years, I didn't acknowledge their disease until it was a senior nephrologist in our institution who described to me her experience with receiving gadolinium and the fact that she had two weeks afterwards a feeling, she said, "like being filleted with a knife through her arms."

I thought to myself, well, she's not looking for money from me. She doesn't even want her name to be out there. So that was, to me, the real turning point to realizing that this disease is real. So be very assured the disease is real.

Now, the good news is that I don't think everybody gets it, so I'm not saying remove

gadolinium. I'm saying we have to figure out who these patients are, and we also have to treat them. So we've actually had running an FDA-approved trial of using DTPA, which is currently the best treatment for these patients, but it's also probably not enough.

I have to finish shortly, so it's like a teaser that I'm finishing with. We've got to do more. So I've been working with physicians of other disciplines, and that's what we have to do. It can't be a bunch of radiologists sitting around. We need immunologists. We need geneticists. We need toxicologists to figure this disease out.

They need more than just re-chelation if they had gadolinium deposition disease. Gadolinium storage condition, I think chelation would be perfect in working out their treatment. But we're looking at immune modulation and mediating the immune system that these patients will require. Thank you for your attention.

DR. HERSCOVITCH: Thank you very much.

The open public hearing portion of our

meeting has now concluded, and we will no longer take comments from the audience. The committee will, after the break, turn its attention to address the task at hand, careful consideration of the data that we have heard as well as public comments.

We will now take a 10-minute break. Panel members, please remember that there should be no discussion of the meeting topic during the break, and we will resume at 2:12. Thank you.

(Whereupon, at 2:02 p.m., a recess was taken.)

Questions to the Committee and Discussion

DR. HERSCOVITCH: I'd like to reconvene the meeting. We will now proceed with the questions to the committee and panel discussions. I'd like to remind the public observers that while the meeting is open for public observation, public attendees may not participate except at the specific request of the panel.

Just as an introduction to the five questions from the FDA, we need to consider each of

the five questions separately. I've been asked to read each question as an introduction to each discussion so that each question is formally entered into the transcript. And for panel members, the questions are in your FDA booklet.

We will be focusing on each specific question at a time, and after each of the first three discussions, I will try to summarize the key points, although we may not have reached any definitive conclusions. Note, however, regardless of what I say, that all our comments are being recorded and will be publicly available, so your comments will be important.

A reminder that we're considering not only retention in CNS but also other body tissues, and given the concerns about retention and the nature of the data available, the FDA would like a broad discussion of what approaches and standard they should use in moving forward.

Also, an important reminder that the FDA is not looking at this time for discussion of overall risk-benefit issues for specific organs or specific

agents. That's a much broader discussion for another time. We have been asked to focus on gadolinium retention.

Just a special note for the voting committee members, especially the ad hocs, the last two questions will not really be much of a discussion beforehand, but they do require a vote. And the vote will be recorded through your microphones and then immediately made public. But after each vote, each member will be asked to explain the aspects of our deliberations that prompted their vote yea or nay.

I will now read into the transcript the first question, which is a discussion question, not a vote question.

"In the evaluation of risk of gadolinium-based contrast agents in 2009, the FDA considered several issues: the thermodynamic stability of the drugs; the in vitro kinetics of release of free gadolinium; histopathologic evidence of toxicity in juvenile and adult animals; clinical evidence of toxicity based on reports of systemic fibrosis;

susceptible patient populations, that is, those with moderate to severe renal insufficiency.

"GBCAs were risk stratified based on the totality of this evidence. Risk mitigation steps included warnings and contraindications in the prescribing information, public communications, increased pharmacovigilance, and reporting for systemic fibrosis."

The FDA would like us to discuss the following: "Given the new concerns raised by gadolinium retention in patients with normal renal function, please discuss how FDA should weigh this new finding in relation to the known risks, for example, of gadolinium retention with renal failure.

"In the absence of scientific criteria, for example, toxicological or clinical thresholds to inform risk assessment, which factors should the FDA consider, for example, with regard to guiding regulatory recommendations and their actions

"Please include in your discussion evidence that we've heard for differential intention;

establishment of empirically defined thresholds, for example, retention with linear versus macrocyclic agents; retention levels in specific organs, for example, CNS, skin, or bone; the molecular forms of gadolinium, for example, free versus chelated versus bound to biologic macromolecules."

I'd like to now open the discussion, and during the discussion, I do invite FDA leadership to comment. If they'd have issues they'd specifically like to have discussed, please feel free to participate, Dr. Marzella and colleagues.

I would like to, again, go around the table once to hear from each one of you, and then we may have time for discussion. We will try to conclude by 4:00 p.m. because some folks do have planes to catch. I would like to start on my right with Dr. Frank, and then we'll proceed around the table.

DR. FRANK: It seems to me that there is a lack of association between the brain retention and any clinical effect, and therefore, it's difficult to identify patient subpopulations based on that.

On the other hand, there is correlation with the agents themselves and with the number of administrations and with the class of agent, and therefore, this is where the additional research should be focused.

DR. HERSCOVITCH: Yes, please.

DR. HERNANDEZ-DIAZ: Sonia Hernandez-Diaz. I think that most of evidence presented and most of the interpretations of the same evidence point at a different risk for different classes of agents and maybe even within class. We may not have perfect information, but I think, in general, the evidence points out at some class effect that we cannot ignore.

Maybe we don't have the same information we had in 2009 for that decision, but maybe we are reaching the level of a warning. I think that unfortunately, we do not have enough evidence to propose at this time a risk certification, and we are not able to identify patients that are at risk for more retention or given their retention, at risk of having effects.

DR. HERSCOVITCH: Yes, please.

DR. HENNESSY: Sean Hennessy. The first thing I'd say is there seems to be a suggestion that the adverse effects of gadolinium are not restricted to patients with renal insufficiency, so the renal insufficiency seems to be a risk factor for adverse effects, but it's neither necessary nor sufficient.

Given that and given in toxicities of gadolinium, the reason that we put molecules around it is to spare humans the toxic aspects of the metal, that it is reasonable to give all patients as low a dose as reasonable, the ALARA principle.

I agree that we don't know enough at this point to be able to stratify patients very well with regard to risk. The only factor that we know about so far is renal insufficiency and agent, and a lot more research needs to be done about individual patient factors that predispose to risk. But even in the absence of that information, I think it's going to be reasonable to differentiate the agents with regard to what's known about their

risk currently.

DR. HERSCOVITCH: Dr. Latour?

DR. LATOUR: It seems like there is now clear evidence that the gadolinium isn't clearing at the rate that we thought it was a decade ago, and that's concerning. It's not yet clear to me that there is a strong difference across the patient populations. The connection between the accumulation and the symptoms temporally seems to be related in a population, but it's not yet clear why it's in a limited number and a small proportion of patients.

DR. FURIE: Karen Furie. I agree with the previous speakers, that at this time, there does not appear to be sufficient evidence to implicate one specific agent or class of agents. I think that although there is concern about risk, it should be assessed across the board.

At this time, there don't appear to be any biological variables or toxicologic variables that correlate with an increased risk either of retention or disease resulting from retention. I

think again there, this is an area for research without clear guidance at this time.

DR. HERSCOVITCH: Thank you.

MS. BRYANT: Brenda Bryant. I feel like there is not enough evidence right now to go on. It affects people differently, and the FDA doesn't have enough stats right now to make a real good decision.

DR. HERSCOVITCH: Yes, Dr. Vaughan?

DR. VAUGHAN: Bill Vaughan here. Back to Dr. Bird and the Canadian study that focused on children, if it's retention in all of us, the Canadians had actually suggested maybe try not to do an MRI on a pregnant woman because there is enough sign of trouble. So I hope we concentrate some research in that area.

I know Dr. Toledano has good points on all the confounding issues, but the paper by Dr. Ray spends, as you know, pages trying to deal with that.

Just the other thing is Dr. Semelka's -- I hope I said that right -- we're never going to ban

these contrast agents, but clearly some people are rabidly reactive to them. Let's concentrate on finding out what those triggers are.

DR. HERSCOVITCH: Yes, please, Dr. Siegelman.

DR. SIEGELMAN: Right. Just wanted to say I'm an abdominal radiologist, and there are a couple of things we can quantify in the abdomen. Specifically, we can quantify hepatic fat and hepatic iron and cardiac iron.

There is a difference between -- we're talking about brain now and brain gadolinium, and unfortunately, it looks like there is going to be quite a challenge out there to correlate hyperintensity with actual gad concentration. That's because of the different relaxivity between the different agents.

I just think it would be interesting research out there if somebody could study this in an animal model or in the set of patients that only receive one type of gadolinium agent that we might be able to correlate the degree of T1 shortening,

i.e., how the degree of high signal intensity we see in these areas of the brain to come up with a quantitative or semi-quantitative evaluation of how much gadolinium is actually deposited.

DR. HERSCOVITCH: Please, Dr. Dainiak.

DR. DAINIAK: Yes. Nick Dainiak. Two major themes emerged for me here. One was that the linkage between the brain deposits and NSF is unclear to me. We heard from the speaker from the Guerbet group hypothesize that there may be a continuum, that this could be a form -- i.e., I'm interpreting it to be a possibility that the brain deposits may occur prior to eventual evolution to NSF; that's a hypothesis. But the question is what is the linkage between the two.

The second thing that has occurred to me is that we've heard a lot about the linear versus macrocyclic agents and whether one or the other is more likely to cause the effect. And then we've heard whether the associated versus disassociated forms are more responsible.

Frankly, I don't know that we'd actually

seen a dose-response curve. I don't know that there would be a dose-response curve. We're assuming that there is, but that may not be so. That was hinted throughout the morning session.

In terms of pathways, I think we need to focus on the clinical syndrome. It has to be better defined whether or not that includes, for example, mental clouding we saw earlier.

I think we've heard through some of the additional speakers this afternoon about the possibility of inflammation. There has been some papers out there on active infection being an important predictor. But we need to better define the syndrome, and we've had an offer from one program, The Lighthouse program, for example, to use their patients in that program.

I think we need more population-based studies. We've heard a little bit about the aging population at Mayo. I would be interested in cohorts of patients within that patient database.

I think we have to look at something else; it was brought up this afternoon, which is

decorporation. We saw in the world of radionuclides, we use decorporating agents for plutonium, for example, DTPA.

There are other agents that have been developed that may be actually more effective at decorporating agents. For example, the HOPO agents that are being studied by Rebecca Abergel out at Berkeley. She's in charge of their decorporation program using animals. So they're, in this case, nonhuman primates.

Those are my general feelings, my general thoughts.

DR. HERSCOVITCH: Thank you.

DR. JACOBS: I'd like to primarily address just this question 1, which is what we should do in the absence of criteria. When we get to question 3, I'd like to make some recommendations --

DR. HERSCOVITCH: Thank you.

DR. JACOBS: -- about what sorts of things we would want to do next. But here, the problem is, as I see it, is that we don't know if there is,

in fact, damage. We don't know if there is clear toxicity.

We do know that it's not normal to have gadolinium in your body. That's not the natural state of affairs. In a way, that's a relevant thing because if there's gadolinium there, we've put it there.

I think that using -- I believe I heard another mention of the ALARA principle, that one of the things that at this point in time, until we know, the most appropriate response would be to figure out how we can minimize this kind of retention.

In the process, I think we should be considering a lot of the things that we did hear today like there may be differential retention. It's certainly in different organs. I think the brain was freaking everybody out, but in fact, the body organs, the skin and the bone get a great deal more. That seemed to be reflected in some of the symptomatology that people are experiencing or reporting, and whether it's due to this or not, we

don't know. But those are the things I think we should be considering, which may be the molecular form.

The other thing here is I think at this stage, with the lack of information, that we should primarily focus on in vivo data. Test tubes are nice, but I think we're better off with animals and humans in terms of what actually is there and what its chemical form is. That's probably relevant, too, but again, we don't have enough information.

DR. HERSCOVITCH: Thank you very much.

Dr. Applegate?

DR. APPLEGATE: Thank you. I'd like to add on and agree with what the last speaker just said. I think, first of all, as a practitioner, there is no question that gadolinium MR saves lives, and I use it every day. So that's my first statement.

However, we do have a lot of uncertainty in current state about what its effects are in terms of risk, and I think we need to continue to collect data and review it. Just like any scientist, we have to always be open minded about what we're

going to find and what we don't know because we don't know. I feel that we should be responsible for anything. As Dr. Semelka said, anything we put in the body is something that we have to be knowing could potentially have harmful effects.

I think that there is some emerging question about, I think, less so much the brain. I think that's just something that we pick up because we do so many brain MRs. That's the number one thing we do in children, by the way, but it's really the other body parts that I'm most interested in and curious about.

I want to speak to an example of bone marrow. That has a lot of very active activity in children. So I would say that we do have some concern. I think there are some specific populations that we may want to look at.

I think the evidence that we heard today shows that there were more adverse events that were presented by several people in women more than men, even with normal renal function. I think that we had some question about pregnant women, as one of

the other panelists mentioned, and I would add children. So I think that I would suggest that we consider those populations.

I also think that the approach would be one of what I call Image Gently, that philosophy, what other people are calling ALARA, which is that we know this agent with MR is a wonderful agent, but we have to use it appropriately, and we have to use it optimally.

So do we use half dose, do we use full dose, do we use macrocyclic? We don't want to restrain our clinical use of it. We don't want to necessarily ban it, but we want to give people the right educational information to know that there may be a risk.

So I think we want to move forward by telling people that we have some uncertainty, and we don't want to prevent the public from knowing about it, the clinicians who order these tests from knowing about it. Because you know what, we want to sleep at night, and we want to be clear that we have some uncertainty, and we're going to move

forward, and we're going to try to learn as much as we can about this. But if it's your family member, what do you want to have happen to them?

That's the whole Image Gently belief. We don't want to prevent current knowledge from moving forward, but we also want to continue to use these agents to save lives. So let's do it in the best way we can.

Let me give you one scenario that I want to raise from thinking about the cross-reactivity that we've heard a little bit about but not enough about. And I'll just bring this up for potential future research by the FDA or others, which is the cross-reactivity with calcium and other metal agents.

Consider this. We have babies and children who get these MR with gadolinium studies for brain tumors or for whatever reasons. What if they just get one? They get the gadolinium that goes to their bone marrow or their bone, stays there. We don't know for how long. They go on and have a happy life, and if they're female, they get

pregnant. At that time, most young women have to mobilize bone marrow to make the bone in the fetus.

I'm just going to speculate that like what happened with lead deposition in bone before we decreased the lead gasoline, if we gave gadolinium that we are depositing in the bone, in girls that later on have children, we could potentially be adding to toxicity in our environment in girls that grow up to women and have children, and we have added effects that are unintended.

So these are just things to think about that nobody probably has raised, but an unusual scenario that we have to think about. There are unintended consequences to things we do, so we want to minimize unintended consequences and unnecessary use of agents that may cause harm decades down the road that we never thought about. Thank you.

DR. HERSCOVITCH: Thank you. I think some of your comments, which you may want to bring up again with the next question with regard to specific populations. Thank you.

Dr. Toledano?

DR. TOLEDANO: Thank you, Dr. Chairman.

I will start with the bottom line first. I strongly believe that FDA should weigh this new finding of gadolinium retention in patients with normal renal function at least as heavily as the known risks and now well support.

I know that the clinical information is immature. We don't have enough to go on, but there are a lot more patients with normal renal function than there are with impaired renal function. And we need to publicly acknowledge, FDA needs to publicly acknowledge -- we are doing as a panel here today -- that gadolinium deposits inside and outside of the brain.

We need to make doctors, techs, people who are performing the MRIs, people who are ordering the MRIs, people who are interpreting the MRIs aware of the risks independent of the patient's kidney function so that these physicians and medical practitioners can think twice about the choice of gadolinium-based contrast agent, about the dose of that agent before ordering the scans.

How do we inform the risk assessment? What should we be considering? Honestly, we don't know yet, so we just have to make our best guesses and get on the stick. Let's move forward. Let's talk to people who have suffered from these toxicities. Let's look at the over 65s. Let's look at the pediatrics, the cancer kids, the chronic populations, people with MS, and generate these hypotheses. And yes, we can talk more about that in the later questions.

Regarding the evidence of the differential retention and everything that's listed in the second paragraph, that's still settling. We don't even know the way to get two studies of ostensibly the same thing to be done in a way that would allow them to agree. So we need that to settle, but we definitely need to acknowledge and act. Thank you.

DR. HERSCOVITCH: Thank you. Dr. Brent?

DR. BRENT: It seems to me that as we consider this very important question, that we keep first principles in mind and we try to stick as faithfully as we can to where the scientific

evidence leads us and to try to take data that is not completely evidence-based and use that as a jumping off point to indicate that these are the areas of ambiguity that we really need to study further.

We are in an unfortunate situation here. This is not an easy scientific question. What we do know without any question is that gadolinium is retained, and it's retained in at least some patients irrespective of how good their renal function is.

What we really don't know is whether that has any physiological consequences at all. We have some anecdotal data -- some of it is very powerful, some of it is very emotionally concerning -- that it may be harmful to some people, but that is fundamentally anecdotal data. Sometimes following our emotions in this kind of data can lead us in unscientific directions.

What we really need to do is to focus our attention on determining what, if any, the adverse consequences are of this gadolinium retention

before we decide how we should act on it or to what degree we should be making restrictions, to what degree we should be changing our clinical practice.

These are very difficult studies to do because there are some implicit very difficult to overcome confounding issues when we look at patients who are the ones that are at greatest risk, namely, patients who may have had multiple MRIs because they're not the same as the other patient populations.

Hopefully, with some deliberation, we can come up with some reasonable epidemiological and basic science approaches to try to elucidate the consequences, if any, of retained gadolinium. In the interim, however -- because this is not going to be sorted out for some period of time.

I don't want to jump the gun too much because we're probably going to talk about this later. I just will mention that there probably are things we could reasonably do to be precautious in terms of evaluating if there are consequences of gadolinium retention, which agents are the ones

that are most likely to be responsible for gadolinium retention -- I think we heard a good deal of data on that today -- and to maybe make some recommendations, suggestions, changes in package inserts, and so on about that so that we can start to take steps to minimize gadolinium retention while we're trying to figure out what the actual consequences are.

We know NSF is a disease. It's a very clear-cut unambiguous disease caused by gadolinium retention in patients who have renal failure. It's interesting to contrast that with the gadolinium retention disease we're hearing about today in patients with normal renal function. NSF is an unmistakable, easy to diagnose, clear cut, limited but devastatingly serious clinical condition, limited in the sense of clinical manifestations.

What we heard about today is multisystem, multisymptom disease without any unifying presentations that would suggest a physiology that would seem to make sense. So there are a lot of questions here about what this actually is, if it

actually is a disease.

In summary, I think we should start by acknowledging gadolinium retention exists, be sure that that word gets out by way of package inserts and guidance, and figure out ways of minimizing exposure to agents that are most likely going to lead to gadolinium retention, and while we do that, figure out ways of studying to see what the consequences are of gadolinium retention in patients with normal renal function.

DR. HERSCOVITCH: Thank you. I'll now ask the two members participating by telephone, Dr. Bolch.

DR. BOLCH: Yes. Wes Bolch, University of Florida. Can you hear me?

DR. HERSCOVITCH: Yes, please go on. Thank you.

DR. BOLCH: I find it remarkable the comparison between what we've been dealing with in ionizing radiation CT, fluoroscopy, nuclear medicine, that optimization of the radiation dose and the medical benefit, the image quality, the

risk is to some extent theoretical. We use radiation cancer risk models from the atomic bomb survivors, and we project what the secondary cancer rate to a child would be from a head CT or a body CT. But that has still led to, as Dr. Applegate had mentioned, the campaign like Image Gently.

The key is optimization; that is, in this case, let's try to administer as low a concentration of gadolinium but still providing the diagnostic quality of the image. I would support statements made by people earlier that you can't look at just classes. You need to look at each and every agent, whether it's cyclic or linear or ionic or non-ionic because they have different relaxation properties, so the step in selectivity is going to be different.

So I think there needs to be some optimization studies that are rigid and look at what is the minimum amount of administered gadolinium-based contrast agent needed for the diagnostic purpose.

I would also support previous statements

that we need to look at susceptible populations like pregnant women and children. If there are susceptible classes of patients, maybe a genetic basis of it, we need to identify that.

I would also support continuing the epidemiology studies and the animal studies, but it seemed to be clear that those are done somewhat ad hoc and that there is very much concern about standardization of those protocols so that we can do a meta-analysis and look across studies and come up with concrete conclusions. That's my comments.

DR. HERSCOVITCH: Thank you. Dr. Weisman?

DR. WEISMAN: Thank you. As a rheumatologist who has lived through breast implants and L-tryptophan, I can assure the committee that you really are at the right place right now. I think the story that we heard all along of the interest and excitement and enthusiasm of Dr. Wagner and his colleagues when they saw this problem rear its ugly head, it really led to the development of technology to examine the question of what is the meaning of gadolinium in the body

other than its use as a contrast agent.

That has led to the discovery that there is gadolinium retention in people with normal renal function, and that's really an important issue. But to draw conclusions about starting and stopping agents right now, as we've heard, is a little premature.

I think that all the comments I've heard to this point are really right on, and there is a need to be able to look at this issue from the standpoint of environmental and genetic risk, susceptible populations, et cetera. But it's also led us to examine how often and how frequent are contrast MRIs done when, in fact, there might be other tools to get the same answers or to be able to use these tests less frequently.

In rheumatology, we hardly need contrast because the resolution for our diseases is so good without it, and we learned that lesson early on. Maybe that lesson can be learned in other specialties as well.

In summary, you're right on. You don't have

an answer. There is a loud noise out there, and people are really thinking about what to do next. I think that that's an important conclusion from this discussion.

DR. HERSCOVITCH: Thank you very much.

I'll try to summarize these comments. Not all of them specifically address the first question, and they'll come up in the second and third question, and we can briefly repeat some of these issues.

I think some of the things that I heard, at least, is that we need more information, in summary. But I think being more specific, at least at this point, that it may be a little premature, and there may be differential risk not only for the different classes of these agents but also within classes. And at this point, there's not enough data to differentiate between them or to lump them, and not enough data in general for risk stratification except for those patients, as we know, with renal insufficiency.

There were suggestions, which may seem

contrary, but both of which seemed to be important, that is, the need for population studies, which though would look at subgroups of patients and specific populations, which may be more at risk, but also to consider specific patients because the relationship between their symptoms and exposure to gadolinium and gadolinium retention still has to undergo much more rigorous scientific and medical investigation. Some people may be more reactive to these agents, and we need to focus on them and on their symptoms.

There is a lot of unknown, not only about the class of agents but the different chemical forms, linear versus macrocyclic classes, but also whether there is free gadolinium or gadolinium as it's originally used in agents or perhaps bound to other macromolecules in the body.

Then this goes to even the issue of making measurements. Most of the data will be coming from humans. For example, the issue of brain scans, of course, we don't do biopsies of the brain. We have to have ways of perhaps inferring in a better way

the relationship between the signal as seen on MRI and the ultimate molecular events related to gadolinium which are causing those signals.

Many people, although this wasn't a specific part of the question, noted that regardless of the data we do or don't have, we should consider how gadolinium contrast agents are being used, when they should be used, and then the appropriate dose, and optimizing the dose for the specific imaging question, in some ways following the principles of ALARA, which is used for radiation exposure, of imaging procedures.

There is a lot of focus on the brain today, but several people noted that we have to look at deposition not only inside but also outside the brain, and this may require large population studies. We do have to develop more in vivo data both for humans and from animal models, and any such studies, methods of standardization, which are quite different for animals as for humans, but experiments should be standardized.

I think that's it. Some of the other

comments will be addressed in the next questions. We'll have to move on fairly quickly because we do have two more questions and then two votes to take.

The second question, which I have to read, I apologize, "Based on FAERS and literature reports, is there evidence of a causal relationship between symptoms and signs in patients with normal renal function now and gad retention?

"Please consider when we discuss this the shortcomings of the FDA Adverse Event Reporting System and other uncontrolled data sources. Also, please discuss the potential risks of gadolinium retention with regard to specific patient groups, pregnant women, young patients; those with inflammatory or other systemic diseases and diseases in other organs; patients with chronic conditions that require multiple exposures to gadolinium contrast agents; and other vulnerable populations."

Again, is there a causal relationship, the shortcomings of the data, and vulnerable populations? Some of you have already spoken

eloquently to some of these points. You could obviously briefly reiterate them, but let's focus on these questions to help guide the FDA.

I'm going to start this way and go around, so first I'll ask the two folks who are on the telephone. Dr. Bolch first.

DR. BOLCH: Yes. I believe the evidence in reading the briefing materials and the presentations today that it's very difficult to say there's a causal relationship between the symptoms and what we're seeing.

DR. HERSCOVITCH: Thank you. Our second telephone participant?

DR. WEISMAN: Dr. Weisman. The answer is no to your question.

DR. HERSCOVITCH: Thank you. Now Dr. Brent, please.

DR. BRENT: The question as specifically asked is, is there a causal evidence based on the FDA adverse event reports and literature reports, I think based on that, going back to my earlier question, it's all anecdotal, so we cannot say for

certain. It certainly raises the question, but at this point, it has not been established, in my mind, that there is such a syndrome.

With regard to the second paragraph, the shortcomings of the adverse event reports, it's anecdotal, the data's incomplete, and it doesn't really help us in this instance.

Is there a potential for risk in the populations listed? Well, the question says, "where there might be potential." The word, quote, is "might." Well, of course, there might be. We don't know if there is. Until that's sorted out, I think we should take that same cautionary approach we've all been talking about in terms of labeling and being cautious about the number of studies we do. But beyond that, I think we need scientific data to elucidate whether there actually is such a syndrome.

DR. MARZELLA: If I might elaborate --

DR. HERSCOVITCH: Please, Dr. Marzella. Thank you.

DR. MARZELLA: This is Dr. Marzella. We are

particularly interested in whether or not there potentially needs to be labeling restrictions or labeling special considerations in these patient populations. So even though the risk is hypothetical, we would appreciate the committee's advice on how we should deal with these specific patient populations.

DR. BRENT: Thank you for that. I'd really like to address that question, and that is I think the public needs to know that there is retention and that we don't know what the significance of that retention is. If it were up to me, I would certainly suggest that it be put in the labeling with the appropriate qualifiers that we don't know if it has any significance at all.

DR. HERSCOVITCH: Dr. Toledano?

DR. TOLEDANO: Thank you. It's Dr. Toledano, and I am going to be agreeable and then disagreeable. I agree with the preceding panelists; no, we don't have evidence of a causal relationship.

Now I'll be disagreeable. It's the wrong

question. The more important question is whether we have evidence that gadolinium retention in patients with normal renal function does not have adverse consequences, and we don't.

So that's the cautious approach. Just because you have no evidence that it's red doesn't give you evidence that it's blue. You have to look at the right question.

The evidence, the shortcomings of the FAERS, the shortcomings of the uncontrolled data sources, one great way to address that is by following up. I don't know the mechanisms of doing that. I don't know the practicalities of doing that, but certainly, adverse event reports that are submitted to a company, the company can follow adverse event reports that are submitted voluntarily.

People who screw up their courage and contact FDA, they want to talk to you. They want to talk to us. They want to be heard. So let's hear them. Let's give them a venue to be heard.

The subgroups, we already talked about before. Pregnant, yes; pediatric, yes.

Inflammatory, I think so. Chronic conditions, absolutely. The MS Society keeps changing their recommendations. Get an MRI every year. Get an MRI only if the symptoms change. Oh, wait, there are some people whose symptoms don't change, but they get deposits or they get new lesions, not deposits yet. They're still not on the retention.

All of this stuff, you've got patients willing and able to provide information, so let's capitalize on it.

DR. HERSCOVITCH: Dr. Applegate, please.

DR. APPLEGATE: Yes, I would echo what we just heard. We don't have a causal relationship that's been presented. We do have questions, and I think from a safety perspective, we do want to be cautious about vulnerable populations like pregnant women and pediatric patients, not because they may be at higher risk but because they have a longer lifetime to be exposed to gadolinium.

We don't know about any risk to their cognitive development. We just don't know, and to their bone growth and also to their mobilization.

As I said before, if the girls were to become pregnant and to grow a fetus -- and I don't know if anyone knows this story about leaded gas, but it's a fascinating one. When the public health service in some states were taking blood samples in pregnant women, they discovered high lead levels. So it's just a cautionary thing that took us a long time to figure out.

DR. MARZELLA: This is Lou Marzella. If I may ask for elaboration from the experts, the pediatricians, are there specific pediatric subgroups that one should be more concerned about in terms of susceptibility to gadolinium?

DR. APPLEGATE: Well, you know what might be interesting is, as the rheumatologist who was on the phone said, we might want to selectively look at autoimmune and inflammatory disease, juvenile inflammatory arthritis patients. And we might want to say would we want to start a registry or start studying those patients who were exposed to gadolinium, and we could do it prospectively and retrospectively. But it seems to me that parents

would be more than happy to enroll and give urine and maybe a skin biopsy. They're not too keen on blood, but the other two likely.

DR. HERSCOVITCH: Thank you.

DR. APPLEGATE: One other thing.

DR. HERSCOVITCH: I'm sorry. Excuse me.

DR. APPLEGATE: Registries, registries, registries. These are the huge shortfalls of these --

DR. HERSCOVITCH: Yes, that would be in question 3, yes, but I think we're hearing that message. Thank you. Dr. Jacobs?

DR. JACOBS: I agree with everyone else that the evidence of a causal relationship is not there. I believe that some of it is suggestive because some of the symptoms reported seem to be similar to the NSF symptoms. So that to me is suggestive, but it's nowhere near there.

In terms of labeling, obviously, we need to put something in the labeling. The language that Optimark suggested and put in theirs seems very reasonable.

In terms of vulnerable populations, I'll point out that in general traditionally, if we don't have evidence of safety in vulnerable populations, we restrict them. You do not give radiation to children unless you absolutely have no choice, again, because you know that intrinsically, they are likely to be more vulnerable if there's something. I think the same would be true of both pregnant women and obviously to their fetuses.

I would think that we would be able -- I don't know if you are free to put into your labeling, but it should be that extreme caution should be used or something like that. There are wordings that people use for things that have never been tested in these populations. I think that would be appropriate to put in.

A public education campaign would be appropriate. It's hard to have an education campaign around, hi, we don't know what this does, but that's the truth of it, and patients deserve to know that. I think it's an important thing.

DR. HERSCOVITCH: Thank you. Dr. Dainiak?

DR. DAINIAK: Yes. I concur with the last three speakers about there is simply no evidence to establish or to reject the hypothesis that exposure or deposition of gadolinium has caused the signs and symptoms that we've heard about today.

That's primarily because there are no well-controlled studies because the controls that are conceived are inappropriate, in some cases becoming a fatal flaw. Really, you need to have MRIs with and without contrast as the appropriate control. We need those studies in order to shed light on that first question.

In terms of subgroups, I think that the subgroups that have been identified, pregnant women, the pediatric cases, and those who are going to require multiple studies because of chronic conditions, are the appropriate ones to identify as high-risk groups.

In the pediatric group, I would be concerned about leukemia, lymphoma, lymphosarcoma. We heard about the deposition of gadolinium not only on the surface of the bone but also within the bone

marrow. If that's the case, that's going to be around for a long time. We would like to know if there is any influence on the differentiation of those cells in the marrow and predisposition to leukemia.

I think we need to establish teratogenicity studies in animals, and that's it.

DR. HERSCOVITCH: Thank you. Yes, Dr. Siegelman?

DR. SIEGELMAN: For the first paragraph, I agree with the prior panel members that right now, we don't have evidence of a causal relationship. I'm fairly sure that close to 100 percent of folks do not give gadolinium to pregnant patients. That's considered a contraindication.

Does anybody on this panel do this?

(No response.)

DR. SIEGELMAN: No. So it's not done, and gadolinium does cross into the placenta and fetus so that's considered an absolute contraindication. We also try not to radiate these women. So we do all ultrasound or non-gadolinium enhanced MRI. So

that would be a population at risk that we always screen for.

DR. HERSCOVITCH: Thank you. Dr. Vaughan?

DR. VAUGHAN: It's just Bill. Bill Vaughan. There's no scientific evidence of this causation, but I'm sure glad Chuck Norris isn't here to hear us say that. There's clearly a bunch of people who are in trouble and that the spotlight [sic] people have pointed to.

I think the EMA, the potential that if you put a toxic rare earth element and your body hangs onto it for years, there's a chance something is wrong. It's the potential that I wish we would worry about a little bit.

On FAERS, neat program, but I think the data shows, what, 10 to 20 percent of what actually happens gets into FAERS, I think is the number. So it would be neat to do a more structured observational trial. You can't get your car checked or stay at a motel without three, four emails asking how it went. We could do some good follow-up on people who have had these contrast

MRIs, something better than just FAERS.

DR. MARZELLA: With the chairman's permission, I'd like to follow up on Dr. Dainiak's question --

DR. HERSCOVITCH: Oh, please, yes.

DR. MARZELLA: -- regarding the preclinical safety characterization of these products.

DR. HERSCOVITCH: Please do.

DR. MARZELLA: Thank you.

DR. LANIYONU: There was a reference to the need for reproductive and development toxicity studies. I'd like to point out that these studies aren't normally done for these class of products, and virtually all the gadolinium compounds have really been specific to what's found during those reproductive and development toxicity studies.

I think one takeaway message that I'm hearing is that perhaps there is a need for longer term follow-up studies in children and in more studies. Some of the sponsors have started -- they have initiated those studies. So you're pointing out perhaps there is need for greater harmonization

amongst those studies amongst the classes of compounds than it is at the present time.

Sorry. My name is Adebayo Laniyonu, and I'm the supervisor of pharmacologists for the Division of Medical Imaging Products.

DR. HERSCOVITCH: You don't have to apologize your name to someone called Herscovitch.

(Laughter.)

DR. HERSCOVITCH: Yes. I think we'll continue now. Ms. Bryant?

MS. BRYANT: I agree that there is not enough evidence of a causal relationship between the symptoms and signs in patients with normal renal function and gadolinium retention versus patients with chronic illnesses.

A patient might have been exposed several times, have an MRI over several years, versus a healthy person who might have been in an accident or something and has to have an MRI and have a reaction the first time versus someone who's been exposed to it over several years.

So where do we find the line and where do we

get the stats to say that if you have a chronic illness, you're going to be more affected, you're going to have more gadolinium retention in your kidney versus a healthy person? We don't have enough evidence to say that. We don't have enough stats.

DR. HERSCOVITCH: I believe we have a comment from the FDA.

DR. PINHEIRO: Very quick reaction. Simone Pinheiro from the division of epi, about what Dr. Siegelman mentioned in terms of use of gadolinium in pregnancy. I wanted to remind you that we've done -- Dr. Bird presented some Sentinel data showing actually a vast use in pregnancy, so there may be differences in how these are done in practice. This is on slide 28 of the OSC presentation.

DR. HERSCOVITCH: Thank you. Please?

DR. FURIE: Karen Furie. I do not believe that there is evidence of a causal relationship at this time.

In terms of the second piece, I think that I

would separate out that we don't know whether the retention of gadolinium is differential across different groups, and that may be based on renal function as we heard, that it might be a continuum or there may be other patient-specific factors that are related to whether or not there is gadolinium retained.

In addition, gadolinium retention may interact with other patient-specific factors like comorbid conditions or underlying inflammatory states and therefore go on to increase risk of secondary complications. So I think at this time, those elements are really unknown.

DR. HERSCOVITCH: Thank you. Dr. Latour?

DR. LATOUR: We can't draw conclusions based on the current FAERS data and the case reports and case series. However, we wouldn't expect to. I think the open public forum said it best that the clinicians are probably not going to make the connection between the gad exposure and the symptoms, and most of the patients -- until recently, we haven't recognized this potential for

retention, so the patients may not know. And in some cases, the symptoms seem to be presenting late. So I don't think we have the surveillance system where we could draw conclusions yet.

DR. HERSCOVITCH: Thank you.

DR. HENNESSY: Sean Hennessy. We usually don't rely on spontaneous reporting systems to provide compelling evidence of causation, and if all we had were the spontaneous reports that have gone to FDA, it wouldn't provide very strong evidence of causation.

We know that free gadolinium is toxic. We know that the toxicokinetics of the drug are different than what we thought they were a few years ago, and it's retained longer than we used to think. We know that in patients with renal insufficiency, it causes a well-described syndrome that everybody agrees is real.

Renal function, it's not that you either have renal dysfunction or you don't have renal dysfunction. There are different degrees. It's a continuous variable.

My null hypothesis wouldn't be that the drug is safe in the absence of spontaneous reports. My null hypothesis would be that it's got the effects of gadolinium unless demonstrated otherwise. I am puzzled by the large number of cases that appear to exist in registries that haven't been reported the FAERS system, and I'm not sure why that is.

DR. HERSCOVITCH: Thank you. Please.

DR. HERNANDEZ-DIAZ: Sonia Hernandez-Diaz. I agree. I don't think there is scientific evidence of a causal relationship for the clinical consequences for the reasons mentioned, but I believe also that there is a theoretical compelling mechanism and that we don't have evidence of safety, either. So as Dr. Toledano said, lack of evidence is not an evidence of safety, and we need to put boundaries to what we know about the safety.

Just briefly regarding the vulnerable populations, I think it makes sense for us to consider them as special risk. And for pregnancy, I agree with Dr. Pinheiro. Pregnant women are exposed in the first trimester, sometimes because

they need to, but also because over 40 percent of the pregnancies in the U.S. are unplanned, not saying unwanted but unplanned. So by the time we realize the women are pregnant, we might have already exposed by them, as shown by a paper with thousands of women exposed.

If we really don't want them to be exposed, we should be considering pregnancy tests or contraception or some method because otherwise there will be exposures.

DR. HERSCOVITCH: Thank you. Dr. Frank?

DR. FRANK: I feel compassion for those who spoke during the open public session who feel that they've been harmed by this, but the answer to the question of causality having been proven I think is no.

What we're talking about here is not what is proven but what is prudent, and in that regard, I agree with the comments of Dr. Applegate. I agree with Dr. Toledano's comments about do we know that it doesn't cause things and Dr. Jacobs' comment about vulnerable populations.

With regard to the adequacy of the FAERS database, we all believe, I think, that it's good at low frequency events, and we're talking about a few hundred reports among a few hundred million exposures. So it certainly seems to be a low frequency, if there is a causal relationship. But what FAERS is bad at is long latency items, and it suffers from variable quality of reports. Therefore, it could be enhanced, in some way perhaps, to gather more information, more in-depth information than what is gathered now.

I think when we get to a couple of the other questions 3 and 4, we'll have a fuller explication of that.

DR. HERSCOVITCH: Thank you very much.

With regard to briefly summarizing our discussion with regard to FDA questions, I think there is fair uniformity that there is no evidence of a causal relationship between the symptoms and signs in patients with normal renal function and the retention of gadolinium.

There was, though, mention by some folks of

the anecdotal data in FAERS, which do raise questions, and some of these symptoms are, in fact, even similar to those seen with NSF. But I think it was felt that the FAERS data and other anecdotal reports really perhaps raise questions, but in themselves do not have a scientific foundation for reaching any conclusions.

With regard to patient populations, which may be more at risk, I got the sense again that we feel there isn't enough data, but some groups perhaps should be given special attention, for example, pediatric patients and patients who are pregnant because as a result of gadolinium exposure, they might have a longer time to experience any deleterious effects, and especially on the pediatric group, they also have a developing nervous system issue.

There was mentioned that more attention should be made or perhaps they may be more vulnerable with regard patients who have autoimmune and inflammatory diseases. They may potentially be more at risk along with consideration of patients

who are getting multiple doses. But again, there isn't a lot of data to inform us with regard to vulnerable populations.

I actually wrote down, and I will repeat it because I think it's important to say as sort of a summary of our discussion, Dr. Toledano, Dr. Frank and other folks who pointed out that absence of evidence is not evidence of absence of toxicity in patients with normal renal function, and even pointing out that renal function is not either normal or abnormal, but as one of our discussants pointed out, it's a continuum.

Though in spite of this absence of evidence, a concern was expressed -- and this relates to our ultimate decisions -- that some action or caution could be appropriate in certain populations even though there is or perhaps because of the absence of data.

Some of you actually answered the next question, so I'll briefly say with regard to other studies, it was felt that we need better controlled studies, and I would say both clinical studies with

positive and negative controls, if possible, and definitely better controlled animal studies with some standardization.

Population studies are important at one end, but perhaps animal studies looking at the effect on bone marrow, especially, again, in pediatric patients in the subgroup of patients with leukemia and other hematologic disorders. Also, teratogenicity studies were felt to be a gap.

That, I think, will lead us into the third question --

DR. MARZELLA: If I may comment.

DR. HERSCOVITCH: Yes, please, Dr. Marzella?

MR. MARZELLA: We did not agree at this point that there are teratogenicity studies are a gap because at the preclinical level, they have been conducted. We would agree that additional studies would be needed, but to the extent that the preclinical characterization was done, I just wanted to acknowledge that.

DR. HERSCOVITCH: Thank you for pointing that out to me and to Dr. Dainiak. Thank you.

We will now move on to the third question, which some of you have actually already answered. "There are gaps in our understanding of gadolinium retention, including toxicological thresholds, potential mechanism of toxicity, potential clinical and subclinical manifestations of toxicity in the central nervous system and other organs."

We are asked to discuss "the types of preclinical studies, for example, comparative toxicokinetic studies, of levels of gadolinium retention and functional and pathologic correlates in both the CNS of juvenile and adult animals.

"Clinically, please discuss what clinical studies should be performed to better understand any potential safety risk associated with gad retention and include in your discussion prospective studies such as registries; epidemiological surveys; parallel-arm studies of neurologic function; and also, retrospective studies using existing databases."

Some of these points have been already addressed. We do have to save some time for our

votes for question 4 and 5, but I'll go around if any of the speakers have some additional suggestions with regard to question 3, further types of preclinical and clinical studies.

DR. FRANK: Having started my career as a clinical pharmacologist in the pharmaceutical industry, I'm very attracted by the notion of the mass balance studies that were suggested earlier, but I think that's a little outside the scope of this question.

I think for adverse effects that have a long latency and a low frequency, randomized controlled trials are really infeasible, and therefore, something else like registries would be necessary in order to achieve that.

There's been some discussion of what is the appropriate comparator group, acknowledging the confounding effect of concomitant disease or even the disease for which the procedure has been ordered, and therefore, the only real comparison is the same patient, everything else being the same with and without the gadolinium. This is a

particularly difficult question to answer, but RCTs would be infeasible for this.

DR. MARZELLA: If I may comment. This is Lou Marzella.

DR. HERSCOVITCH: Please.

DR. MARZELLA: I would like for the committee, if possible, to include in your discussion the potential of parallel-arm studies, which would be looking at functional, neurologic function let's say in two parallel arms.

DR. FRANK: There's been a lot of work in cognitive studies in the Alzheimer's area, so I think there's been a lot of development of what those metrics might be. Despite their subjectivity, they're getting pretty refined.

I was addressing the parallel-arm question. There's been discussion earlier about what's the appropriate comparator group. I think it can only be the patients with everything else being the same, including the disease, who had an MR without gadolinium.

DR. MARZELLA: Exactly. So it would be a

situation where you would have a largely normal patient population who happened to have an MRI or two and who could be compared to another group if one could find a sensitive sufficient test that could be powered to detect some clinically meaningful deterioration, let's say, neurologic function.

DR. FRANK: And it would be difficult to do that retrospectively because you'd need to base --

DR. MARZELLA: No, it would have to be a prospective study.

DR. HERSCOVITCH: Comments?

DR. HERNANDEZ-DIAZ: I actually think that we have passed the time for clinical studies, and we can go into the clinical studies, and for that, I think the first thing to realize is which question do we want to answer. We may have many of them; some of them that we pick. If we want to differentiate the retention by specific agents and the effects by specific agents, then we want to have biopsies on skin thickness measures and levels, and cognitive measures, and detailed

neurological measures, then we need to prospectively enroll patients in registries and follow them intensively.

But no way we are going to have the numbers in registries to get to the more potentially rare, infrequent effects. For that, I will propose to use the data that is already available that is going to produce family information, that has a large sample size with multiple agents and multiple indication, multiple populations and that may be able to answer to the question of risk quantification and also risk prediction, and then potentially risk management strategies, so who is at risk.

A third question that may be beyond our discussion today but has been raised is the potential identification on treatment of cases. So if there are cases eventually, can we prove a treatment? I know that was not part of the discussion today.

Then I have a long list of things to consider in the design. I don't know if you want

me to go first or to allow that for the discussion later. They're all challenges that we're going to find in the design like the definition of the outcome and so forth.

DR. HERSCOVITCH: I think we should probably move on because we do have to vote. Again, I'm moving on. Just anything that we haven't discussed already with regard to preclinical or clinical studies.

DR. HENNESSY: Thank you. Sean Hennessy. I think maybe we can learn a lot from NSF. For example, comparing genetics and metabolomics in people with and without NSF may help us to learn about the effects of gadolinium in patients with normal renal function. I think studies of the toxicokinetics in normal patients would be helpful.

For outcome studies, we need to figure out which outcomes we want to study. It may be imprudent to lump everything into one outcome because the different outcomes could have different causes, so we may need to identify a few of the more common, more serious outcomes and come up with

definitions for those and then follow highly exposed patients, patients who get, for example, screening tests compared with an appropriate control group. I'm not sure who that would be. Maybe there are patients who have an indication for frequent screening, but who don't understand frequent screening might be a valid control group. And I'll stop there.

DR. LATOUR: Just briefly, I'd like to know more about how the gad's getting there and where and which cells it's in, if there's an inflammatory response, and if it's happening patients that we know have an intact blood-brain barrier compared to those we're treating.

DR. HERSCOVITCH: Thank you.

DR. FURIE: Karen Furie. I just wanted to respond to Dr. Marzella's question about the parallel design. One of the confounders is that gadolinium is used for specific conditions and not in others. So it's not as though you're going to find stroke patients with and without gadolinium or tumor patients with and without gadolinium. It

would probably be unethical or at least impossible to enroll people if you were to say to them as part of the trial, you will get gadolinium or you won't even though it wouldn't be clinically indicated.

So I do think there's an inherent problem here in trying to tease -- with a retrospective or even a prospective observational design the issue of the underlying problem for which the gadolinium is being administered.

DR. HERSCOVITCH: It's okay if you don't have any further suggestions or if you have no comments, or if your suggestion has already been made, then we can move along because we are running short.

DR. DAINIAK: Just a quick one. There are no toxicological thresholds that have been defined, and we get into the issue of parallel studies being unethical. I think one way around it is through animal studies. If thresholds are found, you then have to go down the pathway of identifying the molecular pathways that are involved and then developing mechanistic models.

Retrospective studies are an important group to look at, and I would consider looking at databases of AER reports that manufacturers maintain.

DR. HERSCOVITCH: Dr. Jacobs?

DR. JACOBS: Just a couple of things that weren't mentioned so far. One possible way to organize looking at this going forward on a scientific basis would be to try to put together a consortium of people who would address the designs and come up, for example, with common clinical or preclinical protocols that could be used. That could involve industry, academic, regulators in a way that didn't violate any proprietary issues so that everyone would be open and above and be part of it.

One model for this is studies that are done through the Foundation for NIH and their biomarker consortium. They work this way, and those projects basically are independent of the funders who tend to be industry, but industry gets to decide if they're going to fund them. That's one possible.

The other thing I want to mention that I haven't heard anybody say anything about, in animal studies, doing some studies in established disease models; obese animals; animals with kidney; with diabetes; obviously, hypertensive; animals with MS. These models are not perfect, but they might recapitulate -- we use them to develop drugs, so they might recapitulate some of the abnormalities that might be contributing to this. And those models exist. Those are relatively simple animals studies.

Finally, it would be interesting to see if some non-rodent species would be a little bit better. I know it's more difficult to deal with dogs instead of mice, but it still might have some value to look at that. Larger animals, mini-pigs, for example, are much more like humans than dogs are, and dogs are closer than mice.

DR. MARZELLA: If I might respond to that question, I think that the idea of collaborative studies in an important one. We've heard at least I thought some industry speakers speak in favor of

collaboration. We have had some experience with the different contrast agents where there has been collaboration in looking for the potential incidence of pediatric hypothyroidism, so that's an important consideration.

We also don't have time to get into this, but there have been other animal models that have been looked at in terms of developing a fibrosis, which potentially could be more sensitive. But that would require a separate discussion, but it's a good thought and a good suggestion.

DR. HERSCOVITCH: Thank you. We'll move now. Just please ask the remaining speakers to be very brief because we do have to move on to the votes. I apologize. Dr. Toledano?

DR. TOLEDANO: This is Dr. Toledano. I'll just say into the record that Dr. Applegate shook her head and said, "No, I've got nothing." She doesn't have nothing. She's got a lot of stuff, but I also have a lot of stuff.

I'm done with the preclinicals. I'm totally done with the preclinicals. We have to really

balance the, wow, it would be really great if I knew that with what we need to do for the public health right now in the real-life patients in the clinical studies. And I agree with Dr. Hernandez-Diaz that we need to know our questions, but we're not there yet.

So yes to all the stuff that's already happening listed in the question. Think about not just retrospective case control studies in the existing databases. Think about prospective cohort studies within the databases.

Think about being opportunistic with your populations when you're looking for the rare signal. Your chronic people, they give you a great opportunity to look at what happens on a first MRI if you're diagnosing relapsing MS before they're really sick, and then you can follow them, and you need to follow them. We need to know the indications for MRI, and we need to know why the contrast was ordered, what does it really benefit the patient.

I know it's hard with HIPAA and fractured

care delivery and time crunches and different specialists. I don't know how we round out FAERS in this system, but we need to. We need to within patient timelines, and we need the long-term follow-up.

That was, I think, everything that I need to say here, so thank you.

DR. HERSCOVITCH: Thank you. Dr. Brent?

DR. BRENT: If I might, and I will be very brief, just a couple of points. These are very important agents, and this is a very, very important question, So it really does need to be studied.

The first prerequisite for designing any study is to define the question. We need to figure out what the actual endpoints we're interested in looking at, what our outcomes would need to be. I think one source of information we can go to for this is the gadolinium support groups. At least they can tell us, look, this is what we think the disease is, so we can see if we could figure out what endpoints we want to be looking at, what are

people complaining of, so we know what we should be looking for.

Then I think what this requires is really a three-pronged attack. It requires animal studies. I realize many of them might have already been done as part of the NDA for these agents, but we might want to do some with some other specific endpoints in mind. They might be behavioral, for example.

The human prospective studies, definitely. Registries have been mentioned. I love the idea of registries. My primary research is at National Registry. Thank you, FDA, you partially support it. But actually, a registry would not be the way to go here because a registry is fundamentally uncontrolled, and what we need is prospective cohort studies.

Prospective cohort studies, it would be very nice if some of our colleagues there from industry would all get together and decide to support such a study. But those prospective cohort studies should only go forward once we have already defined what the outcomes and what the endpoints we're looking

for are. They shouldn't be fishing trips.

Lastly, another approach that I would suggest, the issue has come up of gadolinium chelation. I'm just adding some of it is being done legitimately as part of a FDA-sponsored trial. I know there are a lot of very illegitimate doctors out there that are chelating people with the gadolinium. But a controlled chelation study would be actually potentially very useful, a placebo-controlled study to the people who chelated better compared to the ones who don't. And that would be the third arm that I would suggest. Thank you for this time.

DR. HERSCOVITCH: Thank you.

DR. MARZELLA: Just a minor correction, that the FDA is not sponsoring the chelation study, but since it was already cited publicly, we can acknowledge that it's being done under IND. We're not sponsoring the study.

DR. BRENT: I'm sorry. I thought it was represented as being sponsored.

DR. HERSCOVITCH: Dr. Bolch? Hello?

Dr. Bolch?

DR. BOLCH: Yes. Can you hear me?

DR. HERSCOVITCH: Yes, please, go on.

DR. BOLCH: Just a quick comment. When designing animal studies to look at tissue-specific toxicity, it would be beneficial to look at dose escalation as relevant for optimizing imaging protocols and coupling that with image quality assessment. This follows along with the suggestion of the ALARA principle. Thank you.

DR. HERSCOVITCH: Thank you. Dr. Weisman?

DR. WEISMAN: The issue about what to do next, I would like to just comment on. I think we may have forgotten a little bit about what we learned from the NSF patients and the CAT space and narrow pathways. There may be patient populations with defects in those areas, and one could take a look and see whether or not there's been an unusual amount of toxicity or accumulation of gadolinium in those populations.

It's low-hanging fruit, but it's an interesting area. At least the idea is to take

advantage of what we already know from the pathologic data from the NSF patients. That's what I'd like to add to your comments about what kind of studies to do next.

DR. HERSCOVITCH: Thank you very much. I think many of you had many different and I think very valuable suggestions, so I won't try to repeat everything that everybody said, but some themes overall in animal studies but also human studies, the importance of standardization and better controlled studies; the importance potentially of collaboration among industry and I would say also academics to help explore these important issues.

Population studies and cohort studies, especially prospective ones was an important theme; also, what we can learn from specific patient populations with perhaps specific symptoms, extrapolating from the NSF symptomatology. But of course to do that, we have to have a better definition of outcomes. There was also a mention of looking at controlled chelation studies. So thank you for all these valuable comments.

I'd like now to move on to items 4 and 5. These are the votes. With regard to the votes, there will only be questions or discussion with FDA folks about the wording. We aren't going to reiterate specific discussions. But after the vote is taken, we will be asking each one of you what aspects of our discussion prompted your vote, and note that there can be different reasons for disagreeing. You may think an action is too strong and vote no, or you may think an action is not strong enough and vote no. So that will come out when we go around the table to discuss your votes.

The first vote is question numbered 4, but it's the first vote. "The FDA's plan for addressing the potential consequences of gadolinium retention is to revise the prescribing information for GBCAs as a class to include a warning for retention for all agents with greater retention of all or some of the linear agents as compared to macrocyclics in certain organs, including the brain, recommended risk mitigation steps for certain populations."

That is the question, and we're asked to vote yes or no. Does anybody have any questions about the wording of this question?

DR. DAINIAK: I do. After the semicolon, it looks like a dangling participle almost. Is that a second question, or is it incorporated into the whole question as one?

DR. MARZELLA: It's all inclusive. So it would be a warning, as Dr. Fedowitz described earlier, and also requires that we include risk minimization steps to the extent that we can.

DR. DAINIAK: Do you have those steps in mind?

DR. MARZELLA: It would be the same as we talked about, that there would be special concerns for patients that receive multiple exposures, recommendations to restrict use only when clearly indicated, maybe special consideration about pregnant women. Those would be the considerations.

DR. JACOBS: I have a question about, quote, "with greater retention of all or some of the linears compared to the macrocyclics."

That would be a class statement or would you individualize the linears? Because there are some that, like for example, are used for liver-specific. Would you individualize the general purpose ones, general purpose linear versus special purpose linear, versus --

DR. MARZELLA: I don't think that we need to get to that level because, frankly, we will need to reach that decision later on. It's just we want some comment about the general approach, whether, as Dr. Fotenos said earlier, is this enough, is this too little, is this too much, is this too late?

DR. HERSCOVITCH: Now we can move on to vote, and the buttons are at the base of your microphone. Please press the button on your microphone that corresponds to your vote, and there's a yes, no, or abstain, but I would prefer yeses or nos.

You will have about 20 seconds to vote. Press the button firmly. After you've made your selection, the light may continue to flash. If you

are unsure of your vote or you wish to change your vote, please press the corresponding button again before the vote is closed.

Commander Shepherd, when do we begin pressing our buttons?

LCDR SHEPHERD: Now.

DR. HERSCOVITCH: Now, please, press your buttons yes or no for question 4.

(Voting.)

DR. HERSCOVITCH: It can still flash according to Commander Shepherd, and the folks on the phone are emailing their votes.

LCDR SHEPHERD: For the record, the vote is 13 yes, 1 no, 1 abstain.

DR. HERSCOVITCH: I will begin in the other direction with the folks on the phone first. Now that the vote is complete, we'll go around the table and have everyone who voted state your name, your vote, and it says if you want to, but I think the FDA would appreciate, the reasons why you voted as you did, reading your opinions into the record.

The folks on the phone first, Dr. Bolch?

DR. BOLCH: Yes. I voted yes. I would qualify that the focus on brain I think may be overstated as we had talked about bone marrow and skeleton are also important.

I don't know if it's appropriate at this point, but at some point, by not having a certain agent, you may be lowering specificity of the medical imaging. I think there needs to be some balance of statement of risk versus loss of benefit. Thank you.

DR. HERSCOVITCH: Thank you. Dr. Weisman?

DR. WEISMAN: I voted yes. Words matter. They were very well chosen. It was appropriate to state that there may be differences among the agents that need to be explored. It's also appropriate to state that risk strategies need to be looked at more carefully, and there are populations that need to be addressed such as the populations that may overutilize this particular type of contrast imaging. I think the words were very well chosen.

DR. HERSCOVITCH: Thank you. Dr. Brent?

DR. BRENT: I voted yes. I think it's all the other issues we've discussed. There clearly is some concern here. We don't know how important that concern is, but there clearly is concern, and people need to know. Emphasizing the concern about linear agents is I think a good idea, and simply, risk minimization is the objective. So I voted in the affirmative.

DR. HERSCOVITCH: Thank you. Dr. Toledano?

DR. TOLEDANO: Thank you. This is Dr. Toledano, and I voted no. I am the holdout. I absolutely agree with Dr. Brent that people need to know, people, all the people, not just the doctors. And I don't think this plan is sufficient.

It is hard to dismiss an anecdotal report when you are the anecdote. A life ruined is a life ruined. What does a patient when doctors and everyone she or he turns to for help pooh-poohs her or his concerns and doesn't order a test, a simple urine test? When a patient finally does get tested and is found to have gadolinium retention but there is no FDA-approved antidote, what does that patient

do?

The disconnect noted in Gena Norris' statement is so true all across this country every single day. Who prescribes the gadolinium-based contrast agent? Who chooses the agent? Who sets the dose? Is it the oncologist or neurologist or whatever specialist is ordering the imaging? That person may not be able to request a specific agent or a specific dose.

There are lots of MRIs that happen in places without choices of agents. Not every MRI happens in an inpatient context in a tertiary care hospital. Sometimes it's just whatever the facility has. This is what we do for all the patients, and if you ask us if it's safe, we're going to tell you sure. Just drink some water when you get home. You'll be fine.

How often do patients see any labeling? Almost never. When do patients get the opportunity to ask those questions? When someone gets an order from their neurologist or their oncologist to go to the hospital or the imaging facility and get an

MRI, they show up. They're asked to sign a consent form. What happens if they say no? Where does that go? Who talks to that patient?

I know these concerns. We do not have evidence on which populations we need to minimize risk. We do not have effective means -- or maybe we do, but we haven't yet exercised them -- to engage the public with communication. There's not a simple fact sheet.

If a patient goes to get an MRI at Community Radiology Associates here in the D.C. metro area -- and I'm not picking on them because they're necessarily different; they're just a big one -- the person they speak with at the desk may not even be aware of the FDA safety warnings.

The communication has to be to the patient, and we need the active pharmacovigilance, so I voted no because as beautiful as this wording is, I do not believe it is sufficient.

DR. HERSCOVITCH: Thank you very much for that important explanation.

DR. MARZELLA: With the chairman's

permission, may I please comment?

DR. HERSCOVITCH: Please, Dr. Marzella?

DR. MARZELLA: Thank you for those comments. I just wanted to comment for the record that the dechelation approach is considered experimental, and given that we do not know what the correlates, either clinically or toxicologically, are for retention, that despite the anecdotal information, we would view that as being investigational. It's being done appropriately under IND.

DR. TOLEDANO: I absolutely agree. It's Toledano saying I agree. And that's why I say you don't know if there's an antidote. It's still investigational. Thank you.

DR. HERSCOVITCH: Thank you. I think Dr. Brent earlier mentioned that that is an area for future investigation.

Dr. Applegate?

DR. APPLEGATE: Kimberly Applegate. I voted yes. I think it is well worded. I'm very encouraged by the last bit that says, "Recommended risk minimization steps for certain patient

populations." I hope it will be for all populations as was eloquently just stated by a prior speaker because I think that if we all collaborate to educate and understand what this is and what it's not, I think we're going to all be better off, and our patients will be better off.

I will again go back to Image Gently, which provided brochures for parents to understand all the imaging that has ionizing radiation involved with it so that they could understand it in 20 languages. It's free on the website. We could maybe think about that same approach as we go forward, and for all of the healthcare workers as well. Thanks.

DR. HERSCOVITCH: Peter Herscovitch. I voted yes. I'll just be brief, that in spite of the lack of evidence, there's obvious concern been expressed by both the medical community, industry, and patient populations, and the public. I think it's important that information be put out there with regard to gadolinium retention.

Given, though, our weak database and again,

although there's no clear cut evidence, several members, and I agree with them, did identify certain patient populations that could be more at risk. In the abundance of caution, I think it would be good to have that included as well in the label and discussions.

DR. JACOBS: Paula Jacobs. I voted yes. Basically, I think this is the prudent way to go for something that can be done now. It should not preclude continuing experimentation, attempts for public education. The Image Gently profile is a very good example of how this can be done.

DR. DAINIAK: Nick Dainiak. I voted yes. GBCAs may be actually deleterious to human health, and the FDA should warn others of this fact. Secondly, risk minimization is needed for special groups that we discussed.

DR. SIEGELMAN: Evan Siegelman. To quote Spike Lee, "Do the right thing," it's the right thing to do.

DR. VAUGHAN: Bill Vaughan. I voted yes. I wished I could have voted for the EMA proposal, but

this was the next best thing. I've been moved by Sharon Williams' quote or letter to the FDA. "So why is it okay to keep injecting the least stable gadolinium-based contrast agents into patients when it is highly likely that those people are going to retain some unknown amount of a toxic metal?"

DR. HERSCOVITCH: Thank you, and thank you for referring to one of our public commenters. Their input is very important to this meeting.

DR. MARZELLA: If I may comment, I think we would accept a reconsideration of your vote because if you believe that the FDA should withdraw these products from the market, then we would put an asterisk next to your yes and say that your considered opinion is that these products -- whichever products you're recommending --

DR. VAUGHAN: It's beautifully drafted. I wish it were a little stronger. So yes, sir, an asterisk, please.

DR. MARZELLA: Thank you.

DR. HERSCOVITCH: Ms. Bryant?

MS. BRYANT: Brenda Bryant. I voted yes because I believe relabeling will bring more communication between the medical profession and the patient.

DR. HERSCOVITCH: Thank you.

DR. FURIE: Karen Furie. I voted yes. I think the wording walks the line between notifying people of a potential concern without causing sort of a panic that could adversely patients who need contrast imaging.

DR. HERSCOVITCH: Yes, Dr. Brent?

DR. BRENT: May I as well add an asterisk supporting the EMA position?

DR. HERSCOVITCH: Fine. Thank you. I guess if we could have the record record that from Dr. Brent.

Dr. Latour?

DR. LATOUR: Larry Latour. I voted yes. I think this is the appropriate warning level, appropriate step to take right now. I think going beyond that like the EMA on a class is a step too far until we learn more, but we need to pay very

close attention. This will serve the purpose of warning the practitioners and educating them, and hopefully that gets communicated down to the patients as it did with NSF.

DR. HERSCOVITCH: Dr. Hennessy?

DR. HENNESSY: Sean Hennessy. I abstained. I was convinced that you get a higher dose of gadolinium with the linear agents than you do with the macrocyclic agents. And because of that, I think that the decision of whether or not the linear agents should remain available is a risk-benefit decision. And we explicitly didn't have a risk-benefit decision because we only had a one-day meeting, and that would take a two-day meeting.

The EMA apparently did consider other risks, including hypersensitivity, and they considered benefit like better images with one class compared with the other. It seems that, by and large, their conclusion after reviewing all of that evidence was that the linear agents shouldn't be available except under special circumstances.

We haven't had that deliberation, so I'm not

sure what vote I would have made had we had that, but I think the decision of whether or not the linear agents should remain available is a risk-benefit decision.

DR. HERSCOVITCH: Thank you. Dr. Hernandez-Diaz?

DR. HERNANDEZ-DIAZ: I voted yes because I think that the warning may be sufficient at this point, but the EMA had a language about the theoretical clinical consequences, and based on that not proven but theoretical consequences, they voted one way.

I think even if we go with the warning, my qualification would be that perhaps it can be added to the warning, something along the lines of with unknown clinical consequences or with clinical consequences under investigation, something that points in that direction.

DR. HERSCOVITCH: Thank you.

We won't be hearing from Dr. Frank because he is a nonvoting member. We'll have to now proceed to question number 5, and we'll follow the

similar procedure. First, I do have to read the question.

"A number of clinical and preclinical studies are ongoing, and the FDA might request that manufacturers conduct additional studies that will inform the FDA's decisions about the need for further regulatory actions, including withdrawal of approval and restriction of indicated populations. Do you agree with this plan?"

Again, we will vote. Then we will go around, and all voting members will be asked to explain their vote. Same procedure.

Commander Shepherd, tell us when we can begin to vote. You can begin now, please. The two telephone members are emailing in their votes, and they will be recorded.

(Voting.)

DR. HERSCOVITCH: The voting results, Commander Shepherd will read them.

LCDR SHEPHERD: For the record, the vote is 15 yes, zero no, zero abstain.

DR. HERSCOVITCH: We will now be asked to

discuss our votes, and I will call on Dr. Siegelman, who has a train to catch. So if you could please explain your vote, add to discussion.

DR. SIEGELMAN: Right. As William Osler said, "Medicine is the science of uncertainty and art of probability." And there's a lot of uncertainty that we heard about today, and I think getting more data will help to maybe elucidate some of these issues.

DR. HERSCOVITCH: Thank you.

Is there anyone else who really has to leave now to catch a plane? Because we do want to hear from everybody. If not, then we will go around the table. We'll start with Dr. Hernandez-Diaz.

DR. HERNANDEZ-DIAZ: I voted yes because I think it was clear. We need more information to optimize the treatment. We need these agents, and we just need to reduce the adverse events that may be happening.

DR. HENNESSY: Sean Hennessy. I voted yes. In the event that a risk-benefit assessment can't be done conclusively because of lack of data on

either the benefit side or the risk side, then we need more research to clarify that.

DR. LATOUR: Larry Latour. I voted yes. Given that we're recognizing retention of gadolinium and a cluster of symptoms that could be plausibly related or causally related, we're obliged to try to figure that out or exhaust our concerns.

DR. FURIE: I voted yes -- Karen Furie -- because today's discussion really raised more questions than answers, and I think the public deserves to know what the risks and benefits are.

MS. BRYANT: Brenda Bryant. I voted yes because the manufacturers should do more studies so we can find out what is causing the retention to remain in patients' bodies.

DR. VAUGHAN: Bill Vaughan. I just ditto Dr. Furie.

DR. DAINIAK: Nick Dainiak. I voted yes. There are a lot of uncertainties. They have potentially valuable registries. They have expertise in agent design, and they have the

resources to conduct for the research.

DR. JACOBS: Paula Jacobs. I voted yes because I think the potential toxicity issues and risk to public health are serious enough that the FDA should be able to require certain studies.

DR. HERSCOVITCH: Peter Herscovitch. I voted yes. I think it's quite clear we need more information. The manufacturers have not only resources to do further studies but also I think a responsibility. So I was in favor of the first part of the question.

Also, noting with regard to withdrawal of approval or restriction, my understanding is the FDA does need a firm scientific basis upon which to make such judgments, and this would hopefully lead to more scientific data.

DR. APPLEGATE: Kimberly Applegate. I also voted yes. I think there are opportunities for collaborations with large centers and industry; for example, internationally as well, to look at ways to use the gadolinium and compare it prospectively, as you had indicated interest in trials that would

compare without gadolinium and with, for example, using diffusion techniques that don't require gadolinium. Some centers are doing that already in diseases like inflammatory bowel disease. So there are opportunities to do those comparisons. Thank you.

DR. TOLEDANO: Alicia Toledano. I voted yes on this one. FDA definitely needs more evidence, high quality evidence, and I hope that they'll get some funding earmarked in the federal budget for their efforts. Don't want to make an unfunded mandate.

I do hope, as Dr. Jacobs mentioned, sponsors can work together. She mentioned this earlier today. There are things like platform trials and basket trials, and you have all your professional societies. So I hope that will help move these things forward.

DR. BRENT: Jeffrey Brent. I voted yes, and I think it's been abundantly clear that a consensus has emerged today that there is a serious question here that needs to be investigated. It's an

important public health problem. These are very important agents, and we want to understand not only their upsides but their downsides so that we can adjust to them.

I was impressed this morning to hear the industry presentations that industry seems already very interested in looking into this and to devoting resources to study this, and I appreciate that very much. I think an industry, FDA, academic collaboration to study the questions that have been outlined today is the way to go.

DR. HERSCOVITCH: Dr. Bolch?

DR. BOLCH: Yes, as well. I agree with many of the statements that were made previously, that we need more animal studies and human studies.

I would also point to some statements made by speaker 9 and then also speaker 13 concerning the benefit aspects of the European ban of all linear agents. I do believe that we were presented with evidence that some of the linear agents have a higher sensitivity and specificity than some of the macrocyclic agents and maybe even a higher toxicity

than some of the macrocyclic agents. So I think there is absolutely more questions that need to be addressed both in animal and human studies. Thank you.

DR. HERSCOVITCH: Thank you. Dr. Weisman?

DR. WEISMAN: I voted yes because it's very obvious that the statement is correct, and the fact that the agency put into it the threat of withdrawal of approval will give it some teeth, and the companies will pay attention. So it's a very good statement.

DR. HERSCOVITCH: Thank you.

Before my final comments, I would like to ask if there are any final comments from the FDA.

DR. PINHEIRO: I do have a very quick clarification, if I can.

DR. HERSCOVITCH: Please identify yourself.

DR. PINHEIRO: Simone Pinheiro, Division of Epidemiology.

From Dr. Hernandez-Diaz from a comment that she made on the first question about epidemiology studies and designs, I was curious if you have any

recommendations in a setting where potentially you need a large number of people and you don't have an outcome and a long follow-up. So I didn't know if you have any specific recommendations when you mentioned that for us.

MS. HERNANDEZ-DIAZ: Well, I have a list of potential challenges, but just to clarify, my two recommendations were a registry -- and I meant with that a controlled registry, not an uncontrolled registry -- to get to the details that need more access to patients and samples.

Then I was proposing a database, but again, a longitudinal database. And there is a list of challenges there because you need long follow-up, huge sample size, access to the specific agents that are used. Not all the databases will have it.

So it is not easy. I'm happy to give you my list of details, but those were the two designs that I think would make sense to consider.

DR. PINHEIRO: Sure. Thank you.

DR. HERSCOVITCH: Dr. Marzella?

DR. MARZELLA: I just wanted to thank the

advisory committee for a very productive discussion. I also want to acknowledge and thank the patients and the patient advocates that spoke so eloquently about these concerns.

We have a lot of think about now. We'll go back and look at the transcripts. We took plenty of notes. And we would welcome additional comments. Perhaps they can be directed to --

DR. HERSCOVITCH: Commander Shepherd?

DR. MARZELLA: -- Commander Shepherd perhaps.

DR. HERSCOVITCH: Before closing, I also want to express my thanks to the permanent as well as the ad hoc members for all the work that they did coming to this meeting. I also want to thank industry for their comments and also highlight the important comments from members of the public. This is an important public health issue with a lot of important questions that have been raised. So I thank the public participation as well.

One final comment, brief from Dr. Bolch before we adjourn.

DR. BOLCH: Mr. Chairman, just wanted to emphasize that in the area of ionizing radiation, we're optimizing the protocols to lower radiation dose, and some of the protocols requests are if you can do an MRI, try to avoid the exposure to ionizing radiation.

This issue now completely turns that up, so the issue of what imaging modality needs to be done in terms of risk-benefit analysis, they're now coupled. I just wanted to point that out to the committee.

DR. HERSCOVITCH: Thank you for that comment. I think we have just a brief last comment from Dr. Toledano.

DR. TOLEDANO: Tiny from Toledano. I would like to thank all of the sponsors, the manufacturers of these imaging agents for making them, and for following their safety, and for allowing them to be used in the public to help maintain the public health. Thank you.

Adjournment

DR. HERSCOVITCH: Thank you.

I'm supposed to now remind all the panel members and everybody to take their personal belongings with you as the room will be swept clear. Leave your name badges on the table for recycling. But again, thank you everybody in the room for your participation. I declare the meeting adjourned.

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