



U.S. Food and Drug Administration

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FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Joint Cardiovascular and Renal Drugs and
Drug Safety and Risk Management Advisory Committees

TUESDAY, DECEMBER 8, 2009

8:00 a.m. to 5:00 p.m.

Washington Hilton DC North/Gaithersburg
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P R O C E E D I N G S

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8:00 a.m.

6

DR. HARRINGTON: Could we ask people.

7

to take their seats and we'll go ahead and get

8

started?

9

My name is Bob Harrington. I'm a

10

cardiologist at Duke University, and I'm pleased to

11

chair this joint Cardiovascular and Renal Drugs and

12

Drug Safety and Risk Management Advisory Committee

13

today. Our charge for the day is to discuss the

14

safety considerations related to FDA-approved

15

gadolinium-based contrast agents as they are used

16

with MRI scanning.

17

I'm going to ask the committee to

18

introduce themselves and to let us know your name,

19

your institution, and just a brief statement as to

20

your area of expertise so that the audience can

21

keep that in perspective.

22

DR. PAZDUR: Richard Pazdur, Director of

1 Office of Oncology Drug Products, FDA.

2 DR. BOUCHER: Robert Boucher, Division
3 Director, Pharmacovigilance II, Office of
4 Surveillance and Epidemiology, FDA.

5 DR. RIEVES: Dwaine Rieves, Imaging and
6 Hematology Division, FDA.

7 DR. KREFTING: Ira Krefting, Safety
8 Officer, Division of Medical Imaging and
9 Hematology, FDA.

10 DR. HALPERIN: Jonathan Halperin,
11 clinical cardiologist at the Mount Sinai Medical
12 Center in New York.

13 DR. HECKBERT: Susan Heckbert, general
14 internist and epidemiologist, with an interest in
15 pharmacoepidemiology and drug safety.

16 DR. KRANTZ: I'm Mori Krantz, general
17 cardiology, University of Colorado.

18 DR. ZITO: Julie Zito, University of
19 Maryland-Baltimore, pharmacoepidemiology.

20 DR. FOGEL: Mark Fogel. I'm the
21 Associate Professor of Cardiology and Radiology at
22 the University of Pennsylvania and I'm the Director

1 of Cardiac MR at Children's Hospital in
2 Philadelphia.

3 DR. HUNSICKER: Larry Hunsicker. I'm a
4 kidney doctor from the University of Iowa, with
5 expertise in clinical trials and epidemiology and
6 transplantation.

7 DR. WOLFE: Sid Wolfe. I'm a general
8 internist. I'm from the Health Research Group of
9 Public Citizen. I'm very interested in drug safety
10 and efficacy.

11 DR. TATUM: I'm Jim Tatum, I'm a
12 radiologist/nuclear medicine physician and I'm from
13 the Division of Cancer Treatment and Diagnosis at
14 NCI.

15 DR. O'BRIEN: Donna O'Brien, a healthcare
16 consultant, Community Healthcare Strategies in New
17 York, with a healthcare operations and strategy
18 background.

19 DR. MCGUIRE: Darren McGuire, University
20 of Texas Southwestern at Dallas, general
21 cardiology, clinical trials and epidemiology.

22 DR. FERGUSON: Elaine Ferguson,

1 Designated Federal Official.

2 DR. ROYAL: Henry Royal, Washington
3 University-St. Louis. I'm a radiologist and
4 nuclear medicine physician.

5 DR. LESAR: Timothy Lesar, Director of
6 Clinical Pharmacy Services, Albany Medical Center,
7 medication safety.

8 DR. JONES: Elizabeth Jones, Chief of
9 Clinical Operations, Radiology Clinical Center,
10 NIH.

11 DR. GROSS: Peter Gross. I'm Chief
12 Medical Officer at Hackensack University Medical
13 Center and former chair for the Drug Safety and
14 Risk Management Advisory Committee.

15 DR. MORRATO: Elaine Morrato. I'm a
16 pharmacoepidemiologist from the University of
17 Colorado-Denver and my area of expertise is in drug
18 safety and risk management evaluation.

19 DR. CHOYKE: I'm Pete Choyke. I'm a
20 radiologist at the National Cancer Institute.

21 MR. COUKELL: I'm Allan Coukell. I'm a
22 pharmacist and Director of the Pew Prescription

1 Project at the Pew Charitable Trusts and I'm the
2 acting consumer rep on the Cardiovascular and Renal
3 Advisory Committee.

4 DR. KAUL: Sanjay Kaul. I'm from the
5 Cedar Sinai Heart Institute in Los Angeles,
6 cardiology, clinical trials and epidemiology.

7 DR. NELSON: Lewis Nelson. I am an
8 emergency physician and medical toxicologist at
9 Duke University.

10 DR. NEATON: Jim Neaton, a
11 biostatistician from the University of Minnesota.

12 DR. KRAMER: Judith Kramer, Duke
13 University, general internist, interest in clinical
14 trials and pharmacoepi, and I'm the current Drug
15 Safety and Risk Management Advisory Committee
16 chair.

17 DR. PAGANINI: I'm Emil Paganini. I'm an
18 adult nephrologist, critical care nephrology
19 consulting, and a senior consultant for critical
20 care nephrology at the Cleveland Clinic.

21 DR. BURLINGTON: Bruce Burlington. I am
22 an infectious disease internist, the industry

1 representative to the Drug Safety Advisory
2 Committee, and I'm currently an independent
3 consultant, following a career in industry and at
4 FDA.

5 DR. HARRINGTON: Terrific. I'm expected
6 to read this opening statement and then I'll try to
7 set some of the rules of order for the day.

8 For topics such as those being discussed
9 at today's meeting, there are often a variety of
10 opinions, some of which are quite strongly held.
11 Our goal is that today's meeting will be a fair and
12 open forum for discussion of these issues and that
13 individuals can express their views without
14 interruption. Thus, as a gentle reminder,
15 individuals will be allowed to speak into the
16 record only if recognized by the chair. We look
17 forward to a productive meeting.

18 In the spirit of the Federal Advisory
19 Committee Act and the Government in the Sunshine
20 Act, we ask that the advisory committee members
21 take care that their conversations about the topic
22 at hand take place in the open forum of the

1 meeting.

2 We are aware that members of the media
3 are anxious to speak with the FDA about these
4 proceedings; however, FDA will refrain from
5 discussing the details of the meeting with the
6 media until its conclusion. The committee is also
7 reminded to please refrain from discussing the
8 meeting topic during breaks or lunch. Thank you.

9 Now, before I turn it over to Elaine to
10 read the conflict of interest statement and then to
11 Dr. Krefting to provide the FDA opening remarks, it
12 doesn't come as a surprise, this is a very big
13 panel and I'm going to need everyone's help in
14 trying to keep things organized and flowing.

15 I'm very committed to staying on time.
16 For the sponsor, I will end your presentation if it
17 is going over time. We want to be respectful of
18 everybody's time in the room and I absolutely want
19 to have the committee have plenty of time to ask
20 questions.

21 So for the sponsor, I'd like to reserve
22 the last five to seven minutes of your

1 presentation, each one of you, for questions from
2 the panel. So please try to plan appropriately or
3 the committee might not have a chance to ask their
4 question until the afternoon, in which case, we'll
5 be a little more pressed for time.

6 Elaine will help me keep track. Raise
7 your hand, signal her. We'll keep a list. We will
8 get to everybody and make sure that everybody is
9 heard.

10 Elaine?

11 DR. FERGUSON: Okay. First of all, I
12 regret to inform you that our patient
13 representative will not be able to join us today.
14 We were recently informed that she is ill and is
15 not able to attend.

16 The Food and Drug Administration, FDA, is
17 convening today's joint meeting of the
18 Cardiovascular and Renal Drugs Advisory Committee
19 and the Drug Safety and Risk Management Advisory
20 Committee under the authority of the Federal
21 Advisory Committee Act, FACA, of 1972.

22 With the exception of the industry

1 representative, all members and temporary voting
2 members of the committees are special government
3 employees, SGEs, or regular federal employees from
4 other agencies and are subject to federal conflict
5 of interest laws and regulations.

6 The following information on the status
7 of this committee's compliance with federal ethics
8 and conflicts of interest laws covered by, but not
9 limited to, those found at 18 USC Section 208 and
10 Section 712 of the Federal Food, Drug and Cosmetics
11 Act, FD&C Act, is being provided to participants in
12 today's meeting and to the public.

13 FDA has determined that members and
14 temporary voting members of this committee are in
15 compliance with the federal ethics and conflict of
16 interest laws under 18 USC Section 208.

17 Congress has authorized FDA to grant
18 waivers to special and regular government employees
19 who have potential financial conflicts when it is
20 determined that the agency's needs for a particular
21 individual's services outweighs his or her
22 potential financial conflict of interest.

1 Under Section 712 of the FD&C Act,
2 Congress has authorized FDA to grant waivers to
3 special and regular government employees with
4 potential financial conflicts when necessary to
5 afford the committee essential expertise.

6 Related to the discussions of today's
7 meeting, members and temporary voting members of
8 this committee have been screened for potential
9 financial conflicts of interest of their own, as
10 well as those imputed to them, including those of
11 their spouses or minor children and, for purposes
12 of 18 USC Section 208, their employers. These
13 interests may include investments, consulting,
14 expert witness testimony, contracts, grants,
15 CRADAs, teaching, speaking, writing, patents and
16 royalties, and primary employment.

17 Today's agenda involves discussions on
18 safety considerations related to FDA-approved
19 gadolinium-based contrast agents with magnetic
20 resonance imaging, MRI, scans. An MRI is a medical
21 imaging technique that does not require x-rays.
22 These scans outline the internal body structure,

1 such as organs and soft tissues.

2 Contrast agents are substances injected
3 into the body before an MRI scan, helping doctors
4 to better see and interpret MRI findings. FDA-
5 approved gadolinium-based contrast agents include
6 gadopentetate dimeglumine-MultiHance, gadodiamide-
7 Omniscan, gadopentetate dimeglumine-Magnevist,
8 gadoteridol-ProHance, gadoversetamide-OPTIMARK,
9 gadoxetate disodium-Eovist, gadofosveset-Vasovist.

10 This is a particular matters meeting
11 during which specific matters related to
12 gadolinium-based contrast agents used with MRI
13 scans will be discussed. Based on the agenda
14 for today's meeting, no conflicts of interest
15 waivers have been issued in connection to this
16 meeting.

17 To ensure transparency, we encourage all
18 standing committee members and temporary voting
19 members to disclose any public statements that they
20 have made concerning the product at issue.

21 With respect to FDA's invited industry
22 representative, we would like to disclose that Dr.

1 Bruce Burlington is participating in this meeting
2 as a nonvoting industry representative, acting on
3 behalf of regulated industry. Dr. Burlington's
4 role at this meeting is to represent industry in
5 general and not any particular company. Dr.
6 Burlington is self-employed.

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

13 Dr. Shawn Cowper has acknowledged that he
14 has received a speaker's fee from Mallinckrodt a
15 few years ago for a nephrogenic systemic fibrosis,
16 NSF, lecture. He has also acknowledged being an
17 uncompensated advisor on the issue of NSF to Bayer,
18 General Electric and Mallinckrodt in the past.

19 Dr. Jeffrey Weinrab has acknowledged that
20 he has been a principal investigator and co-
21 investigator for a research project concerning
22 magnetic resonance imaging, MRI, contrast agents

1 sponsored by Bayer, GE Healthcare, Squibb, Salutar,
2 Epix, Sterling Drug, Sanofi Winthrop, and Advanced
3 Magnetics.

4 He has received consulting fees and is a
5 scientific advisor for Bayer and GE Healthcare. He
6 has been a paid participant in educational programs
7 sponsored by Bayer, General Electric Healthcare,
8 Bracco and Providian. And lastly, he is an expert
9 witness for Bayer regarding nephrogenic systemic
10 fibrosis.

11 As guest speakers, Drs. Cowper and
12 Weinrab will not participate in the committee
13 deliberations nor will they vote.

14 We would like to remind members and
15 temporary voting members that if the discussions
16 involve any other products or firms not already on
17 the agenda for which an FDA participant has a
18 personal or imputed financial interest, the
19 participants need to exclude themselves from such
20 involvement and their exclusion will be noted for
21 the record.

22 FDA encourages all other participants to

1 advise the committee of any financial relationships
2 that they may have with the firm at issue.

3 I would like to remind everyone to please
4 silence your cell phones, if you have not done so
5 already. And I would also like to identify the
6 press contact, Karen Riley, if she happens to be
7 present now.

8 Thank you, Karen.

9 DR. HARRINGTON: Terrific. Thank you,
10 Elaine. We'll now go to the opening comments of
11 the FBI -- of the FBI --

12 [Laughter.]

13 DR. HARRINGTON: -- FDA by Dr. Krefting.
14 He's had a busy few days.

15 DR. KREFTING: Good morning. Yes, I am
16 with the FDA. Welcome to Gaithersburg. There are
17 several government agencies here. I'm with the
18 FDA. And good morning to all of you and good
19 morning to people watching this proceedings via
20 Webinar, and good afternoon to those who are
21 watching the proceedings in Europe, again, via the
22 Web. Welcome, again, to the joint meeting of the

1 Cardiovascular and Renal Drugs and Drug Safety and
2 Risk Management Advisory Committees.

3 I'm Ira Krefting. I'm the Deputy
4 Director for Safety in the Division of Medical
5 Imaging and Hematology Products. Today, the
6 committee members and audience will hear a
7 discussion concerning gadolinium-based contrast
8 agents used in magnetic resonance imaging and their
9 association with nephrogenic systemic fibrosis.

10 To set the stage for today's discussion,
11 I will provide a very brief regulatory history of
12 the United States' experience with gadolinium-based
13 contrast agents. These agents rely on gadolinium's
14 paramagnetic properties to improve the diagnostic
15 capabilities of MRI, an imaging modality which is
16 critical to the diagnosis of many conditions.

17 MRI is particularly notable among the
18 imaging modalities in that it does not employ any
19 ionizing x-ray exposure. The FDA, in its
20 presentation today, will focus on the five
21 gadolinium agents with the most extensive post-
22 marketing experience. They are listed for you

1 there on the slide with their date of approval.

2 These agents consist of Magnevist, ProHance,

3 Omniscan, Optimark, and MultiHance.

4 This experience has relevance for the two
5 newer agents because of multiple similarities among
6 the agents, similarities that resulted in the FDA
7 recognizing all these products as members of a
8 specific pharmacologic class, the gadolinium-based
9 contrast agents.

10 As you can imagine, the post-marketing
11 experience is much more limited for the two newer
12 agents, Eovist and Vasovist, products which were
13 approved last year. Vasovist has recently changed
14 its name to Ablavar.

15 In 2006, the FDA learned of a possible
16 association between gadolinium agents and
17 nephrogenic systemic fibrosis, or NSF. NSF
18 appeared to be a relatively newly identified
19 disease process that consisted of skin lesions and
20 fibrotic reactions within organs that occurred
21 almost exclusively among patients with severe renal
22 failure.

1 Epidemiologic exploration associated
2 gadolinium exposure with this condition of NSF.
3 Initial reports cited Omniscan exposure, but
4 subsequent reports also cited Magnevist, Optimark
5 exposure, as well as exposure to unidentified
6 gadolinium agents and combinations of these agents.

7 In response to this new NSF concern, in
8 2006, FDA issued on its Website public health
9 advisories. Subsequently, in 2007, FDA requested
10 manufacturers to revise their product labels to
11 describe the risks for NSF and ways to minimize
12 these risks. FDA also requested additional
13 clinical trials to help characterize the risks for
14 NSF.

15 I apologize. This slide is a little
16 fuzzy. Hopefully, the message isn't. The 2007
17 labeling changes were the same for all the agents
18 and consisted of a boxed warning, as well as new
19 warning information. The boxed warning noted the
20 agent's increased risk for NSF within two
21 categories of patients, those with acute or chronic
22 severe renal insufficiency and patients who have

1 acute renal insufficiency of any severity due to
2 the hepato-renal syndrome or in the perioperative
3 liver transplant state.

4 The changes provided additional details
5 about the risks and provided ways to minimize the
6 risks. Among the recommendations was screening of
7 prospective imaging patients by either obtaining a
8 renal function history from the patient or
9 laboratory testing of renal function.

10 The 2007 labeling also made it clear that
11 while some risks may apply to all the agents, the
12 magnitude of the risks may vary among the agents.
13 For example, the warning text noted that with
14 respect to post-marketing reports -- and you can
15 read it there -- where a specific agent was
16 identified, the most commonly reported agent was
17 Omniscan, followed by Magnevist and Optimark.

18 The extent of the risk for NSF following
19 exposure to any specific gadolinium-based contrast
20 agent is unknown and may vary among the agents.
21 The possibility of a differential risk is the main
22 topic for our discussion today, approximately two

1 years after the initial labeling changes that you
2 have just seen.

3 Let's now take a look at the recent
4 recommendations from the EMEA, the European medical
5 agency. More gadolinium drugs are approved for use
6 in Europe than in the United States. So I will
7 cite only the drugs that are relevant to today's
8 discussion.

9 Within Europe, gadolinium agents are
10 classified into three categories of risk, high,
11 medium and low risk, based upon chemical, pre-
12 clinical and post-marketing clinical data.

13 However, as we will hear later today,
14 these data do not readily characterize all the
15 agents, particularly the newer agents, where post-
16 marketing data is very limited. For now, note that
17 the high risk category contains Omniscan and
18 Optimark, two nonionic linear agents, and
19 Magnevist, a linear ionic agent. The medium risk
20 category contains linear ionic agents and the low
21 risk category contains the macrocyclic agent
22 ProHance.

1 Within the new European drug labels, high
2 risk agents are contraindicated in patients with
3 severe renal failure or recent liver transplants.
4 The label requires lab testing and it states that
5 it should be done. For the medium and low risk
6 agents, lab testing is recommended.

7 Over the past couple of years, imaging
8 practices have changed around the United States
9 following FDA and professional group
10 recommendations and more laboratory and clinical
11 data has become available to all of us.

12 FDA has convened this committee to
13 discuss a possible differential NSF risk among the
14 gadolinium agents. If the committee concludes that
15 the magnitude of the risk varies among the
16 gadoliniums, the FDA also seeks advice on how to
17 best communicate this risk to both patients and
18 healthcare providers. FDA also seeks advice on the
19 best way in the future to screen patients for NSF
20 risk factors, such as renal insufficiency.

21 The plan of the morning presentations is
22 listed on this slide. As you have heard, we will

1 have introductory talks by two experts, Dr. Cowper,
2 a dermatopathologist at Yale University, who has
3 established the NSF registry, and Dr. Weinrab, also
4 from Yale -- we have the Ivy League presentation
5 today -- a radiologist, who has published
6 extensively on NSF and the clinical implications
7 for a practicing radiologist.

8 We will then have presentations by the
9 gadolinium sponsors, followed by the FDA
10 presentations as we approach the noon hour.
11 Following lunch, we proceed to the open public
12 hearing and, finally, our discussion.

13 Thank you all for your attention and I
14 return the podium to the chairman, or the chairman
15 to the podium. Thank you.

16 DR. HARRINGTON: Thank you very much.
17 That was helpful to lay out the objectives and what
18 the FDA hopes to get out of this today.

19 We'll now turn to our first guest
20 speaker, who has already been introduced, Dr. Shawn
21 Cowper, Associate Professor of Dermatology and
22 Pathology, from Yale.

1 DR. COWPER: Thank you for the
2 opportunity to come and address the committee.
3 Thank you, also, Dr. Krefting, for making that
4 invitation, and the chair of the committee.

5 My goal is to discuss nephrogenic
6 systemic fibrosis, its history, its diagnosis, and
7 the registry. I also want to make a comment. I'm
8 not making a sartorial commentary here. I actually
9 forgot my tie. So moving along.

10 January 1997, the first case of what
11 eventually came to be known as nephrogenic systemic
12 fibrosis was identified in San Diego, California at
13 Sharp Memorial Hospital in a transplant center, and
14 it was identified amongst a series of patients who
15 had recently had a renal transplant and had a,
16 quote, "stormy" clinical course following the
17 transplantation.

18 These patients were developing an unusual
19 condition in which the skin of their extremities
20 primarily was starting to thicken up, sometimes to
21 the point where it was limiting the range of motion
22 of these patients.

1 The biopsies were conducted at Sharp.
2 They were felt to be an unusual presentation of a
3 rare disease called scleromyxedema and, because of
4 this unusual presentation, were sent to my mentor
5 at the University of California-San Francisco, Dr.
6 Philip LeBoit, who was the first one to gather a
7 series of these cases, and present them to me when
8 I joined him as a fellow in 1999 as an interesting
9 process I might want to look into a little bit.

10 Well, what, of course, occurred as a
11 result of this was, one, the first clinical
12 pathologic diagnosis and differential guideline on
13 a disease called nephrogenic fibrosing dermopathy,
14 which has since changed names -- I'll explain why
15 later -- the disease manifested clinically in a
16 variety of ways, chiefly extremity-related. You
17 see here that there is an area of induration,
18 brawniness. You can't appreciate the induration,
19 which would be the swelling and hardness of the
20 tissue, but you certainly can appreciate the
21 coloration changes.

22 In very severe cases, there is marked

1 fibrosis. If you were to palpate this, this would
2 feel somewhat like a rock. Patients will develop
3 contractures; in time, with severe cases, this
4 being considered an end stage case, would be
5 confined to a wheelchair, very commonly. It also
6 limits the ability of the patient to use their
7 hands. So, obviously, it affects the mobility and
8 their ability to carry out regular activities of
9 daily life.

10 What I'm going to show you, also, are
11 some epidemiologic slides that represent the newest
12 data I have available from our registry. The
13 registry is an outgrowth of the initial
14 investigation that occurred in California and I
15 took the registry with me to Yale when I joined
16 them in 2001.

17 So now with an N of 345
18 histopathologically verified cases of NSF, we see
19 that females slightly out-edge males 53 percent to
20 47 percent. The age of onset -- this is critical.
21 It's not the age that the diagnosis is made, but
22 the age in which the symptoms of NSF begin -- using

1 an N of 270 from our database, in which we could
2 determine that -- has a median of about 53.8, but a
3 range running from about six to 87.5 years of age.

4 The status of the patient, their renal
5 status at onset is as follows: 80 percent are some
6 sort of dialysis, either peritoneal, as you see
7 here, or hemodialysis or, in this case, the end
8 stage renal disease, where it was not specified.

9 Also, you'll note, in the white and
10 yellow zone, these patients are non-dialysis
11 patients who have some degree of renal
12 insufficiency. Stage 4 CKD, right here, Stage 5
13 CKD in the darker yellow, Stage 5 outnumbering
14 Stage 4 by two-to-one; renal insufficiency not
15 specified; and, acute kidney injury, which has been
16 singled out in the black box warning, is
17 represented here as being 10 percent of patients.
18 There's also a small slice here representing
19 patients who are post-transplant at the time they
20 developed these.

21 By 2003, I had a number of cases reported
22 from centers all around the United States and,

1 also, by 2003, some additional articles started to
2 become apparent in the literature. In the Journal
3 of the American Academy of Dermatology, a
4 description of scleral plaques in patients with
5 NFD.

6 These plaques are something, at that
7 time, we had not noticed, but we didn't have a
8 large clinical experience with it. We were getting
9 reports from other institutions. Well, since then,
10 we've noticed this in a large number of patients, I
11 would say maybe, it is estimated, around 70
12 percent.

13 Scleral injection, which eventuates into
14 a yellow-white plaque, is present symmetrically,
15 bi-temporally, medially, as well, and, in the rare
16 cases in which we have autopsy material from this,
17 increased cellularity, increased collagen
18 deposition. And you see this purple metachromatic
19 granularity here, which represents mineralization,
20 either calcium or, in some cases, gadolinium.

21 Archives of Dermatology, later that year,
22 identified the first patient with an autopsy. And

1 as a result of some of the findings from this
2 autopsy and the result of some additional
3 information learned afterwards, we decided to
4 change the name to nephrogenic systemic fibrosis,
5 as it really represented what we understood about
6 the disease at that time; that, in fact, it was a
7 systemic process, not merely a cutaneous one.

8 Other important features. There is a
9 known history of Antithrombin III and Factor II
10 deficiency in this particular patient. We've
11 noticed hypercoagulable disorders from the very
12 beginning with this disease. It's not present in
13 every patient, but it's present in enough patients
14 to warrant attention. We don't know how that works
15 in terms of causation or just an epi phenomenon.

16 This particular patient elected, because
17 of his terrible morbidity, to discontinue his
18 dialysis, which, of course, is the only thing
19 keeping him alive. I have noticed that in at least
20 two additional patients in our registry. That will
21 give you a sense of the seriousness of this problem
22 for the patient and their family.

1 In this particular presentation, there
2 was fibrosis noted in the esophagus, diaphragm and
3 psoas muscle. There have been additional autopsy
4 reports, including some that I have not published
5 yet, but I am studying, that show fibrosis present
6 in some other organ systems, as well.

7 Some representative examples of what you
8 see elsewhere in the system rather than the skin,
9 we have, on the left side, skeletal muscle. That's
10 normal skeletal muscle fibers, these pink-purple
11 fibers here with nuclei around the outside. Here,
12 they are atrophic, with large hyperchromatic nuclei
13 that are clumped together.

14 This is cardiac muscle. This is from a
15 patient who was in his younger 20s, who died with
16 the disease. He had no reason that was
17 identifiable clinically to have had cardiac
18 fibrosis; yet, on autopsy, he had marked cardiac
19 fibrosis. What you see here as pale pink is the
20 fibrosis between these cardiac muscles in, again, a
21 very young patient.

22 It's harder to tell in patients who are

1 significantly older and have lived with diabetes
2 and hypertension for a long period of time -- it's
3 hard to tell whether that fibrosis is due to their
4 underlying other conditions. But with somebody as
5 young as this, it really strikes home that this
6 does appear to be fibrosis related to NSF.

7 In 2003, later, my colleague, Dr. Richard
8 Bucala, and I discussed the possibility that the
9 cells involved in the production of collagen in the
10 skin in nephrogenic systemic fibrosis may be a cell
11 that he identified some 10 years earlier in a
12 series of rat studies. And in those studies, he
13 identified a cell that had its origin in the bone
14 marrow, circulated as a white blood cell, and was
15 present in normal individuals. And this cell
16 stained, with special techniques, with collagen in
17 CD34. CD34 is a stem cell marker.

18 He asked me to study my slides to see if,
19 in fact, this might be the case in my set. And, in
20 fact, these cells, which are the cells in NSF, in a
21 skin biopsy, the red here represents collagen-1 and
22 the brown here represents CD34.

1 Where the staining is a little bit
2 different, different parts of the cell, there are
3 clearly cells that are staining for both of these.
4 And through this evidence and additional evidence
5 that's introduced in that article, we concluded
6 that this disease is caused by circulating
7 fibrocytes that, for whatever reason, have
8 localized themselves to the skin in these patients.

9 Another article later that year
10 summarized information I had in the registry to
11 that point and I pointed out at that time that
12 there were a number of reported thrombotic events
13 and/or hypercoagulable states immediately preceding
14 the onset of the disease.

15 In addition to these, there were a number
16 of patients who had had vascular surgery
17 immediately preceding the disease. At the time,
18 there were some thought as to what things might be
19 in common between these, and there's more than you
20 might think, especially looking at it in
21 retrospect. But certainly, the big question was
22 what do these have in common, and I think that

1 really takes us up to 2005, when I, at Yale, had
2 come to the conclusion that contrast agents might
3 be at the root of this. And we were in the process
4 of trying to verify that before making a report, a
5 formal report, that, in fact, they were, when Dr.
6 Grobner, in Austria, came out with this article,
7 "Gadolinium: A Specific Trigger for the
8 Development of Nephrogenic Fibrosing Dermopathy and
9 Nephrogenic Systemic Fibrosis."

10 That's the first published association of
11 NSF with gadolinium and, of course, when I saw
12 that, I knew he was correct, because we were
13 approaching it from a slightly different angle, but
14 we had come to the same conclusion that it seemed
15 gadolinium was highly associated with the disease.

16 Gadolinium will be discussed much more,
17 I'm sure, this afternoon, but I'd point out that
18 it's a member of the lanthanide series there. It's
19 a metal. It's paramagnetic. As Dr. Krefting
20 pointed out, it makes it uniquely qualified to be
21 an MRI contrast agent.

22 It is not a naturally occurring element

1 in humans, however. And as my friend, Dr. Kanal,
2 is apt to say, if it's there, we put it there.
3 Well, in fact, if you study the tissue of patients
4 with NSF by electron microscopy with fancy
5 techniques that identify the atoms within the
6 electron microscopy, you can identify gadolinium
7 very specifically within the tissues. And not only
8 do you identify the gadolinium, which shouldn't be
9 there so many months after exposure, but areas in
10 which there is marked fibrosis tend to have more
11 gadolinium than those areas that don't have as
12 marked fibrosis.

13 This evidence, to us, suggested that the
14 gadolinium -- an additional layer of evidence
15 suggested that gadolinium may be causative of NSF,
16 and, of course, that is the big question.

17 So this is the technique right here.
18 Electron microscopy and various types of mass
19 spectroscopy can identify the gadolinium within the
20 tissue, and here, specifically, you can see a
21 particle of gadolinium and one of iron.

22 One of the articles showed gadolinium

1 depositing around vessels. An article I did with
2 Dr. High showed it present within macrophages,
3 which might be important in terms of understanding
4 the stability of these agents.

5 From the registry, what I can see is that
6 patients in whom there is a temporal association,
7 where there's a good history, we can associate the
8 onset of the disease with the receipt of some
9 gadolinium-containing contrast agent. Fifty
10 percent of them will have onset of their first
11 symptoms before five weeks.

12 Now, you see some of these patients are
13 very far out here and what you'll notice is that
14 there are actually cases of NSF in which the
15 diagnosis is very difficult to identify and the
16 patient themselves may not identify that they have
17 NSF, or any diagnosis, and may be picked up by a
18 physician who is keen to this diagnosis and does
19 the biopsy quite late.

20 So nailing exactly when the patient has
21 their onset of symptoms can be very tricky,
22 especially with patients who at are several years

1 later. But I would say that you see the bulk of
2 these agents seem to be associated with the disease
3 at about five to 15 weeks after exposure.

4 So there's been a question of whether
5 dose is related. This is the most specific
6 information I have related to dose. As it turns
7 out, in the registry, those patients in which we
8 can identify a gadolinium exposure, 46 percent of
9 them have their onset of NSF following a single
10 dose of an agent. That's important to keep in
11 mind. A single dose does seem capable of
12 triggering this in patients with NSF.

13 In addition, MRA versus MRI procedures,
14 you'll see that 67 percent of the patients had MRI
15 procedures and 32 percent had MRA procedures.
16 Since MRA commonly uses two to three times the MRI
17 dose, this would tend to suggest that a single MRI
18 dose in patients is capable of triggering the
19 disorder.

20 There are additional scientific studies,
21 which I'm sure some of the pharmaceutical people
22 are going to talk about today. What's important is

1 that fairly early on, when the pharmaceutical
2 companies were made aware of the possibility that
3 their agent might be associated with this disease,
4 there were some animal studies done.

5 I had the opportunity to look at some of
6 them early on and others I did not. But the
7 information that came from these studies shows that
8 when you inject an animal with a dose of gadolinium
9 that replicates what one with renal disease would
10 see in their system, many of them do develop this
11 disorder in which the virtus (ph) appears and the
12 skin becomes kind of cobblestone texture
13 erythematous, simulating what you see in NSF. It's
14 not a perfect model of NSF, of human NSF, but it's
15 compelling that both clinically and pathologically,
16 it resembles the disorder.

17 In other studies done where human
18 fibroblasts were exposed to gadolinium-containing
19 contrast agents, the fibroblast grew larger and
20 produced more collagen and ground substance
21 material in association with that exposure than did
22 the control fibroblasts. So there does seem to be

1 some sort of interplay occurring between these
2 spindle cells that produce collagen and ground
3 substance and gadolinium-containing contrast
4 agents.

5 So we have developed criteria for
6 clinical-pathologic scoring, which I'm going to try
7 to cover very, very quickly here. Clinical-
8 pathologic scoring is what we use for the Yale
9 registry. It requires that the patient be seen not
10 only clinically, but they have a biopsy performed
11 and that both of them are scored. This helps
12 to eliminate competing differentials.

13 So on the clinical side, the major
14 criteria we use are the presence of patterned
15 plaques, joint contractures, cobble stoning
16 phenomenon in the skin, indurated skin. You see
17 that the examiner is pressing here. There's hardly
18 any play in the skin, yet they're blanching out
19 their own finger capillary bed. So they're
20 squeezing very hard.

21 Minor criteria are puckering, thin
22 macules, papules, and, of course, the scleral

1 findings I discussed earlier, particularly in
2 patients less than 45 years of age, as older
3 patients can have similar findings in pinguecula.
4 We try to eliminate that confounding effect.

5 So you take this clinical scoring and you
6 basically summit like this. Greater than one major
7 criterion gives you a four, one major criterion
8 gives you a three, and so forth down to zero, in
9 which the disorder can be excluded on the basis of
10 clinical findings.

11 The path side is done a little bit
12 differently, as you could imagine. I'm a
13 pathologist, so this is my area of expertise. This
14 is a deep punch biopsy of the skin. The epidermis
15 is up here. That's the outside world up here, and
16 this is the deep down into the fat.

17 So we look at thickening of the septa of
18 the lobules between the fat and here, of course, on
19 high magnification, these are collagen-producing
20 cells, as you would expect. So we look for
21 increased dermal cellularity and they're very bland
22 cells. They don't look like much. They don't look

1 like inflammatory cells. They're spindle cells,
2 because they're like fibroblast.

3 CD34 positivity, that marker I talked
4 about earlier that we use to identify a stem cell,
5 the brown you see here indicates positivity and
6 that's way, way, way too much for normal skin.
7 High magnification shows it laying down along
8 elastic fibers, creating this tram-track type
9 pattern.

10 The presence of both thick and thin
11 collagen bundles; the presence of preserved elastic
12 fibers, which actually is normal in the skin.
13 These are the elastic fibers outlined by a special
14 stain. When elastic is missing, then we start
15 considering things like morphea or scleroderma,
16 which this can resemble clinically and
17 pathologically. Lastly, septal involvement, which
18 I pointed out earlier, the septum is thickened.

19 One other thing. There's a sign I call
20 lollipop sign and others have called sclerotic
21 bodies and osseous bodies. It's a relatively new
22 feature we've identified, the presence of these

1 large, well demarcated, pink aggregates of what
2 turns out to be collagen, perforated by elastic
3 fibers like that, looking to me like a lollipop.

4 People believe that this is probably
5 osteoid, which is the soft tissue of bone. This is
6 the equivalent type of arrangement to collagen
7 forming an osteoid type body in the skin and, as
8 far as we can determine, an absolutely unique
9 finding in nephrogenic systemic fibrosis.

10 So for that reason, it gets a higher
11 score, it gets a higher weight. If we see that, we
12 give plus three and the other features, generally,
13 plus one and we subtract one if the elastic isn't
14 preserved.

15 So we add this all up into a score and
16 then the combination of the clinical score here and
17 the pathology score here gets us into a zone of
18 either nephrogenic systemic fibrosis, consistent
19 with inconsistent or suggestive of, in which case,
20 additional sampling may be needed, or excluding NSF
21 or another diagnosis can be made.

22 So this is the criteria which are

1 currently under peer review and hopefully to be
2 published soon, but this is what we use at Yale to
3 make the diagnosis.

4 So the registry in the future, the last
5 part of this talk I'm supposed to do, I want to
6 tell you what we have in our registry. We have 345
7 cases that were histopathologically confirmed, as
8 you just saw there; 93.3 percent represent cases
9 from the United States.

10 Distribution of cases from various states
11 in America, black and darker colors tend to be more
12 cases reported. This is not indexed to population.
13 This is absolute number. You see California and
14 New York, of course, with heavy population there,
15 and Texas, large population, you'd expect a lot of
16 cases.

17 What you notice, also, is Illinois is not
18 many cases, and I know that's not because there's
19 no cases in Illinois, because there are some in the
20 literature. We're getting underreporting from
21 Illinois relative to the other places.

22 You also note Connecticut, where I'm

1 from, where I see probably every case of suspect
2 NSF in the state, it's black, which means, to me,
3 that these places are all not reporting their cases
4 to me. Of course, it's not mandatory that they do
5 so, but it's the only way we'll really get a
6 picture of this entire disease process. So I think
7 that there are a lot more cases than my registry
8 suggests.

9 What's the impact on the patient? Well,
10 morbidity and mortality. From our registry, as far
11 as we can determine, 17 percent are now known
12 deceased. We also know that 9.3 percent of them
13 become wheelchair dependent as a result of their
14 disorder.

15 What we also see here -- again, I'm going
16 to take you back to the date of onset, not the date
17 of biopsy or the date of exposure, the date of
18 onset of symptoms.

19 You'll see that the first cases were
20 described in 1997. This is a cumulative series.
21 You get to about 2006-2007, when the
22 recommendations came out from the FDA to at least

1 consider the possibility that gadolinium might be
2 associated with this disease and throwing some
3 caution to doctors and patients regarding the use
4 of this agent, and you see now that the rate of new
5 cases is starting to level off.

6 To me, that is another independent level
7 of verification that gadolinium itself can be
8 causing this disease. So I want you to keep that
9 in mind when you consider all the discussions
10 taking place today.

11 The last slide that represents the data I
12 have from the registry shows that from our
13 registry, in which an identification of a
14 particular agent can be made, clinical-
15 pathologically and temporally, that is, the agent
16 is given and the patient develops the disease
17 within a short timeframe, 41 percent of those turn
18 out to be Omniscan cases.

19 The blue cases here represent Magnevist
20 or highly likely Magnevist, because I have one
21 institution that knows they use Magnevist way more
22 than they use Omniscan. So these cases are those

1 and these cases are known Magnevist. Nine percent
2 are Optimark. Twenty-seven percent represent cases
3 where we know an agent was given, but for whatever
4 reason, we do not have the identify of that agent,
5 whether it's because of bookkeeping or that hasn't
6 been provided to me.

7 Then there are a couple of complicated
8 cases, one here that's a ProHance-Omniscan, where
9 they received it within one day of each other. And
10 here is an Omniscan-Magnevist, where it was
11 received within one day of each other. But I think
12 you'll be startled to realize that this actually
13 parallels very closely what I've heard described
14 both from Europe and from other researchers and in
15 an overview of the literature.

16 So I think all of the various studies
17 coming out of the registry do indicate that we're
18 talking about the same population.

19 I want to thank the folks at Yale and
20 beyond Yale who have helped with the identification
21 of this disorder and the continued investigation
22 into the disorder. And I hope I haven't gone over

1 time too long. I'll take questions, if there are
2 any.

3 DR. HARRINGTON: Thank you very much, Dr.
4 Cowper. Just two quick questions for you.

5 DR. COWPER: Yes?

6 DR. HARRINGTON: In your experience, have
7 you identified any other risk factor, other than
8 acute or chronic renal failure or acute or chronic
9 kidney disease, that seems to be associated with
10 the disease in such a strong manner?

11 DR. COWPER: Yes. Well, I alluded to the
12 hypercoagulability, and it's quite possible that
13 coagulabilty is actually related to a gadolinium
14 exposure. I'm not sure one way or the other at
15 this point. So that's one that remains open to
16 further investigation.

17 Another is the presence of having
18 received erythropoietin. Erythropoietin, as you
19 know, was used extensively in patients about the
20 time this disease began and it's very hard to
21 correct for that possibility, although we do have
22 many patients who have developed the disorder

1 without erythropoietin. So we do believe that it's
2 not a necessary cofactor, but maybe might be an
3 exacerbator. We cannot entirely exclude that.

4 DR. HARRINGTON: So I've got three
5 questions coming. There are a lot of folks who
6 want to get in here.

7 Will you be here all day?

8 DR. COWPER: Unfortunately, I have a
9 train to catch.

10 DR. HARRINGTON: So let's take a little
11 more time.

12 DR. COWPER: I'll take as many as you can
13 get.

14 DR. HARRINGTON: Let's take a little more
15 time than I would have.

16 Dr. Gross, you're up, and then Emil.

17 DR. GROSS: Most of the data looks as
18 though it's numerator data. Do you have any
19 individual denominator data for each of the
20 gadolinium agents?

21 DR. COWPER: No, I do not. I do not have
22 that sort of data available to me.

1 DR. HARRINGTON: Dr. Paganini?

2 DR. PAGANINI: Just two quick ones. The
3 registry doesn't have a full penetration of
4 everybody registered. So I'd be very careful about
5 using an N of 79 percentages of that to define
6 what's going on. A comment.

7 But the question that I would have to you
8 is, in the ESRD population, that is, CKD-4, 5 and
9 all of the dialysis supports, do you have all of
10 the other laboratory data that seems to be
11 available in those patients and have you run any
12 type of correlation with that laboratory data
13 beyond just having exposure to gadolinium?

14 DR. COWPER: No. Actually, I do not. I
15 have data in which the patients or, in some cases,
16 attorneys have shared charts with me. But because
17 most of these cases are not at Yale, we do not have
18 access to the full record, unless it's specifically
19 supplied to us. So I imagine there are many
20 additional data that could be certainly mined to
21 look for interesting associations.

22 DR. PAGANINI: Then one final issue. In

1 the MRA, it's a higher dose than an MRI. So you
2 know the percentage of penetration of NSF from MRAs
3 than MRIs, that perhaps leading you to a dose-
4 related exposure.

5 Do we have any of that at all?

6 DR. COWPER: Not beyond what I showed
7 here, that showed, I think it was, two-thirds
8 associated with MRI in those cases that are very
9 well defined. Beyond that, I would hesitate to
10 jump to a conclusion.

11 DR. HARRINGTON: Dr. Royal, and then Dr.
12 Fogel, and then Dr. Wolfe.

13 DR. ROYAL: Could you tell us more about
14 the gadolinium particles that you showed us? What
15 is their size? What is the chemical makeup? Are
16 they found in other organs?

17 DR. COWER: Yes. They are found in other
18 organs. Unfortunately, I can't tell you about the
19 size, because this is a technique that's been
20 employed by colleagues, not by me. I'm no expert
21 in this particular technique.

22 What I can tell you is that it is found

1 in other organs. The distribution throughout the
2 body doesn't necessarily relate directly to the
3 presence of fibrosis in individual organs.

4 When you look at the skin, the highest
5 concentration does appear to be in areas that are
6 specifically involved in the skin, with lower
7 concentrations elsewhere. In fact, we had a
8 patient who had another lesion on their face
9 sampled who also had NSF on a lower extremity and
10 it did have gadolinium in it, but a very small
11 amount. So it can be present all over without
12 producing an effect.

13 I also made reference to the fact that we
14 found it within macrophages and that being
15 important. In that discussion regarding the
16 stability of these agents, if that goes this way
17 this afternoon, it should take into account the pH
18 of the intercellular environmental of a macrophage,
19 which can be 3.5 to 4, very different than
20 physiologic pH.

21 DR. HARRINGTON: Dr. Fogel?

22 DR. FOGEL: Yes. Two real quick

1 questions. You alluded a little bit to this in
2 your presentation. The differential diagnosis, out
3 of other diseases and specifically with
4 scleroderma, can you expand a little bit on that?

5 The second question is out of all the
6 patients who received gadolinium with kidney
7 failure, do you have any data about what the
8 percentage is of those who exhibit NSF versus those
9 who do not?

10 DR. COWPER: The best data I have on the
11 second part of that question is a study that came
12 out of Connecticut that I was involved in, in which
13 an entire population of Bridgeport dialysis
14 patients were identified, and we found that the
15 risk was somewhere in the neighborhood of 3.3
16 percent after exposure to gadolinium in patients,
17 not further characterizing their renal disease,
18 other than to say they were hemodialyzed.

19 I'm sorry. What was the first part of
20 your question?

21 DR. FOGEL: The first question was the
22 differential diagnosis specifically with

1 scleroderma, could you expand on that?

2 DR. COWPER: Yes, of course. Scleroderma
3 does not have this limitation only to the
4 extremities. It does not have an abrupt onset
5 following renal disease, although some patients
6 with scleroderma do have renal disease.

7 They often have a history of vascular
8 over-activity in the fingertips. There are
9 antibodies which can be examined in the peripheral
10 blood. These things, the patients with NSF just
11 don't have.

12 Really, the most challenging one to
13 separate it from is scleromyxedema, which is what
14 it was initially confused with. Scleromyxedema,
15 histopathologically, looks exactly the same, but
16 its onset is in the face, preferentially, head and
17 neck, and then sometimes in the limbs, and they
18 also have a circulating paraprotein that can be
19 identified in almost case.

20 So we feel confident that between the
21 clinical and the pathological, we can exclude these
22 competing differential diagnoses.

1 DR. HARRINGTON: Dr. Wolfe, Dr. Kramer,
2 Dr. Nelson, then we'll move on.

3 DR. WOLFE: Two quick questions, also.

4 In your mass spectroscopy or other
5 analytic techniques, were you able to distinguish
6 between free gadolinium and either the linear or
7 the macrocyclic versions of the chelates?

8 DR. COWPER: These techniques, again, I
9 rely on my expert colleagues. These techniques
10 only identify the atom, cannot identify what state
11 it's in.

12 DR. WOLFE: The other question was the
13 age frequency distribution of the cases looked, to
14 me, like it was probably similar to the age
15 frequency of use of MRI. I assume someone has
16 looked at that and since you said that was not a
17 risk factor, I assume that's the case, that there
18 is no evidence that there is some age proclivity
19 where you would be more likely to get it.

20 DR. COWPER: I don't know. It looks, to
21 me, very close to a normal distribution, although I
22 have not done a statistical test to show that. It

1 also looked like there might even be a sense of the
2 bi-modality, but I don't have enough data. N of 79
3 is difficult to draw great conclusions from.

4 I do not know that anybody has compared
5 this to the use of MRI or to the distribution of
6 renal disease, in general. It's interesting to
7 note that even all the way back in the first
8 discussion of the first 15 cases, we had the
9 average age set at about 50 at that point and that
10 hasn't really changed as time has gone on. We've
11 become a little bit more detailed in a larger N,
12 but the median hasn't really changed.

13 DR. HARRINGTON: Dr. Kramer?

14 DR. KRAMER: I'm curious, with your
15 expertise in the pathologic changes of NSF, how
16 much weight you would place in the materials that
17 were submitted in our packet by one of the
18 sponsors, Bayer, who did nonclinical rat studies
19 showing differential susceptibility by dose and by
20 gadolinium-based contrast agent.

21 DR. COWPER: I did look briefly at those.
22 There were, as you know, several hundred pages

1 worth of briefing documents available on relatively
2 short notice. But I am familiar with their
3 studies. It doesn't surprise me that a larger dose
4 may relate to more disease, more significant
5 disease.

6 I find it interesting that their studies
7 suggest that de-chelated gadolinium might be
8 associated with a more florid course of the
9 disease. Certainly, that's been discussed amongst
10 experts. I'm not sure that we've all come to a
11 conclusion on that one yet, though.

12 But regarding other agents, I'm always
13 hesitant to make a decision unless I have had the
14 opportunity really to examine the data myself very
15 carefully. But I will say, as a general kind of
16 overarching principal, that the clinical and
17 pathologic manifestations in these animals does
18 very closely approximate what happens in a human,
19 without being exact, but very close approximation,
20 but not being precise.

21 DR. KRAMER: Specifically, the difference
22 between the ionic and non-ionic linear agents, any

1 comment on that, pathologically, in the rats?

2 DR. COWPER: Yes. Well, I believe that
3 the Magnevist study showed very little, if
4 anything, happening in the Magnevist rats, whereas
5 the GE Omniscan material showed a larger
6 fluoridity, if you will, to the pathology.

7 The only hesitancy I have is that I want
8 to make sure that these studies are carried out for
9 a long enough period of time in the animals. I
10 know that in some of the early studies done by
11 Bayer, the animals were terminated fairly early and
12 may have been terminated before the study really
13 reached its conclusion, whereas I know that the
14 Optimark-studied animals were studied for, I
15 believe, a year or for at least a significant
16 amount of time. Maybe it was seven months, but for
17 a very long period of time before they started
18 seeing changes.

19 So I would only caution that in any study
20 in which the study is terminated at just a few
21 weeks, we have to treat that with a little bit of
22 caution, because this disease, actually, in humans,

1 takes some time to develop and to be clinically
2 viewable, seeable.

3 DR. HARRINGTON: Dr. Nelson, then Dr.
4 Halperin, then we'll move on.

5 DR. NELSON: Thank you. Maybe you've
6 answered some of these questions, although I'm not
7 totally sure you have, and maybe this is actually
8 just one long run-on question.

9 I assume that it's implicit in the
10 scoring criteria that the people have been exposed
11 to gadolinium, although I'm not sure you
12 specifically said that. So I guess my real
13 question is, have you seen patients who you can
14 feel qualify for the diagnosis of NSF who have
15 actually not been exposed to gadolinium. I know
16 what the material that we've received said, but I
17 don't know what your clinical practice has shown?

18 A related question is, how do you explain
19 the outliers, the people who developed NSF well
20 removed in time from their exposure?

21 DR. COWPER: Well, to answer the first
22 question, certainly, every case identified up to

1 2006, the diagnosis was made without any input of
2 gadolinium at all, because that wasn't really on
3 anybody's radar screen at the time.

4 The criteria we've developed have
5 purposely excluded gadolinium, because we found
6 that to be unreliable. Patients will often tell
7 you that they have had no exposure to gadolinium.
8 Doctors will tell you there has been no exposure to
9 gadolinium. Yet, if you test the tissue, you will
10 find gadolinium within it. So you know there's
11 been an exposure sometime along the way.

12 One of the reasons I got tripped up in
13 the early days when I first identified it is I had
14 a patient who claimed he had no exposure and the
15 patients claim they had no exposure. So I didn't
16 want to go forward without knowing we had an
17 exposure.

18 Well, only after Dr. Grobner's article
19 came out did we, in fact, learn that this patient
20 had an exposure and it was at another hospital and,
21 for whatever reason, he was not aware of it.

22 So the more recent cases, because

1 gadolinium is now so right in front of us, those
2 cases usually come with a history appended to them.
3 That's provided to us, but it's not a factor that I
4 use in making the diagnosis.

5 DR. HARRINGTON: Do you want to comment
6 on the late occurrence?

7 DR. COWPER: The late occurrence, yes.
8 If you've seen cases, relatively mild cases of this
9 come on, it comes on very surreptitiously. These
10 patients often have extremity edema as a result of
11 their underlying renal condition. Sometimes
12 they're in the ICU and sometimes they're non-
13 ambulatory. So these findings, in a very subtle
14 case, may take some time to actually be recognized
15 by somebody.

16 Many patients, I'm sure, are used to
17 seeing edema and fibrosis of their skin and pretty
18 much treat it as being part of their renal disease
19 and don't seek specific care for it. And my guess
20 is those who do not wind up in wheelchairs as a
21 result of it, there may be a large number of
22 patients living with this disease who don't even

1 realize they have it.

2 DR. HARRINGTON: Final question, Dr.
3 Halperin.

4 DR. HALPERIN: First, thank you very much
5 for your excellent presentation. Given the
6 associations you describe with thrombosis and
7 collagen deposition, have you observed any
8 association of NSF with tobacco exposure?

9 DR. COWPER: I haven't specifically
10 looked for it. So I couldn't comment one way or
11 the other on that.

12 DR. HALPERIN: Thank you.

13 DR. COWPER: Sure.

14 DR. HARRINGTON: Thank you, Dr. Cowper,
15 for your presentation and your willingness to
16 answer questions. We'll now move on to our next
17 speaker, who is Dr. Jeffrey Weinreb, also from the
18 Yale School of Medicine, who will speak to us on
19 the use of gadolinium contrast agents in clinical
20 practice.

21 DR. WEINREB: Thank you for the
22 invitation to talk this morning. I've been asked

1 to present a radiologist's perspective on this
2 disease and I'm going to speak rather quickly to
3 get through the slides and hopefully leave some
4 time for questions.

5 First of all, I think most of the people
6 in this room understand why we use gadolinium-based
7 contrast agents, or GBCAs, and that's to improve
8 our diagnostic capabilities with MRI. MRI without
9 GBCAs is a very powerful tool and, in many cases,
10 you don't need a GBCA. But there are cases
11 unequivocally where GBCAs help improve the
12 detection, characterization, staging of diseases, a
13 whole range of diseases. It can also improve your
14 confidence level.

15 So I think most people would agree that
16 GBCA-enhanced MRI plays an essential role in modern
17 medical diagnosis. And just to give you a sampling
18 of where we use it, in a range of diseases in the
19 brain, it's really the premier way to look at
20 diseases in the spinal cord. It's used to diagnose
21 diseases in the vascular system, in the head, in
22 the neck, the aorta, the renal arteries, the

1 peripheral arteries; in fact, all of the vascular
2 areas in the body.

3 It's being used more and more to evaluate
4 diseases in the kidneys, the liver, the pancreas,
5 for gynecologic malignancies. It's been used in a
6 diluted form as an injection into the joints to
7 evaluate for soft tissue injuries. It's being used
8 to evaluate ischemic heart disease and cardiac
9 viability. And the fasting-growing application of
10 GBCA-enhanced MRI happens to be for detection and
11 staging of breast cancer. I think in light of the
12 past couple of weeks, I'm going to stay away from
13 talking about MR mammography.

14 The point that I want to make here is
15 that a lot of these applications are off label and
16 that includes, for the most part, contrast-enhanced
17 MRA. Right now, there's only one FDA-approved agent
18 for contrast-enhanced MRA and it's only approved
19 for aortoiliac occlusive disease, a very limited
20 application, which means that there are more than a
21 million GBCA MRA procedures performed each year in
22 the United States using GBCAs that are not approved

1 for MRA. And although some are, many of these
2 agents are not approved for higher doses, faster
3 injection rates, or pediatric patients.

4 This is some industry data from AMR and
5 I'm grateful for their help in providing this data
6 to you. In green, it shows you the number of MR
7 scans performed per year in the United States and
8 you can see that the number has gone up over the
9 last decade, so that in 2008, the last year for
10 which data is available, there were more than 36
11 million MR procedures in the United States. Of
12 those, a little less than a third used a GBCA, and
13 the percentage of MR procedures using GBCAs has
14 steadily slightly increased over the last decade.
15 I suspect if we had the data for 2009, it will have
16 leveled off or probably gone down.

17 This is another slide provided by AMR and
18 it shows what parts of the body the GBCAs are used
19 and, not surprisingly, the most common use is in
20 the central nervous system. That's far and away
21 the most common application of MR in the United
22 States. But I want to focus a little bit on the

1 MRA, MR angiography, and that accounts for 13
2 percent of the GBCA utilization in the U.S. And I
3 want to focus on this, because it is important, as
4 has already been pointed out during the questions,
5 in regards to NSF and there are some misconceptions
6 about MRA.

7 First of all, MRA is a way of making
8 images of the vascular system that simulate the
9 types of images we get from conventional
10 angiography. In patients with bad renal function,
11 MRA was a preferred way of getting images of the
12 vascular system without using iodinated contrast
13 agents.

14 What's important to understand is that a
15 lot of people are making this distinction between
16 MRA and MRI. They are exactly the same thing.
17 There is no distinction. MRA is the type of MRI we
18 do to look at the vascular system.

19 If we're looking at the, for example,
20 small bowel, we'll call it MR enterography. If
21 we're looking at the biliary system, we'll call it
22 MRCP, MR cholangiopanteatography. MRA is just a

1 convenient name for a type of MRI procedure. It
2 uses the same equipment and the same contrast
3 agents.

4 Now, what about using contrast for MRA?
5 One of the most attractive features about MR from
6 the very earliest days was the potential for making
7 images of the vascular system without a contrast
8 agent, and in the late 1980s or early 1990s, we
9 tried doing that, with a little bit of success.
10 But the fact is that in many cases, particularly
11 when you got outside of the neck, we could not make
12 diagnostic quality, routinely diagnostic quality,
13 time-efficient scans of the vascular system without
14 contrast agents.

15 There were a lot of artifacts and the
16 scanners just were not technically capable of doing
17 this. And it really wasn't until we got into the
18 sort of mid-1990s that the scanners got better,
19 technologically got better, and that people like
20 Martin Prince, Manny Kanal, who is here, and other
21 people taught us how to use contrast agents to get
22 MRAs, and then we could make diagnostic quality

1 MRAs in virtually anybody. But to do this, and
2 this is an important point, at this point in time
3 and even beyond this, we had to use high dose. We
4 could not do this with the single FDA-approved dose
5 of gadolinium in many cases.

6 Now, jumping to 2009, we now have
7 scanners and techniques available to us, becoming
8 available to us, more widely available, that allow
9 us to give diagnostic quality MRAs without contrast
10 agents, as is illustrated here. However, I think
11 it's important to understand that a lot of these
12 techniques have not yet been validated in every
13 part of the body. They are not widely available.
14 And even if they are validated, there are many
15 scanners in the United States that are not capable
16 and will not be capable of doing this.

17 Here is some more data provided by AMR
18 and what it shows is the number of GBCA MRA
19 procedures in the United States and, again, you can
20 see that there's been rapid growth through 2006 and
21 then in 2006, it appears to, more or less, have
22 leveled off. But, again, there's more than 10

1 million performed per year and I suspect if we were
2 looking at 2009, the number would probably go down.
3 The volume of contrast used per MRA procedure has
4 also leveled off and has started to go down since
5 the association was made with NSF.

6 Prior to the link with NSF, GBCAs were
7 commonly and often preferentially used in patients
8 with renal insufficiency, particularly to evaluate
9 the vascular system, because they were felt to be
10 less likely to harm the kidneys than the iodinated
11 agents that we use in CT and we also use in
12 angiography, and this, in fact, has held up.

13 Also, importantly, although iodinated
14 agents and the GBCAs can all result in adverse
15 events, it's less common with the GBCAs than the
16 iodinated agents. And although the severe adverse
17 events are rare with both iodinated agents and
18 GBCAs, it's even more rare with GBCAs than the
19 iodinated agents.

20 So that in 2005, if we were trying to
21 make a decision, in a particular patient who needed
22 a contrast-enhanced diagnostic study, whether we

1 should do a contrast-enhanced MR or a contrast-
2 enhanced CT, we would look at the fact that the
3 GBCAs had fewer reactions. There was less likely
4 to be a problem with contrast extravasation,
5 because the doses were lower and the injection were
6 lower, and we didn't really have a substantial
7 problem with CIN with the GBCAs compared to the
8 iodinated agents used in CT.

9 In addition, there's the issue of
10 radiation, not to be forgotten. It's really
11 started getting into people's consciousness a
12 number of years ago and it's very important, and MR
13 doesn't use radiation. So if we were weighing MR
14 versus CT, all of these things would weigh into the
15 equation and that's why we were using the
16 gadolinium agents in doing MRAs.

17 As far as the choice of GBCAs, prior to
18 the link with NSF, most radiologists believed that
19 all of the GBCAs available were similar in
20 mechanism of action, efficacy, and risk of adverse
21 events. Even if they knew about differences in
22 structure and stability and other characteristics,

1 most radiologists felt they were more or less
2 interchangeable, that they were commodities. So
3 purchasing decisions were based primarily, in many
4 cases, on pricing, GPO contracts, and personal,
5 often anecdotal preferences.

6 So if we go back to before NSF, Magnevist
7 and Omniscan dominated the market with, together,
8 more than 80 percent market share. In any event,
9 it came as a real shock, from the point of view of
10 a radiologist, and I believe everybody, when the
11 FDA issued this public health advisory linking
12 GBCAs with NSF. And when the FDA issued the boxed
13 warning that applied to all gadolinium-based
14 contrast agents equally, radiologists widely
15 misinterpreted this.

16 Even though the FDA said something quite
17 to the contrary, radiologists widely misinterpreted
18 this as meaning that all of the GBCAs have a
19 similar risk of NSF, and this was due to the
20 limitations of the data that was available at this
21 time in mid-2007.

22 Now, in addition to the FDA, there are

1 other organizations that have weighed in on the
2 issue of NSF and GBCAs. This includes, in the
3 United States, the American College of Radiology
4 and the NKF, and there's also a joint working group
5 of the NKF and ACR that has draft recommendations
6 which have not yet been published.

7 It's also important to note that
8 literally every institution in the United States
9 that does MRI has now come up with policies about
10 GBCAs and MRI and NSF. In some cases, these mirror
11 the ACR recommendations and, in some cases, they're
12 tailored for a particular site.

13 There are also guidelines or
14 recommendations from outside of the United States.
15 You already heard about EMEA and there are some
16 other documents from other countries, as well. All
17 of these recommend screening for renal dysfunction.
18 Outside the United States, all of them indicate
19 that the risk factor for NSF varies between the
20 types of GBCAs.

21 Now, moving on to how have clinical
22 practices changed since this linkage was made

1 between NSF and GBCAs. Well, first of all, fewer
2 patients who are on dialysis and are known to have
3 CKD are referred to GBCA-enhanced MRI. Prior to
4 NSF, this was common. Now, it's very uncommon.
5 These patients just are not showing up at our door
6 anymore.

7 At the MRI facility, there is some
8 reluctance amongst a lot of radiologists to use
9 GBCAs. A lot of this information is anecdotal. I
10 don't have hard numbers to back this up. But I
11 hear stories about some MRI facilities that no
12 longer administer GBCAs. I know for sure there are
13 facilities that have really become gun shy and at
14 the slightest hint of some kind of kidney
15 dysfunction, they will not administer a GBCA. And
16 in some cases, these patients are being sent often
17 to hospitals, to other places that are more willing
18 to deal with these cases.

19 Another change has been increased use of
20 alternative imaging tests. So instead of using a
21 GBCA-enhanced MRI in these patients with some kind
22 of renal compromise, we might do a non-contrast-

1 enhanced scan or a low dose CT or some other
2 combination of examinations that don't entail the
3 use of a GBCA.

4 Coincidentally, during this period of
5 time, there's been a reassessment in the radiology
6 and nephrology community about what the actual
7 risks of CIN are from iodinated contrast and
8 whether the risk of CIN in many of these cases is
9 actually clinically relevant, particularly with the
10 modern iodinated contrast agents that are available
11 to us.

12 So in general, I'd say many people think
13 that the risk of CIN from iodinated agents,
14 clinically relevant risk, is lower than we've
15 thought for many years.

16 So in 2006, after this link was made
17 between NSF and GBCAs, if we were weighing
18 contrast-enhanced MR and contrast-enhanced CT,
19 what's commonly been done is you look at what is
20 the perceived risk of CIN versus the perceived risk
21 of NSF, and these things are tended to be looked at
22 in isolation.

1 But I think it's very important for this
2 panel and for radiologists and the medical
3 community to remember there are other issues here
4 and these other risks may outweigh the risk of CIN
5 or of NSF from the gadolinium-based contrast agents
6 in a particular patient, but we weigh these risks
7 in individual patients.

8 Just to give you a flavor of the type of
9 alternative imaging algorithms that could be used.
10 The first patient is a 40-year-old woman with
11 autosomal dominant polycystic kidney disease, a low
12 GFR, and ultrasound showed an echogenic mass.

13 In these patients, we're concerned about
14 renal cell cancer. They have a slightly increased
15 incidence of renal cell cancer. Prior to the issue
16 of NSF, this patient would have gone right to GBCA-
17 enhanced MRI to determine whether this mass is
18 enhancing. If it's enhancing, it's assumed to be a
19 cancer.

20 Now that we have to contend with NSF, we
21 have a bunch of alternative ways of looking at
22 this. One way is to first do a non-contrast-

1 enhanced CT, see if the mass contains fat. If it
2 contains fat, it's an angiomyolipoma, a benign
3 tumor. There's really no reason to go on and do
4 anything else.

5 If it doesn't contain fat, then you might
6 consider hydrating the patient, pre-medicating
7 them, and doing a low dose contrast-enhanced CT
8 with a low osmolality or iso-osmolality iodinated
9 agent, which would limit their risk of CIN.

10 Another way of possibly working this
11 patient up might be to do a contrast-enhanced MRI
12 with an agent which appears to have a lower risk of
13 NSF, such as a macrocyclic or maybe a low dose of a
14 high relaxivity GBCA. So we could still possibly -
15 - some people would still do a contrast-enhanced MR
16 in this case.

17 We also have the option now, possibly, of
18 doing a non-contrast-enhanced MR using one of our
19 modern techniques, like diffusion-weighted
20 scanning. So at our professional meetings and in
21 the literature, there is some indication that you
22 could use, in some instances, diffusion-weighted

1 imaging to determine if this mass was benign or
2 malignant. But I'd have to say this hasn't been
3 thoroughly validated yet, but we may be moving in
4 that direction.

5 The second case I want to discuss briefly
6 is a 25-year-old who, based on a neurologic exam,
7 is suspected of having an intramedullary spinal
8 cord tumor. This patient has a low GFR and we need
9 to know is there a tumor present, what disease is
10 present, what the extent is.

11 Ordinarily, before the NSF era, we would
12 get a gadolinium-enhanced MRI. In the NSF era, we
13 would still do that, and the reason we would do
14 that is because MRI is better than CT and doing the
15 MRI without the contrast agent is going to give you
16 a limited amount of information.

17 Now, you might do it with a lower dose or
18 with a different agent than you used to use, but
19 you'd still probably do a contrast-enhanced MRI.
20 And it makes the point that sometimes, even with
21 NSF and patients with compromised renal function,
22 contrast-enhanced MRI may be the best test.

1 Other things that have changed.

2 Screening has become common. People are screening
3 every which way you can imagine, everything from
4 simply asking a patient, "Do you have a kidney
5 problem," to requiring that every patient who gets
6 a gadolinium agent gets a serum creatinine and have
7 an eGFR calculated. But, remember, screening does
8 entail increased time, cost and convenience, no
9 matter what screening method you use.

10 Other things that have changed. There's
11 decreased use of linear nonionic GBCAs. High dose
12 MRI and MRAs have become less common. Low dose
13 MRIs have become more common. And patients with
14 compromised renal function are less likely to get
15 repeat doses of GBCAs at short time intervals.

16 It's more common now to give weight-based
17 dosing. Prior to NSF, it was not an uncommon
18 practice to just give every patient a vial's worth,
19 20 cc's worth of GBCA for a particular test.
20 Nowadays, more patients are weighed.

21 Another important change is that prior to
22 NSF, it was common practice not to document the

1 exact type of GBCA and the dose of GBCA that was
2 used in a particular procedure. Now, radiologists
3 are documenting the dose and specific GBCA used.

4 As far as the dose goes, this may come as
5 a surprise to a lot of people, but the diagnostic
6 and optimal dose, in many cases, is really not
7 know, because it depends on the specific GBCA, the
8 patient characteristics, the type of MR exam, the
9 particular MR scanner and hardware, and, also, the
10 magnetic field strength.

11 This is an illustration of that. This is
12 a slide given to me by Larry Tanenbaum. And on the
13 left-hand side is an MR scan at low magnetic field
14 strength, 0.2 tesla, with a single dose of a
15 gadolinium agent. And on the right-hand side is
16 the same patient with a single dose at 1.5T. And
17 the little arrow here is pointing to a metastasis
18 which is much better seen with the higher magnetic
19 field strength. And this gets very complicated
20 when you start talking about different doses and
21 moving to 3 tesla. The point is the optimal
22 diagnostic dose is not a simple matter.

1 Now, the last thing I want to address
2 very quickly is the impact on patients. And the
3 questions are, are diagnoses being missed because
4 of the way we've changed our practices and are
5 patients receiving suboptimal care because of a
6 concern for NSF?

7 The answer is I don't know. I don't know
8 of any data that answers this question. I know,
9 anecdotally, I've heard tales about diagnoses being
10 missed because a GBCA wasn't given. I've heard
11 anecdotally about diagnoses not being confident
12 because a suboptimal dose of GBCA was given. But I
13 don't know for sure.

14 I am concerned, however, that in an
15 effort to limit the risk of NSF, some may be using
16 a suboptimal or non-diagnostic dose or, in some
17 cases, no dose at all and they don't know what
18 they're missing.

19 So just to summarize, GBCAs play an
20 important role in medical diagnosis. Off-label use
21 is common. I think the FDA and the ACR and
22 everybody has done a very good job of educating

1 everybody, including the vendors, about the issues
2 and, as a result, there's been a marked decrease in
3 the number of new cases of NSF, but I don't know
4 what the effect is on patient care.

5 Finally, I want to acknowledge a bunch of
6 people, especially my colleagues at Yale. Thank
7 you.

8 DR. HARRINGTON: Thank you, Dr. Weinrab.
9 If there's a burning question or two, we're not
10 going to take a lot, because we want to go ahead.
11 But let me go to Susan, Sid and Julie, and then
12 maybe I'll cut it off so we can keep moving.

13 DR. HECKBERT: Okay. Just a quick
14 question. And that is, you talked about situations
15 where you would use one approach versus another or
16 a higher or lower dose contrast agent. But are
17 there situations where you would use one agent in
18 place of another; for example, one area of the body
19 that you're imaging versus another?

20 DR. WEINRAB: Yes. There are some
21 agents, for example, that are not completely
22 eliminated through glomerular filtration that have

1 a hepatocyte phase and we might use those
2 specifically to look at the liver, for example.

3 The other thing I'd say is there are a
4 lot of people who are using low relaxivity agents
5 to do MRA, with the idea that you get more bang for
6 the buck, in a sense, you get more enhancement with
7 a lower dose. A lot of this is personal
8 preference.

9 DR. HARRINGTON: Thank you.

10 Dr. Wolfe?

11 DR. WOLFE: Almost two-and-a-half years
12 ago, the American College of Radiology started
13 distinguishing between these agents, the different
14 agents, in terms of their risks. Did you support
15 that? And you've alluded in your talk to EMEA,
16 which also did something in 2007.

17 In 2007, were you one of these people
18 that supported the idea of ACR starting to
19 distinguish between the agents in terms of NSF
20 risk?

21 DR. WEINRAB: There was a committee that
22 Manny Kanal chaired, who is sitting in the audience

1 there, and I was a member of the committee. And
2 the committee initially supported the idea of a
3 differential risk between some of the agents, but
4 this is a committee -- there was a statement later
5 that this was the report from a committee and did
6 not represent the official views, I think, of the
7 ACR.

8 DR. WOLFE: What were your views on this?
9 You were on the committee.

10 DR. WEINRAB: At that point in time -- so
11 this was late 2006 and early 2007 -- my personal
12 views were the data was very confounded and
13 incomplete and I wasn't certain about what the
14 relative risks are.

15 I think in 2009, several years later, we
16 have two years more worth of data and I think there
17 probably is a differential risk. But at that point
18 in time, I think it was very hard, at least from
19 this side of the Atlantic, in my view, to make that
20 distinction.

21 DR. HARRINGTON: Dr. Wolfe, in the open
22 public hearing, we will be hearing from Dr. Kanal,

1 who has been referred to a couple times this
2 morning.

3 Dr. Zito?

4 DR. ZITO: Yes. You made reference to
5 severe adverse events and you have some frequencies
6 and comparing iodinated versus GBCA. I'm wondering
7 about the data sources, the metrics that were used,
8 their reliability and their generalizability; other
9 than that.

10 DR. WEINRAB: These come from a variety
11 of sources that I put on the slide and that's an
12 incomplete list. Those were just a sampling. And
13 none of these studies are perfect. Many of them
14 are retrospective.

15 But the trend in all of them is to show
16 that the -- and I think this also mirrors clinical
17 experience -- that the incidence of adverse events
18 with the GBCAs was lower than the -- for severe
19 adverse events is lower with the GBCAs than the
20 iodinated agents.

21 DR. ZITO: And one more question about
22 the funding source for the studies.

1 DR. WEINRAB: I don't know what the
2 funding source was for them. Some of them were
3 supported by industry. Some of them were not.
4 There was a recent Mayo Clinic study, which was on
5 almost half-a-million patients, which I don't
6 believe was supported by industry, which, again,
7 indicated that severe adverse events are rare, but
8 they are more rare with the GBCAs.

9 I think in their series, they had -- I
10 don't remember the exact numbers, but I think there
11 were about 14 or so severe reactions in almost half-
12 a-million cases, of which I think four or so or six
13 were GBCAs and the rest were iodinated agents.
14 They're not well controlled studies, in general.

15 DR. HARRINGTON: Dr. O'Brien?

16 DR. O'BRIEN: Just a quick question. You
17 mentioned radiologists changing their practices and
18 I wondered if you had any sense of if that varies
19 by settings where MRIs are offered.

20 DR. WEINRAB: Settings meaning outpatient
21 versus hospital?

22 DR. O'BRIEN: Yes.

1 DR. WEINRAB: I suspect that it is. I
2 think in a hospital environment, it's, in many
3 cases, easier to know the patient's renal function,
4 because they've got blood tests. And in
5 Connecticut, in fact, it's the law. When they come
6 into the hospital and have a blood test, we know
7 what their eGRF is, whereas in an outpatient
8 setting, in some places, it may be easy to learn
9 the patient's renal function and, in other places,
10 it may be virtually impossible.

11 So I think there are differences between
12 many inpatient and outpatient settings.

13 DR. HARRINGTON: Dr. Weinrab, thank you
14 very much.

15 DR. WEINRAB: You're welcome.

16 DR. HARRINGTON: Are you here all day, if
17 we have more questions?

18 DR. WEINRAB: If I tell you I'm taking a
19 train, do I get more questions?

20 [Laughter.]

21 DR. WEINRAB: I will be here all day.

22 DR. HARRINGTON: Perfect. So we may

1 return to you this afternoon. Thank you.

2 All right. We're going to move to the
3 sponsor part of the presentations and we have seven
4 sponsor presentations. They've all been asked to
5 limit their remarks to 20 minutes. I'd like them
6 to limit their remarks closer to 15 so that the
7 panel can ask questions. We will start with Bayer.

8 I am required now to read a statement
9 prior to the sponsor's presentation.

10 Both the FDA and the public believe in a
11 transparent process for information-gathering and
12 decision-making. To ensure such transparency at
13 the advisory committee meeting, FDA believes that
14 it is important to understand the context of an
15 individual's presentation.

16 For this reason, FDA encourages all
17 participants, including the sponsor's non-employee
18 presenters, to advise the committee of any
19 financial relationships that they may have with the
20 firm at issue, such as consulting fees, travel
21 expenses, honoraria, and interests in the sponsor,
22 including equity interests and those based upon the

1 outcome of the meeting.

2 Likewise, FDA encourages you, at the
3 beginning of your presentation, to advise the
4 committee if you do not have any such financial
5 relationships. If you choose not to address this
6 issue of financial relationship at the beginning of
7 your presentation, it will not preclude you from
8 speaking.

9 So with that, we'll turn our attention to
10 the first sponsor presentation from Bayer.

11 DR. PERING: Thank you, Mr. Chairman,
12 members of the Advisory Committee. Good morning.
13 My name is Christiane Pering and I'm head of Global
14 Medical Affairs-Diagnostic Imaging at Bayer.

15 On behalf of Bayer, I would, first of
16 all, like to thank FDA for organizing today's
17 meeting and inviting us to participate. We greatly
18 appreciate the opportunity to present to you and
19 discuss with you our product-related data and
20 scientific assessment of these.

21 In my presentation, I will give you an
22 overview of the key development activities and

1 post-marketing activities related to Magnevist to
2 date; I will share with you the available
3 nonclinical research results and discuss the
4 available clinical evidence related to Magnevist in
5 the context of NSF; and, last, but not least, I
6 will outline the implemented risk mitigation
7 activities and their effects.

8 Magnevist was the very first contrast
9 agent approved for use with magnetic resonance
10 imaging back in 1988 in the U.S. and in other key
11 countries around the world. The first indication
12 included imaging of the central nervous system in
13 adult patients and, subsequently, further clinical
14 studies were conducted to explore new indications
15 and expanded use.

16 Today's range of approved indications of
17 Magnevist include imaging of various body organ
18 systems and the use in pediatric patients aged two
19 years and older. With more than an estimated total
20 of 100 million administrations worldwide since
21 launch, there is an unmatched clinical experience
22 with Magnevist available.

1 We became aware of the possible
2 association between the occurrence of NSF and the
3 administration of gadolinium agents in early 2006,
4 upon the publication by Grobner. We responded to
5 it by soon thereafter initiating preclinical
6 research to further explore the issue and
7 understand it.

8 Class labeling for NSF was introduced for
9 all markets of gadolinium agents in the U.S. in
10 2007, followed by still ongoing clinical studies.

11 So now let me share with you the results
12 of our nonclinical NSF research. Initially, the
13 reports of NSF were predominantly associated with
14 the administration of Omniscan and, therefore, the
15 question came up whether there are any known
16 differences among the market of gadolinium agents
17 which could potentially explain this phenomenon.
18 And based on chemical structure and related to the
19 co-chemical properties, in particular, the complex
20 stability of the agents, de-marketed gadolinium
21 agents can be divided into three distinct
22 categories. There are the nonionic linear agents,

1 Omniscan and Optimark, which represent agents with
2 the least stability. Then there are the linear
3 ionic agents, including Magnevist, which are agents
4 that are more stable. And then there's a group of
5 macrocyclic agents, of which only ProHance is
6 approved for use in the United States, which
7 represents agents with the greatest stability.

8 The spectrum from agents that are least
9 stable to agents that are most stable is paralleled
10 by the findings in our nonclinical research
11 activities. We looked in our studies at the
12 predilection of various markets of gadolinium
13 agents to release gadolinium in vitro, to cause
14 gadolinium accumulation in rat skin tissue, and to
15 induce NSF-like skin lesions in animal models. The
16 details of these experiments have been outlined in
17 our briefing documents.

18 All of the available nonclinical results
19 of these studies suggest a lower likelihood of
20 releasing gadolinium, causing gadolinium
21 accumulation in skin tissue and inducing NSF-like
22 skin lesions in animals of the ionic linear

1 gadolinium agents, such as Magnevist, when compared
2 to the nonionic linear agents, Omniscan and
3 Optimark.

4 However, it is not clear how relevant
5 these nonclinical findings are in predicting the
6 relative NSF risk of various marketed gadolinium
7 agents in the clinical setting.

8 Next, I would like to review the clinical
9 evidence with Magnevist in the context of NSF.
10 Magnevist is the most widely used and most
11 extensively studied MR contrast agent worldwide.
12 Efficacy and safety of Magnevist have been studied
13 in more than 11,000 subjects in clinical trials
14 worldwide.

15 The clinical use of Magnevist has been
16 evaluated and reported in more than 16,000
17 scientific publications and Magnevist, as I
18 mentioned previously, has been estimated to have
19 been administered more than 100 million times
20 worldwide. That is more than all the other
21 gadolinium agents on the market combined.

22 We are of the opinion that decisions

1 about labeling regarding risk differences of drugs,
2 in this case, gadolinium agents, should be based on
3 reliable clinical data. However, there are no
4 adequate, well controlled, randomized clinical
5 trials available which have compared the NSF risk
6 among marketed gadolinium agents.

7 There are also no adequate observational
8 studies available which have compared the risk of
9 NSF among marketed gadolinium agents. Among the
10 published studies to date, there is, in fact, only
11 one observational study, the one published by
12 Wertman and his colleagues, which states that the
13 study objective was to compare the NSF risk of
14 various marketed gadolinium agents in U.S.
15 institutions.

16 The study results reported a
17 significantly higher risk of NSF with the
18 administration of Omniscan than with Magnevist.
19 Note, however, that the authors of the study made
20 no attempt to adjust for many of the important
21 confounding variables, including the dose of the
22 gadolinium agents used, the number of patients with

1 renal impairment which actually received gadolinium
2 agents, or the number of procedures which were
3 gadolinium-enhanced per patient.

4 However, it should be noted that the odds
5 ratio for the risk of Omniscan when compared with
6 the risk of NSF from Magnevist, as reported by the
7 authors, was greater than 13. Odds ratios of this
8 magnitude may well reflect the true difference,
9 because they are unlikely to disappear following
10 the adjustment of confounding variables.

11 Nonetheless, the available clinical
12 studies do not allow for robust conclusions
13 concerning the potential differences in risk
14 against NSF among marketed gadolinium agents.

15 In the absence of robust observational
16 studies, the current clinical evidence largely
17 concentrates on analyses of adverse events reported
18 to the FDA through the AERS database. These
19 reports have been received through the MedWeb
20 system and they come from various sources,
21 including complaints filed by plaintiffs'
22 attorneys, and often contain very little

1 information.

2 It is well known that there are
3 limitations to interpreting data from the AERS
4 database and drawing robust conclusions is,
5 therefore, difficult. Nonetheless, there are two
6 ways of looking at the available AERS data. One
7 way is to look at all cases of NSF that involved
8 the administration of one or more gadolinium
9 agents, and this slide shows this approach.

10 Striking differences are given between
11 Magnevist and the nonionic linear agents, Omniscan
12 and Optimark, if we take their overall usage into
13 account. Specifically, although Magnevist has been
14 administered twice as frequently as Omniscan, the
15 number of NSF reports involving Omniscan was nearly
16 50 percent greater than the number involving
17 Magnevist.

18 Similarly, although Magnevist has been
19 administered 20 times more often than Optimark, the
20 number of NSF reports involving Optimark was only
21 slightly lower than the number of reports involving
22 Magnevist.

1 Despite the well recognized difficulties
2 in interpreting AERS frequencies, these findings do
3 support the results of both the clinical and the
4 nonclinical studies I just reviewed. All of these
5 support the premise that the risk of NSF with
6 Magnevist is meaningfully lower than with the
7 nonionic linear agents, Ominscan and Optimark.

8 Similar observations can be made when we
9 compare the available data with Magnevist to the
10 available NSF reports with the other marketed
11 gadolinium agents. Although Magnevist has been
12 used approximately 20 times more often than
13 MultiHance, the number of NSF reports involving
14 Magnevist is only about approximately two times the
15 number of NSF reports involving MultiHance.

16 We have further displayed to you the
17 number of administrations of Magnevist since the
18 first observed case of NSF in 1997, which can also
19 be used as a basis to compare the usage in relation
20 to the number of NSF reports.

21 Now, throughout the day, the committee is
22 likely to see two different presentations of the

1 AERS data. The numbers you have seen on this slide
2 are the number of NSF reports which made note of
3 the possible involvement of a particular agent.

4 Patients who received multiple different
5 gadolinium agents, because they underwent multiple
6 different gadolinium-enhanced procedures, are
7 counted in each row for each agent.

8 However, the committee is likely to see a
9 second version of the AERS data. Specifically, you
10 may see tabulations of numbers of NSF reports in
11 which patients who received more than one
12 gadolinium agent are eliminated entirely from the
13 analysis. You will hear this approach referred as
14 a tabulation of unconfounded cases, but these cases
15 actually represent, in our eyes, a biased sample of
16 the total number of NSF cases reported to the FDA
17 for each agent. And the bias involved in such a
18 presentation is well illustrated if we look, for
19 example, at the number of AERS reports for
20 Magnevist and MultiHance.

21 At the first glance, you see the
22 impressive number of 195-to-1 unconfounded cases.

1 But when you would like to interpret these numbers,
2 you have to consider the following facts.

3 MultiHance was approved in 2004 and because of its
4 recent market entry, much of the use of MultiHance
5 was likely to have occurred in patients who have
6 previously undergone contrast-enhanced procedures
7 with other gadolinium agents.

8 If such a patient develops NSF in the
9 months following exposure to MultiHance, this case
10 would actually not be counted in the column of
11 unconfounded reports simply because the patient had
12 a history of having received another GBCA. This
13 NSF case would not be counted in the unconfounded
14 column for MultiHance, even if MultiHance was the
15 gadolinium agent that immediately preceded the
16 onset of NSF.

17 Since Magnevist was the first gadolinium
18 agent introduced to the market and has been on the
19 market for more than 20 years, much of its usage
20 occurred during a period of time when it was the
21 only agent on the market. Magnevist continues to
22 represent at least 50 percent of the gadolinium

1 used in the United States and, thus, it is more
2 likely than with any other gadolinium agent to have
3 patients who have received Magnevist and only
4 Magnevist.

5 In contrast, since MultiHance has only
6 been on the market for five years, it is less
7 likely than with other gadolinium agents to have
8 patients who have only received MultiHance and no
9 other gadolinium agent. This may explain why
10 unconfounded cases account for about one-third of
11 the NSF reports involving Magnevist and only less
12 than 1 percent of the NSF reports involving
13 MultiHance.

14 These principles are summarized on the
15 next slide. First, gadolinium agents that have
16 only recently been introduced to the market or have
17 a low overall market share are particularly likely
18 to be used in patients who have, in the past,
19 already had other gadolinium agents, especially
20 those with a dominant market share such as
21 Magnevist.

22 This is important, since the majority of

1 NSF patients have a history of having undergone
2 multiple gadolinium-enhanced procedures.
3 Therefore, it is less likely for recently approved
4 agents to be used in patients at risk in an
5 unconfounded setting and, thus, it is very
6 difficult to record unconfounded NSF reports.

7 Accordingly, any analyses that focus on
8 unconfounded cases and exclude cases involving
9 multiple gadolinium agents are likely to yield a
10 biased underestimate of the NSF risk among recently
11 approved agents.

12 Thirdly, any analysis that focuses on
13 unconfounded cases will ignore information about
14 the identity of the gadolinium agent that was
15 actually administered in the months preceding the
16 onset of NSF symptoms.

17 Since the awareness of NSF and its risk
18 factors has dramatically increased during the past
19 three years, agents whose use has largely been
20 concentrated during the past three years have
21 probably benefitted from the general avoidance of
22 gadolinium agents in at-risk patients.

1 Magnevist, we can conclude that the existing risk
2 mitigation activities appear to be effective. We
3 still receive reports of NSF in possible
4 association to the administration of Magnevist on
5 an ongoing basis. However, if we look in detail at
6 the date of onset of NSF systems in these reports,
7 wherever we have it, we can say that the reporting
8 of new NSF onset, including NSF reports with
9 documented administration of other agents than
10 Magnevist, has decreased continuously during the
11 past three years.

12 To address FDA requests for additional
13 information, we are currently conducting an
14 observational study as a Phase IV commitment in
15 patients with moderate to severe renal impairment
16 to collect clinical data about the possible
17 occurrence of NSF symptoms following the
18 administration of Magnevist. This study is
19 currently ongoing in 18 sites in the United States
20 and to date, we have not received any single report
21 of NSF suggestive symptoms in any of the study
22 patients.

1 So let me summarize our assessment of the
2 available data related to Magnevist in the context
3 of NSF. Nonclinical studies suggest a lower NSF
4 risk for ionic linear gadolinium agents. These are
5 Magnevist, MultiHance, Eovist and Ablovar, and the
6 macrocyclic agents as compared to the nonionic
7 linear agents, Omniscan and Optimark.

8 Clinical data from spontaneous reporting
9 and observational studies, with all associated
10 limitations I have outlined, indicate a lower NSF
11 risk for Magnevist as compared to nonionic linear
12 agents, Omniscan and Optimark. No data from
13 clinical studies has yielded reliable evidence for
14 differences in risk between Magnevist and other
15 ionic linear agents or macrocyclic agents.

16 Focusing risk assessment on the frequency
17 of spontaneous and confounded reports is likely to
18 yield biased risk estimates, in particular, for
19 recently approved gadolinium agents. And current
20 class labeling and awareness of NSF risk factors
21 appear to have reduced the report of new onset NSF.

22 Bayer concurs with the FDA briefing

1 document that none of the individual data sources
2 provide a clear, unambiguous picture as to the
3 fundamental question of differential NSF risk among
4 the marketed agents and labeling and communications
5 are expected to appropriately describe all the
6 major risks of agents, not solely those related to
7 NSF.

8 Inappropriate labeling for gadolinium
9 agents may result in a shift in clinical practice
10 toward procedures and/or drugs that may even have
11 greater risk. However, if the advisory committees
12 determine that it is, on the basis of the available
13 data, appropriate and necessary to make
14 distinctions in NSF risk among available agents,
15 the available clinical and nonclinical evidence
16 support a distinction between Omniscan and Optimark
17 and all other gadolinium agents.

18 Thank you very much for your attention.

19 DR. HARRINGTON: Thank you. I think
20 we're going to have to move on just to keep
21 somewhat on time here. I'd ask the sponsors to
22 just try to be respectful of the fact that there

1 are seven of you presenting and if there are issues
2 that get brought up by a prior speaker, please
3 don't feel the need to repeat that information.
4 Just try to move along.

5 DR. SPINAZZI: Good morning, everybody.
6 I'll try to be as quick as possible. The
7 presentation will be on ProHance. My name is
8 Alberto Spinazzi and I work for Bracco.

9 ProHance, as all of the agents this
10 morning, is a gadolinium-based contrast agent. The
11 active pharmaceutical ingredient, the drug
12 substance, is gadoteridol. It's a macrocyclic
13 nonionic agent, and so it's highly stable.

14 It was first approved in the United
15 Kingdom in October 1992 and it was the second agent
16 approved in the United States in November 1992. It
17 is now approved in 22 countries for MRI of the CNS
18 and whole body MRI.

19 In the United States, it is approved for
20 MRI of the central nervous system in adults and
21 pediatric patients and MRI to visualize lesions in
22 the head and the neck.

1 Now, the doses that are approved, it is
2 an intravenous injection and the standard dosage
3 approved is 0.1 millimeter per kilogram body
4 weight. That 0.5 molar solution corresponds to the
5 0.2 ml per kilogram body weight. But, also, the
6 second double dose is for use in case of negative
7 or equivocal scans, up to a total dose of 0.3
8 millimole per kilogram body weight, so 0.6
9 milliliter per kilogram body weight.

10 As of October 26, it was estimated then
11 approximately 13.2 million exposures had occurred
12 with ProHance, of which 7.6 were in the United
13 States.

14 Now, you have heard about the working
15 hypothesis for NSF. It occurs in patients with
16 severe renal failure and a number of factors may
17 play a role. It has been suggested the strong
18 association between gadolinium-based contrast
19 agents and the genesis of NSF.

20 It is thought to be due to the release of
21 gadolinium from the chelate and if that is true,
22 also, two factors are important, the dose of the

1 gadolinium given to the patients, to the risk
2 patients, and the stability of the chelate.

3 Now, if stability is important, it is
4 important to consider that what occurs in vivo sees
5 the gadolinium chelate that is exposed to a number
6 of endogenous metals and ions that all work to
7 dissociate the chelate, together with other
8 elements, proteins and others. You see that this
9 makes it unpredictable from an in vitro experiment.

10 So stability data in vivo takes into
11 consideration all these factors. So the hierarchy
12 for stability studies should be that in vivo in
13 humans should be more important than in vivo in
14 animals; also, because of the differences between
15 animals and humans in terms of kinetics sometimes;
16 in vivo more important than ex vivo tissues and ex
17 vivo tissues more important than in vitro.

18 Anyway, I'm showing you some of these.
19 There are many stability studies. This is an in
20 vitro study, very elegant, from the University of
21 Mons in Belgium by Dr. Mortillaro and his team.
22 And you can see here this is putting -- you see the

1 gadolinium chelate in a medium containing zinc and
2 a phosphate ion.

3 So if zinc displaces gadolinium,
4 gadolinium binds to the phosphate ion and becomes
5 insoluble and precipitates. It does not contribute
6 to relaxivity of the solution anymore.

7 So the decrease in relaxivity that you
8 can see here -- I'm sorry. Here is also a
9 proportion to the dissociation of the gadolinium
10 chelate. The faster, the less stable is the
11 chelate. This is Omniscan. This is Magnevist.
12 This is MultiHance. And these are the macrocyclic
13 agents, with no or minimal dissociation in this
14 experiment up to almost 100 hours.

15 The same is ex vivo. This has been
16 tested, I guess, from a Bayer group. And you can
17 see here the nonionic linear chelate, Optimark and
18 Omniscan, with or without the excess ligand and the
19 ionic linear, all very similar, and macrocyclic you
20 see with no or minimal dissociation. But the
21 difference between the ionic linear and the
22 nonionic linear is marked.

1 In vivo, there is this study performed
2 also by Bayer. This was in rats with normal renal
3 function, where the half-life of elimination is,
4 more or less, the same for the various agents. And
5 the agents tested were Omiscan, Magnevist, Gadovist
6 -- not available in the United States --
7 MultiHance, ProHance, Dotarem -- not available in
8 the United States -- and Optimark.

9 The tested agents were injected into a
10 tail vein once daily on five consecutive days, so a
11 very high dose. And there were also control
12 groups, a saline-treated group and an untreated
13 group, and skin biopsies were taken at different
14 time points and up to almost one year after the
15 last administration.

16 This is the concentration of gadolinium
17 in skin in this rat. The highest concentration was
18 with Omniscan. This is a little more than one
19 month after the last injection and this is
20 approximately one year after the last injection.
21 This is the position in skin with Omniscan,
22 Optimark, Magnevist, MultiHance. And, again, the

1 macrocyclic agents have the lowest concentration of
2 gadolinium in the skin of this rat.

3 This is in humans, patients undergoing
4 hip bone replacement. They received the standard
5 dose of Omniscan and ProHance, and the amount of
6 gadolinium or gadolinium chelate in bone was two
7 and a half times lower following ProHance.

8 Now, how to correlate these versus cases
9 of NSF. It's important, this was mentioned before
10 by my colleagues at Bayer, that unconfounded cases
11 of NSF occurring after only one specific agent and
12 confounded, where you have two or more gadolinium
13 agents.

14 Now, it's important to consider that of
15 the confounded cases in the FDA adverse events
16 database, over 300 come from the litigations that
17 are ongoing in the United States. And it's
18 important that product identification is going on
19 in these litigations and ProHance and MultiHance
20 have been dismissed in most of these 300 cases. So
21 it doesn't make any sense to present those
22 confounded cases.

1 So for ProHance, the confounded cases
2 where there was clear identification of ProHance
3 are 20 and the majority are after ProHance and
4 Omniscan, ProHance and Magnevist, or ProHance and
5 Omniscan and Magnevist.

6 There are also two cases of ProHance
7 confounded with other macrocyclic agents. This is
8 ProHance and Gadovist and ProHance and Dotarem.
9 They both come from Switzerland and, actually,
10 especially the one for ProHance and Dotarem, there
11 is very little information, back to 2000, and this
12 one was also from Switzerland and there was very
13 little information about these cases.

14 There are two unconfounded cases with
15 ProHance that we are aware of, one from Switzerland
16 and one from the United States, and no unconfounded
17 cases. So following the sole administration of
18 ProHance from other sources, either literature or
19 our sponsor study, which is a post-marketing
20 requirement.

21 The first unconfounded case with ProHance
22 was reported from Bern, Switzerland, a 51-year-old

1 male patient suffering from end stage renal disease
2 and on dialysis. The exposure was a double dose of
3 ProHance six times over a period of two years, last
4 administration February 28, 2006, for MRI of the
5 abdomen.

6 On September 2006, approximately six and
7 a half months after the last administration of
8 ProHance, there was a diagnosis of nephrogenic
9 fibrosing dermopathy, probably a small lesion in
10 the back of the patient, and this was reported as
11 non-severe, severe, was diagnosed through skin
12 biopsy and histopathology.

13 Bracco contacted the site so many times
14 to get additional information and, in this case,
15 the reporters were not cooperative and didn't
16 provide any additional information on this case.

17 The second unconfounded case was reported
18 in the United States. It's a male subject of
19 unknown age and normal renal function. The
20 exposure was MRI of the parotid glands, with half a
21 dose of ProHance on November 3rd, 2008. In
22 December 2008, it was reported that the patient

1 underwent laboratory analysis, a complete blood
2 work, which found no abnormality. He also
3 underwent a physical exam, complete physical, for
4 which the results were not reported, but an eye
5 checkup showed no abnormalities.

6 The patient reported he developed, on an
7 unknown date, hard, brown skin patches all over his
8 body, mostly around the joint areas, knees and
9 knuckles, and his family physician provided him
10 with a diagnosis of beginning of NSF. No biopsy
11 was performed to confirm this diagnosis. The
12 literature search was extended up to October 21st,
13 2009, no unconfounded cases detected there.

14 This study is probably quite significant,
15 because there was a retrospective assessment of NSF
16 in patients on end stage renal disease and
17 dialysis. So it was 141 patients on dialysis
18 exposed one or multiple times to ProHance. So a
19 total of 141 patients and a total of 198 exposures
20 and no cases detected of nephrogenic systemic
21 fibrosis.

22 In the post-marketing requirement study,

1 we have 19 patients that have been followed for
2 over one year, 24 six months to one year and so
3 forth. Overall, we have 71 patients in the study,
4 11 with a GFR below 30 ml per minute and the rest,
5 60, with Stage 3 chronic kidney disease, the GFR
6 between 30 and 559 ml per minute, and no cases of
7 NSF detected so far.

8 We also thought it was useful, because
9 the post-marketing requirement was studies with
10 gadolinium chelates and to evaluate the incidence
11 of NSF with gadolinium chelates, to have a control
12 study; so patients that have not been exposed to
13 gadolinium agents in the last 10 years and all
14 these patients. And this is documented, so the
15 enrollment has been pretty severe in this case.
16 Eligible patients are followed for two years.

17 We have completed enrollment for the
18 study. We have patients with Stage 4 and 5 chronic
19 kidney disease. Approximately 84 patients have
20 been followed for over six months and we have no
21 cases of NSF detected so far.

22 So in conclusion, it's a highly stable

1 chelate because of the macrocyclic structure.

2 There is a low incidence of unconfounded cases of
3 claimed NSF. The exact mechanism by which NSF is
4 caused is not known yet. However, certainly, the
5 risk-benefit of administering gadolinium chelates
6 should be evaluated very carefully.

7 Based on the available clinical evidence,
8 Bracco believes that more strict measures, such as
9 the contraindication of ProHance for use in at-risk
10 patients, is not justified.

11 Thank you for your attention.

12 DR. HARRINGTON: Dr. Spinazzi, thank you
13 for a clear presentation; also, for helping us
14 remain on time. I suspect we'll return to you this
15 afternoon for questions, particularly on some of
16 the differences in chemical structures amongst the
17 agents.

18 Next will be GE Healthcare.

19 DR. CANTOR: Good morning.

20 Dr. Harrington, Dr. Kramer, members of
21 the Cardio-Renal and Drug Safety and Risk
22 Management Advisory Committees, Dr. Rieves and FDA

1 colleagues, I want to thank you for this
2 opportunity to share our assessment of Omniscan and
3 NSF information with this body.

4 My name is Eric Cantor. I'm a
5 nephrologist and the head of Medical Affairs at GE
6 Healthcare Medical Diagnostics for the Americas.

7 NSF is a very serious disease which
8 affects a small and well defined population.
9 Patient safety is of great concern to all of us.
10 The number of NSF case reports has dramatically
11 decreased over the last three years and, in fact,
12 for Omniscan, we've had no new reports of
13 diagnostic onsets for over two years now.

14 Millions of doses of Omniscan continue to
15 be used in the U.S. and globally. Class labeling
16 in the U.S. has proven very effective in reducing
17 the incidence of NSF to almost zero. By contrast,
18 labeling products differentially is not without
19 risk. Indeed, it may lead to misperceptions over
20 the overall safety profiles of the different
21 gadolinium-based contrast agents.

22 In addition, there is no evidence that

1 differential labeling has achieved superior results
2 with respect to reducing NSF. Since adoption of
3 differential labeling in Europe, NSF cases have now
4 been reported with agents deemed to be of low risk.

5 As we go through today's presentation,
6 you will see that the collaborative approach over
7 the past couple of years amongst the FDA, key
8 societies, industry and clinicians have been quite
9 effective. There is a notable change in how
10 patients are stratified and managed with respect to
11 this disease and the significant impact this has
12 had in the virtual elimination of new onset of NSF
13 reports.

14 Omniscan, as we are all aware, was the
15 first gadolinium-based contrast agent with which
16 NSF was associated. Here is what we know. All
17 gadolinium-based contrast agents have been deemed
18 generally well tolerated, as is evident from their
19 use. NSF is a rare disease and it is associated
20 with all gadolinium-based contrast agents. NSF is
21 limited to those with severe or end stage renal
22 disease and acute kidney injury, which is

1 approximately 0.4 percent of the U.S. population.
2 It is predominantly seen in those receiving higher
3 doses of gadolinium-based contrast agents.
4 Omniscan has the greatest number of NSF reports.

5 As I will show you, since class labeling
6 in 2007, new onset cases of NSF have virtually
7 disappeared. What we don't know is over the past
8 years, there have been several nonclinical
9 investigations which have generated conflicting
10 evidence and theories as to etiology and mechanism
11 of the disease and development of this disease and
12 the differential risk amongst these agents.

13 It is important to consider the overall
14 safety of Omniscan in the context in which NSF
15 emerged after 48 million doses had been given. The
16 presentation will address the assessment of
17 nonclinical studies, what we have learned, current
18 hypotheses around etiology, and, most importantly,
19 where we are with our understanding and managing
20 this disease, followed by conclusions.

21 In order to understand the context in
22 which NSF emerged, it is critical to understand how

1 Omniscan was used. Omniscan was the first GBCA to
2 be approved in the United States market. It
3 rapidly became the second most widely used agent
4 globally.

5 Key characteristics behind this success
6 that led to its preferred usage and especially use
7 of high doses were nonionicity, preferred for
8 minimization of anaphylaxis and hypersensitivity
9 reactions; low osmolality, preferred to minimize
10 complications due to extravasation; and, low
11 viscosity, preferred for use with power injectors
12 for rapid bolus injection.

13 As magnetic resonance angiography, or
14 MRA, procedures rose in popularity, Omniscan became
15 the drug of choice for many due to its proved high
16 dose indication. Omniscan was preferentially used
17 for higher dose needs in those with renal
18 dysfunction, especially those who are at increased
19 risk of contrast-induced nephropathy with iodinated
20 contrast.

21 The increase in MRA dose per procedure is
22 shown here in red. Dose peaked in 2005 and 2006,

1 roughly coinciding with the initial reports of NSF.
2 A dose creep of approximately 30 percent is evident
3 for Omniscan over the five prior years.

4 Conversely, the dose or volume per
5 procedure for routine MRI, in green, has remained
6 essentially unchanged. Use of higher doses
7 contributed to the greater number of NSF reports,
8 and I'll come back to this in a minute.

9 This slide shows Omniscan post-marketing
10 safety by body system since approval in 1993. It
11 includes 48 million doses, with a total of
12 approximately 4,500 adverse event reports. And by
13 standing reporting criteria, adverse events with
14 Omniscan would be considered rare. Most of these
15 adverse events are non-serious, with low frequency.

16 Of the serious adverse events, skin-
17 related events, including NSF, and immune
18 reactions, mostly hypersensitivity and anaphylactic
19 reactions are noteworthy for their frequency. As
20 you can see, Omniscan has an excellent overall
21 safety profile. Risk of these adverse events and
22 overall safety requires consideration in choosing a

1 gadolinium-based contrast agent.

2 A study by Murphy, et al., in 1999
3 evaluated the adverse event profiles amongst the
4 three gadolinium-based contrast agents on the U.S.
5 market at that time. Though the data are limited
6 in that there are retrospective reports from
7 imaging centers, they show a clear difference
8 amongst the three agents. The most obvious
9 difference is in regard to reports of allergic
10 reactions. Of the three agents, Omniscan had no
11 reports that were moderate or serious, while for
12 the other agents, reporting was not insignificant.

13 Evolving data that Dr. Prince has
14 compiled from the AERS database, analyzed and
15 shared with several sponsors of GBCAs, highlights
16 the merits of considering overall safety. This
17 supports the finding in Murphy's paper I showed you
18 a minute ago. It highlights the total events per
19 million doses, excluding NSF, in red, and the total
20 non-NSF deaths per million doses predominantly due
21 to anaphylaxis, in blue, for the five products in
22 the U.S. market.

1 As the incidence of NSF has declined, the
2 overall safety profile, particularly risk of death,
3 associated anaphylactic reactions, the GBCAs become
4 an increasingly important consideration for
5 assessing overall safety or risk. As a clinician,
6 such an assessment is critical to judging benefit
7 versus risk for each agent.

8 Much of today's concerns emanate from the
9 spontaneous reports of NSF and the question of why
10 there are more reports for Omniscan. To put this
11 into context, one must recognize that Omniscan was
12 the first gadolinium-based contrast agent to be
13 associated with this new disease. Some in 2006
14 even thought NSF was specifically an Omniscan
15 disease, which was, as we know now, found not to be
16 true.

17 We were the first sponsors to issue two
18 "Dear Doctor letters," one in June and another in
19 December 2006, raising the awareness of this
20 association, encouraging reporting from healthcare
21 professionals. There was then a tenfold increase
22 in the number of reports over the subsequent eight

1 months. All sponsors then sent a letter when class
2 labeling was implemented in September 2007, as
3 well.

4 This increased awareness of NSF and its
5 apparent association with Omniscan, in the minds of
6 the medical community, may have contributed to
7 reporting bias. Omniscan had and has the second
8 largest market share. Historical differences in
9 time of approval of various agents and volume of
10 usage further contribute to the report numbers.
11 Omniscan, as I mentioned before, was the preferred
12 agent for high dose use.

13 Awareness prompted physicians to
14 retrospectively review patient records and charts
15 to identify those specifically exposed to Omniscan
16 and who had developed skin lesions consistent with
17 NSF. These reviews also made it clear that there
18 were differences in the criteria being used to
19 diagnose NSF amongst physicians, radiology centers
20 and manufacturers. Reports derived from non-
21 healthcare professionals in the U.S. rose
22 significantly during this period, as well.

1 As you can see from this slide, most
2 reported cases come from the U.S. Of the 624 total
3 reports, 351 were from healthcare professionals and
4 273 from non-healthcare professionals. Limited
5 data and duplicate reports from non-healthcare
6 professionals make it difficult to determine if a
7 report is really a new case or report.

8 At GE Healthcare, we erred on the side of
9 conservatism and conclusiveness and counted all
10 reports as unique, all of which has contributed to
11 the number of reports, but not necessarily number
12 of true cases associated with Omniscan.

13 As we drill down on the post-marketing
14 safety data for Omniscan, we see a clustering
15 phenomenon emerge, which is extremely informative.
16 This slide highlights the portion of NSF reports,
17 in red, relative to the product usage, in blue, by
18 country. I would like to highlight data from four
19 countries, the U.S., Denmark, Japan and France, to
20 make a couple of important points.

21 In the U.S., we see the highest
22 percentage of cases and highest percentage of

1 Omniscan sold. What is informative is that 97
2 percent of the reports in the U.S. are from only 2
3 percent of the 2,100 imaging centers. Thus, 98
4 percent of the centers have had no such reports.

5 Conversely, Denmark has had a
6 disproportionate number of reports compared to
7 units sold, 88 percent originating from just two
8 institutions. Japan and France, on the other hand,
9 had an opposite pattern, as the number of reports
10 attributable to Omniscan was much lower than units
11 or volumes sold.

12 This clustering phenomenon is an
13 important finding, as one would generally expect
14 usage to relate to event rate. Though there is
15 significant variability in these data, they do
16 reflect differences in practice usage patterns;
17 that is, the standard of care in Japan reflects
18 usage of standard or lower doses compared to
19 Denmark, where higher dose usage was more common.

20 Given what we mentioned earlier about
21 increasing volume of drug used for MRA, we looked
22 at one of our -- or, I should say, our

1 pharmacovigilance database. In all reports, we had
2 information on last dose. What you see is that 65
3 percent of Omniscan cases of NSF are associated
4 with higher dose usage; that is, greater than 20
5 mls or greater than 0.1 millimole per kilogram.

6 What we have seen in our database as risk
7 factors was substantiated in the largest
8 retrospective review to date of NSF, published in
9 2008 by Prince, et al., data compiled from two
10 large academic medical centers.

11 In this review, more than 80,000
12 patients, most of whom received Omniscan, the
13 incidence of NSF was found to be zero in the 74,124
14 patients given a standard dose of 0.1 millimole per
15 kilogram. On the other hand, of the approximately
16 9,000 patients receiving a higher dose, there were
17 15 cases of NSF. This review demonstrates that
18 these are, number one, rare events; two, occur
19 exclusively in those with severe renal failure;
20 and, three, in those who received a higher dose of
21 Omniscan.

22 Data on this slide supports predominance

1 of risk in those with severe or end stage renal
2 disease. Of the 624 reports of NSF in our
3 pharmacovigilance database, 289 had information on
4 renal function.

5 It is clear that a level of renal
6 dysfunction increases the risk significantly and
7 disproportionately. Of these 289 reports, 91
8 percent are in patients with severe or end stage
9 renal disease and 9 percent in those with acute
10 renal failure. We also reported a single patient
11 with moderate stage disease, though there was some
12 uncertainty regarding the eGFR provided.

13 With this understanding of our clinical
14 data, we also pursued a series of nonclinical
15 studies to, number one, develop an animal model;
16 two, better understand deposition of gadolinium in
17 tissue and the role of free and chelated forms ex
18 vivo; and, three, study the pathophysiologic
19 mechanism of NSF, evaluating the prevailing free
20 gadolinium hypothesis based on in vitro
21 thermodynamic stability.

22 Multiple studies have been carried out by

1 sponsors in partially nephrectomized and intact
2 rats. They were dosed 25 to 100 times normal
3 gadolinium-based contrast agent dose for various
4 lengths of time, which, indeed, revealed skin
5 lesions. However, they were inconsistent with what
6 has been histopathologically shown in human NSF.
7 Key to human NSF is deep tissue fibrosis, CD34
8 positive cell markers, and increased tissue mucin,
9 which were not consistently seen in rat lesions.

10 The histopathology of skin lesions in the
11 rat does not match that seen in human NSF. Even
12 gadolinium levels in skin do not appear to
13 correlate with the intensity of lesions in rats.
14 Reliance cannot be placed on in vitro chelate
15 stability differences, as they do not translate
16 into in vivo chronic kidney disease.

17 Small quantities of gadolinium had been
18 detected ex vivo in patients with and without NSF
19 post-Omniscan exposure. However, with today's
20 technology, it is not possible to determine the
21 form of gadolinium deposited that is free or
22 chelated.

1 In vitro studies clearly show that all
2 intact gadolinium chelates, to a much greater
3 extent than free gadolinium, can stimulate the same
4 cascade of cell changes capable of initiating
5 tissue fibrosis seen in NSF. Therefore, using
6 these nonclinical studies as a basis for defining
7 differential risk would be risky. The conclusions
8 derived from animal studies must be considered as
9 more hypothetical definitive.

10 Revised class label and effective
11 communications and collaboration with the FDA have
12 clearly helped change practice patterns, with a
13 decline in MRA dose or volume per procedure after
14 2006. Note the timing of issuance of the "Dear
15 Doctor" letters, as they coincide with change in
16 practice patterns. And the precipitous drop in the
17 number of new onset NSF reports for Omniscan --
18 none since 2007. The volume or dose has played
19 less of a role for MRI, which you can see in the
20 green line here.

21 These changes in physician practice
22 pattern, selecting proper patients via screening,

1 and choosing the right dose have been effectively
2 incorporated into the American College of Radiology
3 Manual, which reflects the thinking and practice
4 patterns of the radiology community.

5 The American College of Radiology
6 recommends the use of screening, history or lab
7 test, listed here, to identify patients potentially
8 at higher risk of NSF, that is, those with renal
9 disease, and the need to dose them based upon their
10 level of renal function.

11 For patients with an estimated GFR
12 greater than 30 milliliters per minute, use of 0.1
13 millimole per kilogram of GBCA is recommended and
14 for those with less than an eGFR of 30, to use the
15 lowest possible dose if MR is felt to be essential,
16 that is, to follow product labeling.

17 In conclusion, what we know is that NSF
18 has been seen with all marketed gadolinium-based
19 contrast agents in the U.S. Current class labeling
20 has virtually eliminated the onset of new cases of
21 NSF. Based on the weight of existing nonclinical
22 and clinical evidence, differential risk remains

1 unproven.

2 There are no head-to-head controlled
3 clinical trials to serve as a basis for such a
4 regulatory decision. Reporting bias and
5 spontaneous reports due to historical clinical
6 practice patterns should not be overlooked.

7 Nonconclusive data remain inconclusive.
8 It should be recognized that differential labeling
9 is not without risk and can lead to a misperception
10 of one agent being inherently safer than another.
11 And ultimately, the choice of gadolinium-based
12 contrast agent must be based upon individual
13 patient screening, overall benefit-to-risk profile
14 of each agent, and clinical judgment within the
15 confines of current labeling.

16 At GE, we are committed to ensuring
17 patient safety. Class labeling is the safest
18 approach for patients with severe renal impairment.
19 The dramatic drop-off in new onset reports of NSF
20 in the United States is a clear indication that
21 such a class approach has been both appropriate and
22 successful and that differential labeling would be

1 an unnecessary and risky step.

2 Thank you. I don't know if we have time
3 for questions, but we do have Drs. Goldfarb, Oto
4 and Stephenson and the GE team here to address any
5 questions at this time, should you so choose.

6 DR. HARRINGTON: Thank you, Dr. Cantor.

7 In fairness to the other sponsors, I
8 think we'll let Dr. Neuman get his remarks in,
9 we'll break, we'll hear the others, and then we'll
10 have all of you available this afternoon. Thank
11 you for staying on time.

12 DR. NEUMAN: Good morning. I'm Dr.
13 Herbert Neuman. I'm the Vice President of Medical
14 Affairs and the Chief Medical Officer for
15 Covidien's Mallinckrodt, Incorporated business. I
16 want to spend the next several minutes discussing
17 Optimark, our gadolinium-based contrast agent and
18 the subject of nephrogenic systemic fibrosis.

19 Today, I will discuss these topics
20 related to Optimark, in particular, and NSF, in
21 general. The first topic I'll address is the label
22 change for our Optimark gadolinium-based contrast

1 agent.

2 Although the exact cause of NSF remains
3 unknown, we've recently taken the important step of
4 voluntarily contraindicating Optimark in the at-
5 risk patient population that was defined in the
6 previous boxed warning.

7 We did this for four reasons. Clinical
8 practice has changed and Optimark is not
9 preferentially used in at-risk patients; therefore,
10 we desire to have the labeling reflect real world
11 use of our product. Because of slow enrollment,
12 the Optimark registry study is unlikely to yield
13 meaningful data. Because adequate and reproducible
14 animal and in vitro models to facilitate the study
15 of NSF are currently not available, we consider it
16 unlikely that precise causation will be defined in
17 the foreseeable future.

18 Labeling and educational efforts to date
19 have significantly reduce the incidence of NSF and
20 we believe the contraindication will help us to
21 reinforce the progress that we've made to date.

22 This is Optimark's new contraindication.

1 We've carried forward the original risk population
2 from the boxed warning that was established in
3 2007. This definition adequately captures patients
4 who are at risk of developing NSF, while allowing
5 continued access for the vast majority of patients
6 not at risk and who still benefit from the
7 product's use.

8 Although there have been rare reports in
9 NSF in patients with a reported GFR greater than
10 30, the vast majority of reported cases actually
11 occurred with a GFR of less than 15. So these
12 outliers may have been a result of limitations of
13 the eGFR measurement.

14 Given these data, our efforts to improve
15 patient safety around NSF have focused on educating
16 stakeholders on the use of Optimark in the
17 appropriate patient population. We developed a
18 series of educational tools, with the most recent
19 being deployed in November 2009.

20 We use medical conventions, Internet
21 training, and live presentations to increase
22 clinicians' awareness and drive the appropriate use

1 of Optimark. We intend to continue these
2 educational efforts to reinforce Optimark's new
3 labeling.

4 During this time, we were not alone in
5 providing education to the healthcare community.
6 The FDA, professional societies, and the other
7 sponsors here today were all engaged in ongoing
8 educational efforts. It appears that these efforts
9 are effective in limiting new cases of NSF.

10 On this graph, the orange line represents
11 the data of possible Optimark exposure in the
12 reported cases of NSF. All of our reports of NSF
13 reflect patient exposures prior to the third
14 quarter of 2007. The blue bar graph represents
15 total Optimark doses sold worldwide.

16 You can see that despite relatively
17 consistent global sales, NSF cases have dropped
18 precipitously. So while we are still receiving
19 reports of NSF, they reflect Optimark exposures
20 predating the GBCA label change and the Covidien,
21 FDA and industry-wide educational efforts.

22 Let's turn to Optimark's risk-benefit

1 profile. The product has been on the market for 10
2 years and has over nine million patient procedures.
3 Its favorable risk-benefit profile includes a lower
4 reported rate of anaphylaxis, which we'll discuss
5 in a moment. It remains the only GBCA approved by
6 the FDA for power injection, which allows for
7 better image quality. Lower viscosity and lower
8 osmolality are important to reduce the risk of
9 extravasation and related adverse events.

10 Let's expand on the role of physical
11 properties in evaluating the benefits of the class
12 of GBCAs. Optimark is nonionic and as Cochran and
13 others noted, nonionic agents are less likely to be
14 associated with mild and moderate extravasation-
15 related injuries.

16 Optimark has only three times the
17 viscosity of water and is not considered a high
18 viscosity agent. As Herts and colleagues reported,
19 lower viscosity agents require lower pressures to
20 achieve injection rates and they may be better
21 tolerated, especially if extravasation occurs. In
22 addition, as Prince and colleagues noted, lower

1 viscosity agents allow for the use of smaller
2 caliber needles and catheters.

3 Let's take a moment to look at the
4 adverse events for Optimark that are not related to
5 NSF. This chart reflects adverse events per
6 100,000 doses, in which we saw five or more reports
7 over the past two years. The most common adverse
8 events were nausea, urticaria and pruritis. Like
9 other products in this class, the majority of these
10 common adverse events are mild and usually
11 transitory in nature.

12 There's been a great deal of conversation
13 lately about the specific adverse event of
14 anaphylaxis. Here, we see reporting rates of
15 anaphylaxis among the most widely used gadolinium-
16 based contrast agents in the United States. As you
17 can see, Optimark has the lowest reported rate.

18 In fairness, we should point out that
19 adverse event reporting is primarily designed for
20 signal detection rather than a method of
21 determining the relative risk of various agents.
22 We believe the same limitations also prevent us

1 from drawing meaningful conclusions regarding the
2 relative risk of NSF among these agents, and I'll
3 talk more about that in a moment.

4 But even with their imperfections, these
5 data do illustrate that as this committee and the
6 Food and Drug Administration consider differential
7 labeling for GBCAs, there is more to the decision
8 than NSF alone. The totality of the risk-
9 benefit equation should be considered for each of
10 the products and across the class.

11 Now, let's take a look at NSF. As you
12 can see, we received our first report in August of
13 2006 and we have received 95 total reports of NSF
14 subsequent to Optimark administration. It is well
15 understood that post-marketing adverse event
16 reporting generally lacks the rigor and reliability
17 to determine causation.

18 Instead, post-marketing safety analysis
19 is designed to identify possible safety signals
20 that merit further evaluation and study. As you
21 will see, these inherent inaccuracies are
22 compounded in the NSF cases and do not allow for

1 meaningful interpretation or differentiation among
2 the agents.

3 Despite our best attempts and what you've
4 heard from earlier presenters, it's very difficult
5 to get a full data set on these adverse event
6 reports. In fact, 85 percent of them are missing
7 important facts, which complicate our evaluation of
8 the case. And without these data, a full
9 interpretation and understanding of these cases is
10 not possible.

11 As you heard, the guidelines for
12 diagnosis of NSF involve a combination of factors,
13 including a patient exam and a physical exam
14 history, and, most importantly, a biopsy. In the
15 95 cases reported to the FDA, only 46, or 48
16 percent, were confirmed by some sort of biopsy and
17 the type or nature of the biopsy was frequently not
18 reported.

19 An additional 30 cases, or 32 percent,
20 have been confirmed by a healthcare provider. But
21 that leaves a full 20 percent of the 95 reports of
22 Optimark-related NSF that have not been confirmed

1 by either a biopsy or a healthcare professional.

2 There has been much discussion around
3 confounded versus nonconfounded cases of NSF across
4 the various GBCA products. For the purposes of
5 this discussion, we define a confounding case as
6 exposure to Optimark and one or more GBCAs during
7 the patient's lifetime.

8 Sixty-eight percent of our reported cases
9 are confounded by one or more other agents and
10 eight reports are confounded by four other GBCAs.
11 As you can see, we have cases confounded by
12 exposures to each of the most widely used GBCAs.

13 For the reasons described here, post-
14 marketing data does not allow for a reliable
15 interpretation regarding causality or differential
16 risk.

17 Similar difficulties exist when looking
18 at the chemical properties of the agents as a guide
19 to understanding NSF. In vitro, linear chelate
20 complexes appear to be less stable than macrocyclic
21 complexes, because the gadolinium ions are more
22 loosely bound to the chelate ligand.

1 But to put this in context, in vitro,
2 each of these compounds is, in fact, a very stable
3 molecule. Optimark's stability constant is
4 approximately 10-to-the-16th power. While the in
5 vitro stability can be measured, the true in vivo
6 stability is not known.

7 For this reason, stability constants
8 cannot be used to reliably predict the risk of NSF.
9 For example, in this graphic that we took from the
10 FDA briefing document, the thermodynamic and
11 conditional stability constants for marketed GBCAs
12 are presented.

13 I draw your attention to the values for
14 Magnevist and MultiHance. Based upon these
15 calculated stability constants, the risk of NSF in
16 humans should be equivalent. But the review by the
17 Office of Surveillance and Epidemiology of the FDA
18 has recommended placing Magnevist in the highest
19 risk category and MultiHance in the lowest risk
20 category. Clearly, the predicted risk from the
21 physiochemical properties of the agents and the
22 post-marketing surveillance of those agents differ

1 significantly.

2 So let's talk about a path forward for
3 the GBCAs. The precise pathogenesis of NSF remains
4 unknown and while post-marketing safety reporting
5 is always variable and imprecise, it has been
6 compounded by the nature of NSF, the small at-risk
7 population, and the influence of litigation, all of
8 which increase the unreliability of spontaneous
9 reporting.

10 Registry studies are incomplete, as
11 observed in the sponsors' briefing documents. And
12 we recognize that this committee has been asked to
13 explore alternatives to the current registry
14 format. One option would include eliminating the
15 patients with a GFR of less than 30 from the
16 studies and instead focusing on patients with a GFR
17 of 30 to 60, to confirm that a GFR of 30 represents
18 a cutoff for the at-risk patient population.

19 But without the availability of such data
20 today, differentiated labeling based upon perceived
21 NSF risk could actually increase the risk for some
22 patients, because it would ignore other non-NSF

1 adverse events and can imply a more favorable risk-
2 benefit ratio that cannot be proven at this time.
3 Even among at-risk patients, differential labeling
4 may lead to relaxed screening procedures and could
5 put these patients at increased risk.

6 Based on the previous points, we
7 recommend that all GBCAs be contraindicated in the
8 at-risk patient population that was defined in the
9 2007 boxed warning, unless a validated pathogenesis
10 of NSF is determined that establishes a distinction
11 among the agents.

12 As to the issue of patient screening, the
13 current methods are proven to be effective in
14 reducing the incidence of NSF. The existing
15 gadolinium-based contrast agent labeling encourages
16 screening based upon individual patient
17 characteristics. Although we consider this
18 adequate, we would support additional
19 recommendations, such as serum creatinine
20 measurement, as long as they were applied equally
21 across the class.

22 Again, the key is to not create a

1 perception of lesser risk among some agents since
2 this distinction cannot be supported in the current
3 science. Doing so could actually increase the risk
4 to some patients.

5 Changes in clinical practices have led to
6 a dramatic reduction in the incidence of NSF.
7 These changes have been fostered by the boxed
8 warning on all the GBCAs, scientific investigation,
9 and ongoing educational efforts by industry and
10 others.

11 Mallinckrodt has reinforced the progress
12 by contraindicating the use of Optimark in the at-
13 risk patient population. Based on current
14 knowledge and in the interest of patient safety,
15 this same contraindication and any other labeling,
16 risk management or screening recommendations should
17 be applied consistently to the entire class of
18 gadolinium-based contrast agents.

19 Thank you.

20 DR. HARRINGTON: Thank you, Dr. Neuman.
21 I want to thank all four sponsors for their
22 presentations. The data presentations have been

1 clear and succinct. We are actually right on
2 schedule.

3 What I'd now like to do is to take a
4 short 15-minute break, returning at 10:45. We'll
5 begin promptly. Committee members, as a reminder,
6 there should be no discussion of the meeting topic
7 during the break amongst ourselves or with any
8 member of the audience.

9 Again, we'll resume at 10:45.

10 (Whereupon, a brief recess was taken.)

11 DR. HARRINGTON: We're going to continue
12 with our sponsor presentations and we're going to
13 return to Dr. Spinazzi and then move to Bayer and
14 then Lantheus.

15 DR. SPINAZZI: Good morning, again. The
16 second presentation will be on MultiHance, another
17 gadolinium-based contrast agent. The drug
18 substance now is gadobenate dimeglumine, or the
19 acronym Gd-BOPTA. And the molecular structure is a
20 linear ionic agent, as you got several times during
21 the previous presentations.

22 It was first approved in 1997 in the U.K.

1 It's now approved in 44 countries around the world
2 for MRI of the CNS, for MRI of the liver, and MR
3 angiography. In the United States, it was approved
4 in 2004 for MRI of the CNS in adults.

5 The dose is 0.1 millimole per kilogram
6 body weight for MRI of the CNS, corresponding to
7 0.2 milliliter per kilogram body weight. And as of
8 October 2006, approximately eight million exposures
9 have been counted to patients, of which 3.2 million
10 in the United States.

11 You saw before the data on in vitro,
12 transmetallation, and the difference between
13 macrocyclic agents and the ionic linear, the
14 nonionic linear. This is Magnevist and this is
15 MultiHance. The time needed to have a 20 percent
16 reduction in relaxivity and dissociation, it was
17 600 minutes for MultiHance, 250 for Magnevist.

18 You saw, also, this data in the in vivo
19 in rats, with a deposition of gadolinium at one
20 month after injection and one year after injection,
21 and you can see here the data with MultiHance
22 compared to Magnevist and compared to the

1 macrocyclic agents.

2 We also discussed about unconfounded
3 cases of NSF following the administration of one
4 agent only and confounded. And we are now aware of
5 two unconfounded cases with MultiHance. We got
6 information about one case and asked Ms. Ferguson
7 to get additional information on the second case.
8 There are no cases we see from the literature and
9 from the post-marketing requirement study.

10 So this is where we got that. There were
11 two cases actually in the FDA's briefing document.
12 This goes from one to two, from one to two. So
13 this is the only part where it is mentioned that
14 there are two cases. We got information about one
15 case that was reported directly to the FDA by a
16 consumer. It was a female subject, 34 years of
17 age, with a history of asthma and allergic rhinitis
18 and there was no mention of impaired renal function
19 of any kidney disease in the history.

20 She received a contrast-enhanced MRI on
21 March 9th, 2007. It was for an unknown indication.
22 It is indicated it was an intra-arterial injection

1 and for an unknown dosage of the contrast. Two
2 days later, she developed itching in the upper
3 thigh areas; one week later, itching extended to
4 the knees, the buttocks, the arms and the wrists.
5 Three weeks later, the patient underwent a physical
6 exam. The physician observed a slight rash in the
7 extremities and prescribed what we believe is a
8 steroid and an antihistamine drug.

9 On the next visit, the date was not
10 specified, the patient saw a sign of drug
11 interaction with light, documentation of skin and
12 swelling, especially of the ankles. The patient
13 was visited by a dermatologist who ran a skin test
14 and found signs of drug etiology and urticaria on
15 May 10th, 2007, so approximately two months after
16 the administration of contrast.

17 Over the next weeks, the dermatologist
18 observed red and dark patches, skin had a woody
19 feel, and tightening and swelling of skin. On June
20 21st, 2007, three months after the administration
21 of contrast, the dermatologist stated that the skin
22 was showing sign of systemic fibrosis, or NFB. It

1 was not reported if a biopsy was performed to
2 confirm the diagnosis.

3 We performed the same literature search
4 as for ProHance and we found no unconfounded cases
5 with MultiHance. In the FDA's report, there is an
6 article from Dr. Prince, who is in the audience,
7 saying that the prevalence of NSF was 0.02 percent
8 with Omniscan and 0.04 percent with MultiHance in
9 his series, with no cases with Magnevist and
10 ProHance.

11 This is the article published in
12 Radiology 2008. And this is the table that has
13 been used to get that information. You can see
14 here there was a total of 15 cases with all the
15 gadolinium agents at Dr. Prince's institution, and
16 you can see that there were no cases with Magnevist
17 or ProHance and there were 14 cases with Omniscan,
18 for a total incidence of 0.02, and one case with
19 MultiHance, with a total incidence of 0.04 percent.

20 In the article, it is also written that
21 the patient got three gadolinium-based contrast
22 agent administrations, one with an unknown

1 gadolinium-based agent and two with MultiHance of
2 high doses, 48 and 39 days before NSF symptom
3 onset.

4 This time, we had the full cooperation of
5 Dr. Prince and his team and the first contact was
6 in May 2008. May 6th, 2008, actually, the
7 administrations were supposed to be four, two with
8 unknown gadolinium-based contrast agents and two
9 with MultiHance. But Dr. Prince said that he was
10 providing information from memory and that he had
11 to check that information further.

12 A few days later, the administrations
13 were five and two were performed at the reporter's
14 facility and they could have been either with
15 MultiHance or Omniscan, because the two agents were
16 the only agents in the facility's formulary. The
17 reporter believed that MultiHance was administered
18 to that patient since the staff typically used
19 MultiHance for MR angiography. And at that time,
20 the patient was reported to recover from NSF.

21 On August 27th, 2008, the administrations
22 were four, but three at the reporter's facility,

1 not two, and one at another facility. And we were
2 allowed to check, also, the patient's record and
3 the three MRIs at the reporter's facilities were
4 performed, one, on January 4th, 2006. It was not
5 for MRI, for MRA, but for MR
6 cholangiopancreatography prior to a biliary
7 intervention on this patient, and two were
8 performed after the intervention. Actually, there
9 were two, because one had to be repeated -- a
10 procedure had to be repeated because there were
11 problems with the injector. There were no mentions
12 of the contrast agent used for that procedure or
13 the dose used.

14 This chart summary notes nephrogenic
15 fibrosing dermopathy Stage 3/4, bilateral, the
16 lower extremities, thin thickened and darkened,
17 with recommendation for physical therapy to prevent
18 contractures.

19 So in essence, it would be important to
20 reconsider the data in the table in the publication
21 based on the information that we were able to
22 collect, thanks to the cooperation with Dr. Prince.

1 This is also a study that has been
2 published in Radiology very recently. So there is
3 just the electronic publication of that. It's a
4 retrospective study that was prior to the adoption
5 of restrictive policies and after the adoption of
6 restrictive policies for the use of gadolinium-
7 based contrast agents.

8 So there was a better assessment or a
9 deeper assessment of risk-benefit and screening of
10 patients for the detection of patients at risk for
11 NSF or with Stage 4 or 5 chronic disease or eGFR
12 below 30 ml per minute.

13 Half-dose of MultiHance was used for all
14 patients at risk. So patients with a GFR below 30
15 ml per minute, but also for Stages 1 and 2 chronic
16 kidney disease, for neonates or children less than
17 one year of age, and pregnant women, while
18 Magnevist was used in children over one year of age
19 or in patients with no risk factors, as well as
20 MultiHance at full dose.

21 Prior to the adoption, the rate of NSF
22 was 3 percent in Center A in patients with GFR

1 below 30 ml per minute and it was 2.9 at Center B
2 in patients on dialysis. After the switch to
3 MultiHance and the adoption of our restricted
4 policy for risk patients, there were no cases of
5 NSF detected, with a follow-up of nine months.

6 This is from the Website of the
7 University of Wisconsin and I know that this will
8 be published soon. And from July 2005 to June 2006,
9 there were 91 inpatients either with an eGFR below
10 30 ml per minute or Stage 3 chronic kidney disease
11 and pro-inflammatory conditions, and there were six
12 cases of NSF with Omniscan, with a 6.5 rate. The
13 same patients, later on, November 2006 to October
14 2008, 78 inpatients, same conditions and no cases
15 of NSF.

16 Overall, from November 2006 to October
17 2008, and this is followed by Dr. Sadowski, who was
18 one who published the first cases -- one of the
19 first publications with cases of NSF following the
20 administration of gadolinium. In patients with a
21 GFR below 30, there were no NSF cases following the
22 use of MultiHance.

1 The post-marketing requirement, we have
2 234 patients in this study, of which you see over
3 130 are being followed for more than six months, 27
4 patients with a GFR below 30 ml per minute and, to
5 date, no cases of NSF detected in this study.

6 So we saw before the working hypothesis
7 for the pathogenesis of NSF in patients with severe
8 renal failure, and as far as gadolinium is
9 concerned, there is stability. And many people
10 have discussed about stability already, but the
11 second factor is dose.

12 Another property of this agent that is
13 important, as mentioned by Dr. Weinrab before, is
14 relaxivity. So a higher relaxivity, which is the
15 measure of the signal enhancement efficacy, is
16 important, because the higher the relaxivity, the
17 higher the signal intensity of where the agent
18 goes. This is the package insert of MultiHance,
19 and MultiHance is twice the relaxivity of agents
20 like Magnevist, ProHance and Omniscan.

21 This is coming, also, from publication of
22 different magnetic field strength, which is twice

1 or 60 to 80 percent higher than Magnevist. And why
2 is that? Because this is in the presence of human
3 serum albumin, so the higher the concentration of
4 human serum albumin, the higher the relaxivity.
5 And this is the physiological range, so between 3.5
6 to 5.5 grams per deciliter. And you can see that
7 at increasing concentration of serum albumin, there
8 is an increasing relaxivity of the agent, because
9 there is a fleeting interaction with the
10 macromolecules and a reduction in the tumbling rate
11 and an increase in relaxivity for the agent.

12 So the relaxivity is the kind of currency
13 for the efficacy of these agents. You can see here
14 these phantom experiments in test tubes, with
15 increasing concentrations of the various agents.
16 This is ProHance, Magnevist and MultiHance. This
17 is the baseline and this is the signal intensity
18 values at baseline. At increasing concentration,
19 you see an increase in the signal intensity values.
20 But at the same concentration, you always see
21 higher signal intensity values for MultiHance, and
22 this is in a medium containing serum proteins.

1 Now, this is important in clinical
2 practice, because of when the agent can go. For
3 instance, at Dr. Weinrab mentioned, if you have a
4 breakdown of a blood-brain barrier, the agent can
5 cross the BBB, whereas while the BBB is intact,
6 like in a normal parenchyma, you do not have any
7 enhancement of signal intensity.

8 This is data from Bayer. And at
9 increasing doses, you have an increase in the
10 signal intensity in tumors, where there is a
11 breakdown of the BBB, but not in the surrounding
12 parenchyma. So you have an increasing
13 differential, signal intensity, between the tumor
14 and the brain, which is a lesion-to-brain contrast.
15 And this is true, also, for ProHance. You can see
16 that this increases with the doses of the agent.
17 So at increased concentration of the agent, you
18 have an increased signal intensity enhancement and
19 increased contrast ratio.

20 Now, if you take not only the contrast
21 agent variables, like relaxivity and dose, but,
22 also, scanning variables, there is the timing of

1 post-dose acquisition in an MRI of the CNS, and the
2 magnetic field strengths or new technology, as was
3 mentioned before by Dr. Weinrab, and patient
4 variables, type of lesion, the grade stage of the
5 disease, and the type of treatment.

6 You fix all the other variables and you
7 keep just the relaxivity as the only variable, and
8 you compare, in clinical studies, with a crossover
9 design, where you have the same patient, the same
10 administration scheme, and the same exact imaging
11 particle, even the same scanner.

12 You have four studies now that have been
13 published that show that the lesion-to-brain
14 contrast is superior for all the comparisons, this
15 is in all the blinded readers, with MultiHance, the
16 same dose, compared to Magnevist and Omniscan at
17 1.5 tesla and, also, with Magnevist at 3 tesla.

18 Why may this be important? Because the
19 notion that MultiHance can provide a better lesion-
20 to-brain contrast may provide not only information
21 about the potency of MultiHance compared to other
22 agents that make physicians more comfortable with

1 the standard dose or even a lower dose of the
2 chelate and decrease the likelihood of using doses
3 higher than the approved dose. As you have heard,
4 that may happen, especially for certain
5 indications.

6 So in conclusion, most important, the
7 clinical evidence is that we have low to minimal
8 incidence of NSF and especially for unconfounded
9 cases. We are aware of two reports, but we also see
10 centers that have switched from other agents to
11 MultiHance that have not seen cases of NSF since.
12 There are no unconfounded cases from the literature
13 and no cases of NSF from the Phase 4 post-marketing
14 requirements.

15 So, again, of course, extreme caution
16 should be used when using gadolinium-based contrast
17 agents, but based on the available evidence, we,
18 Bracco, do not believe that the more restrictive
19 measures are needed for MultiHance as a
20 contraindication of the agent.

21 Thank you for your attention.

22 DR. HARRINGTON: Thank you, Dr. Spinazzi.

1 Next, we'll turn our attention to Bayer and Dr.
2 Pering.

3 DR. PERING: Thank you, Mr. Chairman,
4 members of the Advisory Committee. It is my
5 pleasure to present to you data on our second
6 gadolinium-based contrast agent marketed in the
7 U.S., Eovist.

8 In this presentation, I will start with
9 an introduction into this new product, followed by
10 a discussion of the available clinical evidence in
11 the context of NSF, as well as the existing NSF
12 risk mitigation activities.

13 Eovist is a new product for U.S.
14 radiologists, as it was only approved very
15 recently, in the middle of 2008, for use in
16 contrast-enhanced MRI of the liver. It was
17 introduced to the imaging community after the
18 heightened awareness of NSF and its potential risk
19 factors and after the implementation of recent risk
20 mitigation measures.

21 Eovist is an ionic linear gadolinium
22 agent, very similar in its structure to Magnevist.

1 To the DTPA backbone of Magnevist, a lipophilic
2 group was added and this moiety enables the uptake
3 of Eovist by hepatocytes and its elimination via
4 the bile.

5 Because an agent's chemical structure is
6 closely related to its complex stability, Eovist,
7 with its ionic linear structure, exhibits a
8 comparable stability as all the other ionic linear
9 gadolinium agents. And all ionic linear gadolinium
10 agents have a greater stability than the nonionic
11 gadolinium agents.

12 Now, nonclinical experiments and studies
13 have led to the hypothesis that an agent's chemical
14 structure and stability is a key determinant of NSF
15 risk. If this hypothesis were true, you would
16 predict that Eovist would carry an intermediate
17 risk of NSF.

18 However, the role played by complex
19 stability in the context of NSF is currently only a
20 hypothesis. Even if this hypothesis were true,
21 this characteristic would represent only one of
22 several key considerations of the development of

1 NSF.

2 The other major factors related to the
3 development of NSF include the administration of
4 the dose necessary for diagnostically-effective
5 images -- this determines the exposure of the
6 patient to gadolinium; the elimination
7 pharmacokinetics in patients with renal impairment,
8 which also determined the exposure of these
9 patients to gadolinium; and, the likelihood that a
10 particular gadolinium agent will actually be
11 administered to patients considered to be at risk
12 to develop NSF, which means patients with severe
13 renal insufficiency.

14 These other factors are all very
15 important in assessing the risk for any particular
16 gadolinium agent, including Magnevist, and they are
17 particularly important in evaluating the NSF risk
18 with Eovist. For example, and Dr. Spinazzi has
19 explained a lot about T1 relaxivity, Eovist has a
20 high T1 relaxivity, which means that even low doses
21 can produce high signal intensities on MR images.

22 As a result, Eovist can produce high

1 quality MR images even though it is administered as
2 at least the fourth of the dose that is recommended
3 for all other agents, and this has been
4 demonstrated in well controlled, randomized
5 clinical trials. This low dose of Eovist means a
6 markedly reduced exposure of the patients to
7 gadolinium.

8 Another unique property of Eovist relates
9 to its elimination pharmacokinetics, which is
10 another important risk determinant in the context
11 of NSF. Eovist has two equally effective pathways
12 for elimination. Approximately 50 percent of the
13 administered dose are eliminated by the kidneys and
14 urine and the other approximately 50 percent of the
15 administered dose are eliminated via the liver and
16 bile.

17 In the event that one pathway is
18 impaired, which is the case in patients with severe
19 renal impairment, whose exposure to gadolinium
20 agents is prolonged and, thus, who are at risk of
21 developing NSF, the other elimination pathway for
22 Eovist, the liver, can help eliminate an increased

1 fraction of the administered dose. This helps to
2 minimize the exposure of the patient to gadolinium.

3 Finally, Eovist is approved for use with
4 contrast-enhanced MRI of the liver, for the
5 detection and characterization of lesions in adults
6 with known or suspected focal liver disease. This
7 is a very specific indication and targeted at a
8 limited patient population, different, for example,
9 as with Magnevist, which has had a broad range of
10 approved indications, as I explained earlier.

11 Agents like Eovist may, therefore, have a lower
12 likelihood to actually be administered to patients
13 considered to be at risk to develop NSF.

14 All of these unique properties of Eovist
15 highlight the importance of factors not related to
16 the stability of the gadolinium agents and
17 determining the risk of NSF. In fact, in most
18 cases, these characteristics may play a far more
19 important role in determining the NSF risk
20 potential than the stability of the agents, and
21 this is well illustrated by a review of the
22 clinical evidence for NSF in patients who have been

1 exposed to Eovist.

2 It is important to note that NSF has not
3 been reported in association with the
4 administration of Eovist in any patient since the
5 drug was first introduced in Europe for clinical
6 use in September 2004. That means we have no
7 reports of NSF in patients who have received Eovist
8 and no other gadolinium agent and we have no
9 reports of NSF when Eovist was used in patients who
10 received other gadolinium agents. Furthermore,
11 also, the FDA has not received any reports of NSF
12 or NSF suggestive symptoms in association with
13 Eovist to date.

14 I want to underscore one point that I
15 made earlier, that when evaluating these AERS data,
16 it is important to focus on all the reports, not
17 simply on the unconfounded reports. Because of the
18 way these agents are used, any focus on
19 unconfounded reports represents a biased analysis
20 that likely ignores a large proportion of patients
21 with NSF who are known to have undergone multiple
22 administrations of gadolinium agents.

1 Therefore, if we focus on the column of
2 all reports, we note that there are more than 300
3 NSF reports for all agents on this slide. The only
4 exception is Eovist. There is not a single report
5 of NSF with Eovist, neither confounded nor
6 unconfounded, in the AERS database.

7 Despite the absence of a single report of
8 NSF in patients exposed to Eovist and despite all
9 the reasons I've reviewed why the risk of NSF
10 should be lower with Eovist than with other
11 gadolinium agents, we do not believe that we can
12 reliably conclude that the risk of NSF is
13 meaningfully lower with Eovist than with other
14 gadolinium agents.

15 The number of administrations is low.
16 Eovist has been used primarily in patients with
17 hepatic disease, not necessarily renal disease, and
18 Eovist was introduced at the time when radiologists
19 had learned how to minimize the risk of NSF. For
20 all of these reasons, we cannot, with any
21 scientific rigor, conclude that Eovist is safer
22 regarding the NSF risk than any other gadolinium

1 agent.

2 As we discussed with Magnevist, we are
3 also conducting, as a Phase IV commitment, an
4 observational study in patients with moderate renal
5 impairment to collect data concerning the
6 occurrence of NSF following the administration of
7 Eovist. This study is currently ongoing and
8 centered in the U.S., as well as in European
9 countries and Asian countries, and, to date, we
10 have not received any report of NSF suggestive
11 symptoms in any of the study patients.

12 We conclude with an FDA briefing document
13 -- no -- the experience with Eovist, with its
14 unique properties, illustrates the difficulties in
15 distinguishing differences in NSF risk potential
16 among the available marketed gadolinium agents.
17 The NSF risk categorization, based on complex
18 stability, represents an effective, but unproven
19 hypothesis. Focusing on the chemical aspects
20 neglects many key clinical considerations in the
21 context of NSF.

22 The results of available clinical studies

1 do not allow for robust conclusions on differential
2 NSF risk of the gadolinium contrast agents.
3 Current comparisons on the basis of spontaneous
4 reports do not adequately address biases inherent
5 in the analysis, in particular, of recent-entry
6 gadolinium agents.

7 Bayer concurs with the FDA briefing
8 document that none of the individual data sources
9 provide an unambiguous, clear picture as to the
10 fundamental question of differential NSF risk among
11 the marketed gadolinium agents and labeling and
12 communications are expected to appropriately
13 describe all the major risks of gadolinium agents,
14 not solely those related to NSF.

15 Inappropriate labeling for gadolinium
16 agents may result in a shift in clinical practice
17 toward procedures and/or drugs that may even have
18 greater risks. However, if the Advisory Committee
19 determines that, based on the available data, it is
20 appropriate and necessary to make distinctions in
21 NSF risk among available agents, the available
22 clinical and nonclinical evidence support a

1 distinction between Omniscan and Optimark and all
2 other gadolinium agents.

3 Thank you very much for your attention.

4 DR. HARRINGTON: Thank you, Dr. Pering.
5 We'll now hear from the final sponsor presentation
6 on behalf of Lantheus.

7 DR. YUCEL: Good morning, and thank you
8 to the committee for this opportunity to present
9 our data on Ablavar. I'm Kent Yucel. I'm a
10 cardiovascular radiologist at Tufts Medical Center
11 and I am here as a consultant to Lantheus, and they
12 supported my travel to this meeting. There are
13 several other experts here, when it comes time for
14 questions, who can address specific features of
15 Ablavar, if questions arise.

16 So Ablavar, like Eovist, it's important
17 to note, is a completely different class of
18 gadolinium agent, with a specific mechanism of
19 action that differentiates it from the general
20 agents. Eovist, as you heard, is taken up
21 specifically by the liver and it is for liver
22 imaging. Similarly, Ablavar binds the serum albumin

1 in the blood and that gives it the ability to give
2 very robust, prolonged vascular imaging and to
3 enhance arteries at a single low dose.

4 It's been approved in 38 countries,
5 first, in the EU in 2005, so we have some clinical
6 experience to report from Europe, and it has been
7 approved in the United States. It was acquired by
8 Lantheus this year and release is pending in North
9 America and Australia.

10 So this is the actual FDA labeling,
11 wording that we're working with now. Ablavar is a
12 gadolinium-based contrast agent indicated for use
13 in magnetic resonance angiography to evaluate
14 aortoiliac occlusive disease in the setting of
15 peripheral vascular disease.

16 Clinical efficacy was established in 21
17 clinical subjects involving almost 1,700 patients
18 and shown and documented that Ablavar MRA was
19 superior to non-contrast MRA for stenting stenosis
20 in aortoiliac occlusive disease. Specifically,
21 superiority was demonstrated in diagnostic
22 sensitivity, noninferiority in specificity, and a

1 significant reduction in non-interpretable
2 examinations. And importantly, Ablavar MRA
3 demonstrated accuracy comparable to the x-ray gold
4 standard.

5 I'd just like to take a couple of minutes
6 to go over the structure. As you heard prior, like
7 Eovist, Ablavar is a linear chelate. This is a
8 linear chelating ligand that binds the gadolinium,
9 which interacts with the water and provides for the
10 brightening effect of gadolinium contrast agents.

11 Similar to Eovist, however, there is
12 extra protein binding, a targeting moiety, in our
13 case, a serum albumin binding moiety that's
14 attached to this backbone. So this moiety that
15 binds to albumin restricts Ablavar predominantly to
16 the vascular space. It provides for the mechanism
17 of action that enhances arterial imaging, and it
18 limits tissue exposure by limiting Ablavar
19 distribution primarily to the vascular space.

20 In addition, this albumin binding extends
21 the plasma half-life and increases the imaging
22 window for MR imaging and, similar, again, to

1 Eovist, this binding to serum proteins
2 substantially increases the plasma relaxivity;
3 i.e., it provides for a similar brightening effect
4 with a lower imaging dose.

5 Interestingly, both compounds with this
6 protein, with this backbone substitution, with the
7 protein binding moiety, in our case, provide some
8 interesting thermodynamic features to these agents.
9 In particular, it restricts the confirmation of the
10 chelator and these provide for greater
11 thermodynamic stability and, also, create a kinetic
12 barrier dissociation; i.e., they create greater
13 kinetic inertness.

14 Now, what does that mean? You've heard
15 about stability a couple of times and let me
16 explain with this graph, which is adapted from a
17 paper that's also been referenced, that we're
18 really talking about two kinds of stability here.

19 One is thermodynamic stability, in this
20 case, conditional, at page 7.4, along the X-axis.
21 And along the Y-axis, we're looking at kinetic
22 inertness. In other words, this is a stability

1 when everything is thermodynamically equilibrated.
2 This is the rate at which that dissociation occurs.

3 So they're both important, and we see
4 these different classes of agents here. In the
5 lower left-hand corner, with the lowest kinetic
6 inertness and thermodynamic stability, are the
7 class of linear nonionics, which you've heard
8 about. That includes Omniscan and Optimark. Then
9 we have, with an order of magnitude, greater
10 kinetic and thermodynamic stability, the linear
11 ionics. That's Magnevist and MultiHance. You can
12 see here the backbone subset of linear ionics endow
13 these agents, Eovist and Ablavar, with another
14 order of magnitude greater kinetic inertness, as
15 well as additional thermodynamic stability. And
16 then on the top, you see the macrocyclics, of which
17 ProHance is in this class, which actually span a
18 fairly wide range of thermodynamic stability, but
19 exhibit significantly greater kinetic inertness.

20 So the pharmacokinetics, in summary, are
21 at recommended clinical dose, note 0.03 millimoles
22 per kilogram. So that is 3 to 10 times lower than

1 the 0.1 to 0.3 doses typically used and recommended
2 for the general purpose agents. The half-life is
3 about 18 hours. The protein binding is about 85
4 percent and that limits the unbound Ablavar that's
5 available for extravascular distribution. And
6 additionally, the 15 percent, if unbound, permits
7 the excretion by the kidneys.

8 So we can think about exposure as the
9 combination of the dose and the time the agent is
10 available in the body. That's called the area
11 under the curve. So if we think about that area
12 under the curve, because of the greater half-life,
13 even at the lower dose, the total area under the
14 curve is a little bit greater than the other
15 general agents. But the unbound exposure, which is
16 only 15 percent of the administered dose, makes the
17 unbound area under the curve available to the
18 tissues for transmetallation significantly lower
19 than the generic agents.

20 So the small volume distribution
21 indicates that there is little or no tissue
22 binding, consistent with the predominantly vascular

1 distribution. Clearance, as I mentioned, is
2 primarily renal, although even in normal, there is
3 some biliary elimination.

4 In renal impairment, the half-life and
5 AUC are both increased, but interestingly enough,
6 the biliary excretion more than doubles. So this
7 provides for an alternate elimination pathway in
8 renal failure, and it's effectively removed with
9 dialysis, like the general agents.

10 There are some nonclinical toxicology
11 studies that were performed before the NSF era that
12 are potentially relevant to NSF risk, and these
13 include high dose rat and primate studies, where a
14 very large total AUC was achieved, much greater
15 than in humans, and no macro or macroscopic skin
16 changes were seen up to 12 weeks follow-up and
17 there was very low gadolinium retention in the
18 skin.

19 In the clinical trials, the adverse event
20 profile is very similar to the general agents,
21 fairly mild and self-limited AEs, typically, a
22 little itching, headache, nausea. Serious adverse

1 events were seen in 13 patients and, importantly,
2 no differences were found in the safety profile in
3 special populations that were studied in the
4 clinical trials, including patients with hepatic
5 and renal insufficiency and dialysis patients, and
6 no events of NSF were seen.

7 Predominantly in Europe, over 90,000
8 doses have been distributed clinically. The AE
9 profile is very similar to that seen in clinical
10 trials, typical AEs for this class of agents,
11 typically resolve within minutes and are self-
12 limited.

13 We do plan, the other companies have
14 indicated, to initiate a Phase IV study looking at
15 patients with chronic kidney disease and that study
16 is planned to be launched in 2010. And no cases of
17 NSF have been reported from Europe in these over
18 90,000 doses that have been administered.

19 So in summary, this is a specific
20 contrast agent with a specific indication and the
21 only agent that's been approved for MR angiography.
22 Like with Eovist, it's in the class of backbone

1 subsidiary linear ionic agents, which provides both
2 increased thermodynamic and kinetic stability. The
3 dose, as with Eovist, is significantly lower than
4 that used for the general agents, 3 to 10 times,
5 and the protein binding limits the extravascular
6 distribution of the agent. No cases of NSF have
7 been reported.

8 In summary, we're comfortable with the
9 current FDA labeling of these agents, this agent,
10 in particular. I don't want to speak to the other
11 agents. But we're comfortable with the current FDA
12 labeling, which discourages the use of these agents
13 in the severe renal population. There simply
14 hasn't been enough experience with this or any
15 other agent, really, to assess safety in that
16 severe renal population, but it still permits
17 doctors to make appropriate risk-benefit
18 adjustments in the specific patient cases, as Dr.
19 Weinrab mentioned may be important.

20 Thank you.

21 DR. HARRINGTON: Thank you very much. I
22 want to thank all seven presenters, a couple of you

1 twice, so five presenters and really for both
2 staying on time, as well as presenting information
3 in a very succinct fashion.

4 I'm going to open up the questions to the
5 panel and I'd like to go until about 11:45, but let
6 me just set some ground rules. First off, as we
7 spoke earlier, just signal Elaine and she'll keep
8 the running tally. But in order to be fair to all
9 of the sponsors, I'm going to ask you to identify
10 the specific sponsor to whom you want to ask your
11 question.

12 If, however, you have a general question
13 that you really don't care who answers it from the
14 sponsors, as long as it gets answered, I will
15 follow in order of the presenting companies --
16 Bayer, Bracco, GE, Covidien and Lantheus -- and
17 we'll cycle through that, as necessary, to be fair
18 to everybody.

19 We had discussed this with the sponsors
20 during the break. So if you have a specific
21 question, please identify that sponsor. But if
22 it's a general question, we will go in order. If

1 you don't feel it's answered, we can ask another
2 sponsor to help out, but we will try to be fair.

3 So let's open it up to questions.

4 Larry?

5 DR. HUNSICKER: Yes. I actually have a
6 question for Lantheus and that specifically had to
7 do with the issue of transmetallation and the
8 reduction of the risk for transmetallation given
9 that there is a lot of protein binding.

10 Do you actually know that that's true?
11 Is the albumin bound agent actually less
12 susceptible to transmetallation? Is that known?

13 DR. YUCEL: I think a lot of what we
14 talked about today somewhat to the mechanism of
15 action is fairly speculative. So the answer is no.
16 We presume that transmetallation occurs in the
17 environment of the tissues where NSF is seen.

18 So to the extent that it is in the
19 intravascular space, it may be less available. But
20 I agree with you. A lot of what we discussed
21 regarding mechanism of action for NSF is pretty
22 speculative.

1 DR. HARRINGTON: Dr. Paganini?

2 DR. PAGANINI: Don't leave; stay in
3 there.

4 One of the things I'd like to add -- two
5 things. One is protein binding of 85 percent does
6 not make it very dialyzable, and yet you said
7 dialyzability after three dialyses. You have a
8 volume of distribution of, what is it, 0.7 of a
9 liter, which is basically intravascular. And so,
10 therefore, non-dialyzability of this makes it a
11 longer stay, even though the volume of distribution
12 is smaller. So could you answer that question?

13 But in the generic, Bob -- this is
14 generic for probably FDA and everybody -- what are
15 volume distributions, molecular weights, charges,
16 protein binding of these various issues? So I can
17 get a handle on how well they're removed, because
18 one of the issues that almost everybody who does
19 this asks for people to be dialyzed right away,
20 within two hours, three hours, and there's no real
21 proof that any of this stuff happens or helps and
22 I'm not sure of the dialyzability?

1 So here we have somebody who says very
2 dialyzable, 85 percent protein binding,
3 nonsecretor.

4 Could you answer that?

5 DR. YUCEL: Yes, I can. I may need to
6 call for help from my pharmacokinetic expert, but
7 let me take a stab at that first.

8 First of all, I would think in 2009, I
9 think it's important to note that I don't think
10 anyone is recommending the use of any of these
11 agents in dialysis patients. So I think that's the
12 first point to keep in mind. But we do have --
13 this is comparison data of dialyzed --

14 DR. PAGANINI: If I could just jump in.
15 But almost everybody is recommending dialysis
16 immediately after they're given this stuff in
17 certain subgroups of patients. So there is a
18 clinical relevance to the question.

19 DR. YUCEL: Certainly. Certainly.

20 So this is the dialysis data of Ablavar
21 compared to the other agents. As you can see, it's
22 actually given the 85 percent. Again, what

1 happens, the way it works with this agent is the
2 unbound fraction is what is dialyzed inertia by the
3 kidney.

4 As soon as that is out, the equilibrium
5 gets reestablished. So despite that the binding is
6 reversible, obviously, that's the mechanism by
7 which it is excreted and dialyzed. So it's not
8 like it's retained forever on the albumin. The 15
9 percent unbound fraction does allow for it to be
10 dialyzed and excreted.

11 This is the data. As you can see, this
12 is first, second and third dialysis sessions of all
13 the agents and, as you can see, there is slightly
14 less dialyzed at each session than other agents.
15 But keep in mind this is a 3 to 10 times lower
16 does.

17 So if you think about a third session, 92
18 percent is out versus 99 percent or 98 percent
19 being out, but starting with one-third or one-tenth
20 the dose, more or less, we're dealing with the same
21 amount of residual gadolinium. That's the only
22 thing I'd add to it.

1 Did that answer your question or did you
2 have some specific PK questions?

3 DR. HARRINGTON: Emil, do you want to
4 hear from each of the sponsors about dialyzability
5 or how far do you want to take this question?

6 DR. PAGANINI: I don't want to overburden
7 the committee on these things, but I think
8 dialyzability is an important issue in a whole
9 series of issues, especially if we're going to
10 start to recommend that perhaps there's a
11 differential in some of the patients who are
12 dialysis-bound or dialysis-dependent may, in fact,
13 be getting it.

14 But I don't want to belabor the question
15 and all that jazz. If the companies have that
16 information and put it together for us, that would
17 be fine. If FDA has it already, that would be
18 fine, too. It would be something I would think
19 that they would want to know.

20 DR. HARRINGTON: Dr. Rieves is indicating
21 that's not going to be part of the FDA
22 presentation; is that correct?

1 DR. RIEVES: No. We're not going into
2 details on that. It's a good point, though, but
3 we're not prepared to make that presentation.

4 DR. HARRINGTON: So maybe I could ask
5 that the various sponsors get together and perhaps,
6 if you have the information, a single slide after
7 lunch with the information that Emil is asking for
8 would be useful to the committee to consider.

9 So, Emil, why don't you lay out what
10 piece of data you would like from the sponsors.

11 DR. PAGANINI: I just need to know how --
12 usually, the elements that are involved depend on
13 volume and distribution, molecular weight, charge,
14 protein binding, it's all that. Then everything
15 else is on the other side, what you use, what kind
16 of membrane, how fast you throw the blood and all
17 that jazz. And usually, that's all I need to know
18 and you can get a fairly good handle on how well
19 things come across, for all of the reasons that I
20 tried to list earlier. That's all.

21 DR. HARRINGTON: Great. So maybe we
22 could come back to that question.

1 Dr. Fogel?

2 DR. FOGEL: Yes. This is more of a
3 general question to all the sponsors. I keep
4 getting struck by the fact that with the
5 introduction in 1988, we don't have a report of NSF
6 for almost 10 years, even though apparently it
7 could be very severe.

8 One of the things I'm struck with is that
9 injectors did not -- MRI-safe injectors did not
10 come into being until the mid 1990s. So I guess I
11 was wondering, from any of the databases, is there
12 any history of NSF with injectors and rate of
13 injection?

14 I guess it goes along with more of the
15 kinetics in terms of a patient with renal failure
16 getting a bolus, a very fast bolus of gadolinium
17 versus getting less so. So I was wondering if that
18 has had any bearing on any of the patients who had
19 NSF, whether there is any history of that and what
20 injector rates are or if they even used injectors
21 or not.

22 DR. HARRINGTON: But it's not to a

1 specific sponsor. So you're happy if we start with
2 the Bayer group and ask them for their perspective.

3 DR. FOGEL: Any sponsor will be fine.

4 DR. GOLDSTEIN: Good morning. I'm Hank
5 Goldstein. I'm with Bayer. You're correct that
6 injectors have been used in some settings. There
7 is no documentation that I'm aware of that would
8 allow us to determine the percent utilization in
9 these populations.

10 DR. HARRINGTON: If there is additional
11 data, please, we'll start with the Bayer group, but
12 feel free to weigh in if there is a different
13 perspective.

14 DR. SPINAZZI: This is Bracco. Most of
15 the reports that I was showing, there is no
16 information about even sometimes the dose and
17 certainly not if a power injector was used. The
18 only case that we're aware of information of is the
19 case that was at Dr. Prince's site, where a power
20 injector was used for MR cholangiopancreatography.
21 But we cannot give any intelligent answer on this.

22 DR. HARRINGTON: Is there another

1 perspective here?

2 DR. FOGEL: I would just settle for even
3 if there's any in vitro or kinetic information and
4 about receiving a fast or a concentration of
5 gadolinium versus a slower one.

6 DR. HARRINGTON: So even preclinical
7 data.

8 DR. FOGEL: Yes, sure.

9 DR. CANTOR: Eric Cantor. My slides,
10 unfortunately, are not coming up. It was in
11 actually the set that we talked about earlier. It
12 doesn't directly answer your question, but provides
13 some information. And what that shows is, in terms
14 of practice patterns, that Omniscan, in particular,
15 was used much more commonly with power injectors as
16 MRA became more prevalent and the volume per
17 procedure rose.

18 So what we see is not that it's the power
19 injector itself or the bolus effect, but the
20 increase of volume per procedure that was used with
21 MRA that seems to correlate with the increased
22 number of cases, and as that volume per procedure

1 has decreased in the market, the number of cases
2 have precipitously dropped.

3 So it just provides some additional
4 information to your question.

5 DR. HARRINGTON: Does that help, Mark?

6 DR. FOGEL: A little.

7 DR. HARRINGTON: I suspect there will be
8 a lot of things that will help a little.

9 Dr. Gross?

10 DR. GROSS: On Eovist, I think we
11 shouldn't conclude that it's unlikely to cause NSF,
12 for the following reason. If you look at the
13 Magnevist data, if the incidence in confounded
14 cases is about one in 76,000 and Eovist has been
15 given less than 100,000 times, I think Eovist would
16 probably have to be given almost a million times
17 and then see no cases of NSF to conclude that it
18 doesn't cause it.

19 DR. HARRINGTON: Would you like the Bayer
20 group to comment on that?

21 DR. GROSS: Yes, please.

22 DR. PERING: We concurred with the

1 statement that there is not enough clinical
2 evidence with Eovist available to draw any realible
3 conclusions with regard to the NSF risk potential.

4 DR. HARRINGTON: Dr. Tatum?

5 DR. TATUM: This is for everybody,
6 including the FDA. Do we have any idea of the
7 percent of NSF cases associated with off-label use?
8 And I bring that up because we're always in a
9 position of the safety versus benefit and I assume
10 things off label do not have the benefit quality of
11 data to make that balance.

12 DR. BOUCHER: The short answer is no.
13 Based on the AERS reports, very few reports had
14 indication data in them.

15 DR. HARRINGTON: Go ahead, Dr. Nelson.

16 DR. NELSON: I guess this is actually a
17 question for Dr. Pering. And it may actually turn
18 out to be a question for FDA and maybe you'll
19 answer this as we go along. But you had commented
20 several times about the difference between the
21 confounded and the unconfounded cases.

22 Is there a way to look into the AERS

1 database and pull out the cases in which the
2 previous exposure was within a reasonable period of
3 time to the exposure kind of question at this
4 point?

5 So in other words, you could have been
6 exposed 10 years ago and you fall into the pre-
7 exposure case and you're confounded. But what
8 we're really interested in are the people who were
9 exposed within the past, say, one year or maybe
10 three years, if you want to go to the final
11 outlier.

12 DR. HARRINGTON: Maybe we'll ask FDA to
13 comment first and then the Bayer group. It sounds
14 like your question was addressed to them.

15 DR. NELSON: Well, they had commented
16 about this, I think, several times when they were
17 doing it, but I don't really know who would have
18 the answer. But it's just to try to kind of
19 quantitate the risk.

20 DR. HARRINGTON: So you want to
21 understand, in these so-called confounded cases, if
22 we have data on the dosing interval and if there is

1 a difference in that dosing interval in terms of
2 the differential effects of some of the agents.

3 In other words, if they're very remote
4 dosing intervals, that may be one category, but
5 more narrow dosing intervals might be a second
6 category.

7 Is that what you're asking?

8 DR. NELSON: Well, in a way. I'm just
9 trying to get a handle -- we're very finely
10 dividing things here. We're lumping everything
11 into you got an exposure today which causes NSF and
12 you had an exposure anytime within the past 15
13 years. We believe, based on some of the data that
14 was showed earlier, that the median time from
15 exposure to developing NSF is just a few weeks and
16 there are some outliers that might go out to a year
17 and then there's some really remote outliers that
18 go out to three years.

19 But if you try to say -- we can say that
20 this new exposure was the likely proximate cause of
21 the new onset NSF. We should look at only those
22 people in the database who have been exposed within

1 some reasonable period of time.

2 DR. HARRINGTON: I think it was Dr.
3 Cowper who showed us the five-week median earlier
4 this morning.

5 DR. NELSON: Right.

6 DR. HARRINGTON: So, FDA, would you like
7 to comment? Then maybe the Bayer group could get
8 ready to comment.

9 DR. BOUCHER: Generally -- and we'll be
10 presenting our adverse events data shortly. But,
11 basically, our approach to this was to look at the
12 so-called unconfounded cases, which were the
13 single-agent cases, and we didn't feel that just
14 looking at the cases as they came in over the last
15 few years, that there would be enough data to do
16 the type of analysis that you would have liked to
17 have seen.

18 As most of you know, the AERS reports,
19 simply, you do not have enough data or are
20 confounded for various reasons, including use of
21 multiple agents and so on. And they are just not
22 well enough reported as a group to have a sample

1 large enough to do the type of analysis that you
2 would have liked to have seen.

3 DR. HARRINGTON: Go ahead, Doctor.

4 DR. KREFTING: Just to follow-up on Bob's
5 statement. I think you will see some data
6 presented in the subsequent presentations by the
7 FDA, where you'll see the number of reports coming
8 in and those for which we have enough data, such as
9 event dates, to make some reportable statements and
10 gather some more data on.

11 So, please, wait for our presentations to
12 further answer your question, from our viewpoint.

13 DR. HARRINGTON: Dr. Pering? And then
14 I'll go to you, Dr. Zito.

15 DR. PERING: With regard to our own data,
16 I can, unfortunately, also, only confirm that in
17 most cases, the information is too limited to be
18 able to give you a precise number of how many
19 patients in a certain time frame have been exposed
20 to multiple exposures. We wanted to highlight the
21 problem of the respective analyses, as outlined.

22 DR. HARRINGTON: Dr. Zito?

1 DR. ZITO: To follow-up with the point on
2 off-label usage, it would seem that a simple audit
3 study done in the post-marketing phase could
4 perhaps enlighten us and, also, then comparison
5 with EMA data would be very useful to see if we're
6 doing things differently in terms of the reason for
7 use and how it bears on risk.

8 The second point is how much information
9 has been gleaned from the clinical trials that have
10 been done.

11 DR. HARRINGTON: Is there a specific
12 question on the clinical trials that you would like
13 one or more of the sponsors to answer?

14 DR. ZITO: Well, with respect to the
15 follow-up, how much time is assessed following the
16 intervention and what, if any, sort of serious
17 adverse events were reported?

18 DR. HARRINGTON: So I think Bracco is
19 next up. So why don't you start that? And then if
20 there are other sponsors who want to weigh in,
21 we'll certainly allow that.

22 DR. SPINAZZI: To start, because I saw

1 that we have more patients than any other company
2 here in the study, the follow-up is for two years
3 and we are at variable times so far and there are
4 intermediate visits. So the protocol has been
5 agreed upon with the FDA and it's the same for all
6 the sponsors. So far, we didn't have any serious
7 event in the study and no cases of NSF.

8 Now, one study with MultiHance has 234
9 patients, of which 27 with Stage 4 or 5 chronic end
10 disease. All the rest are Stage 3 chronic end
11 disease. And with ProHance, we have 71, 11 with
12 Stage 4 or 5 and 60 with Stage 3 chronic end
13 disease, at variable times. But not one patient so
14 far has already completed the follow-up period.

15 DR. HARRINGTON: Thank you. Dr. Tatum?

16 DR. TATUM: I guess I'm a little bit more
17 concerned about this time lapse thing, because I'm
18 beginning to wonder if we've got a long-term
19 exposure here and not just a short-term exposure,
20 and there are a couple of reasons for that.

21 At least one of the nonclinical data, and
22 maybe more nonclinical data would be important

1 here, show that even in the absence of any renal
2 disease, I believe it was rats, you still had
3 gadolinium species, whatever it was, accumulated.
4 And some of those went out quite long and there
5 were still gadolinium species there.

6 So do we have a longer-term effect and
7 this is just kind of the tip of the iceberg?
8 That's one thing.

9 The other part of that, in that curve Dr.
10 Cowper showed, you'll notice it was 50 years of
11 age. I've still been looking at that trying to
12 figure out why that 50. Well, there's one reason
13 it could be and it could be increasing use and
14 total body burden and totally body plus acute
15 actually being part of the event, and I don't think
16 we know the answers to that.

17 So any nonclinical would give me an idea
18 about what's routine in the tissue and how long it
19 stays in the tissue and is there accumulation would
20 be very helpful.

21 DR. HARRINGTON: So you don't have it for
22 a specific sponsor. You're happy with --

1 DR. TATUM: Anybody who can kind of
2 answer and shed some light on this.

3 DR. HARRINGTON: The next up on this
4 would be GE Healthcare, if you want to try to
5 answer. If not, we'll go to Covidien and Lantheus.
6 So, GE Healthcare, if you would like to answer.

7 DR. CANTOR: I'm just going to ask Ben
8 Newton, who is head of research for us on NSF, to
9 address that.

10 DR. NEWTON: I'd just like to make an
11 important point, particularly with respect to the
12 clinical studies and to the preclinical studies,
13 that the actual form of the gadolinium that is
14 being assessed in those studies has not been
15 confirmed --using the tests that were carried out,
16 has not been confirmed. In these studies, the
17 gadolinium could be chelated and it could be
18 unchelated.

19 I'd just like to point out several
20 studies -- well, this study, in particular, with
21 respect to the importance of retained gadolinium.
22 I think Dr. Sieber and Dr. Pietsch had shown

1 previously that retained gadolinium could be a
2 factor and, in fact, in long-term studies that
3 retain gadolinium for a long period of time, it
4 does not lead to lesions, at least particularly in
5 the Pietsch study.

6 But this is a study from Dr. Grant's
7 study. This is Omniscan injection and the level of
8 gadolinium in skin of rats, and you see gadolinium
9 chloride injection and gadolinium citrate injection
10 lead to much, much higher concentrations of
11 retained gadolinium in the skin.

12 If you look at the actual pathology in
13 those skin lesions, you see that there is no
14 correlation whatsoever between the amount of
15 gadolinium in the skin and the lesions themselves.
16 So this is important, because it illustrates the
17 fact that it's the form of the gadolinium that is
18 key, not gadolinium, per se.

19 DR. HARRINGTON: Does that help you, Jim?

20 DR. TATUM: It doesn't make me feel much
21 better.

22 DR. HARRINGTON: Is this the same line of

1 questioning, Larry? Otherwise, we'll go to Emil.

2 DR. HUNSICKER: Yes, it is, actually.

3 There has been a certain amount made of the impact
4 of phosphate on the gadolinium, perhaps
5 transmetallating it more frequently, I assume, by
6 just reducing its activity and whatever.

7 This suggests, actually, my guess is that
8 if you inject soluble gadolinium into the blood,
9 it's going to get precipitated by available
10 phosphorous within 10 nanoseconds or something like
11 that and it's going to be come inert.

12 Do we have any idea whether gadolinium
13 phosphate does anything to anybody?

14 DR. NEWTON: To my knowledge, there have
15 been no studies whatsoever to investigate the
16 direct effect of gadolinium phosphate on cellular
17 systems or in vivo systems.

18 DR. HUNSICKER: Actually, that's what I
19 would have predicted. But I think it's important
20 to just put on the table here that we have no idea
21 what the gadolinium is in there and whether it's
22 active to do anything. We don't know.

1 DR. NEWTON: That's correct.

2 DR. HARRINGTON: Emil?

3 DR. PAGANINI: Bayer. Again, I'm into
4 the elimination mode here. Being a nephrologist, I
5 just am really enhanced with eliminations.

6 [Laughter.]

7 DR. PAGANINI: One of the thing that sort
8 of unstables my world is liver elimination, because
9 everything should really go through the kidney. So
10 here we have half of your drug coming off liver and
11 half with kidney.

12 In acute kidney injury, the liver does
13 not function very well and so, therefore, the liver
14 will not eliminate as efficiently. In chronic
15 renal insufficiency, the liver may not pick up as
16 much as has been intended.

17 So I would ask, in your elimination
18 studies for Eovist, is this a theoretical increase
19 in liver release when kidney failure increases or
20 do you have any studies in any level, whether they
21 be animal, human or whatever?

22 DR. HARRINGTON: So for the Bayer group.

1 DR. PERING: We have studied the
2 pharmacokinetics in various subgroups of patients,
3 also, with the liver and renal impairment and we
4 could demonstrate an increase in the hepatic
5 elimination. I will be more than happy to provide
6 you with the details during the break, because I,
7 unfortunately, don't have the details on that
8 subgroup at hand.

9 DR. HARRINGTON: Go ahead, Emil.

10 DR. PAGANINI: Is that possible? I'd
11 like to see that.

12 DR. HARRINGTON: Yes. I think she
13 referred to she'll get it during the break and
14 we'll bring it back up after lunch. So let's hold
15 that.

16 DR. SPINAZZI: [Off microphone.]

17 DR. HARRINGTON: Sure. And then I'm
18 going to go to Dr. Neaton, Dr. Nelson, and then
19 we're going to turn it over to the FDA.

20 DR. SPINAZZI: We did see, also, for --
21 also, Magnevist undergoes -- sorry -- MultiHance
22 undergoes a certain degree of elimination through

1 the liver and we saw, in a normal subject, it's
2 around 3 to 4 percent.

3 When you go to a patient with severe
4 renal impairment, it goes up to 7, 8 percent, and
5 the same is also for Ablavar. So I expect for
6 Eovist to go up pretty much in patients with
7 chronic kidney disease.

8 DR. HARRINGTON: Jim?

9 DR. NEATON: This is a question for the
10 FDA primarily. Maybe they'll cover this in the
11 presentations. But I was curious as to where the
12 1,000 patients for the post-marketing clinical
13 trials came from. It just strikes me as a number
14 that's way too small given the incidence rates that
15 we've been looking at.

16 Also, maybe related to it, was there any
17 attempt to make the protocols which were being used
18 by the different companies standardized in terms of
19 what we might glean from these data?

20 DR. HARRINGTON: So you want to know the
21 sample size question based on the reported
22 incidence of somewhere in the 1 to 3 percent range

1 for people with severe renal dysfunction, how they
2 came up with 1,000 and whether or not this has been
3 standardized.

4 DR. KREFTING: I must remind you that the
5 protocols were developed or requested around mid-
6 2007, when the rates of NSF were not entirely clear
7 to us and what was felt to be practical in our
8 informal discussions with the sponsors. So in some
9 respects, granted, it's not ideal.

10 The other aspect of it, as you saw in the
11 multiple slide presentations from the various
12 sponsors, it spoke of having approximately 1,000
13 patients, 600 of which would be in the moderate
14 range and 400 of which would be in the severe
15 range. And we've gotten considerable discussion
16 and concern from the sponsors and from IRBs, et
17 cetera, about exposing patients in that more severe
18 group to agents for which IRBs, et cetera, were
19 concerned.

20 The other aspect of your question
21 relating to the standardization, we have made every
22 effort to standardize the protocol among the

1 various sponsors and, as written, I believe they
2 were all standardized.

3 DR. HARRINGTON: Go ahead, Jim.

4 DR. NEATON: Maybe we can just come back
5 to this this afternoon, because it just seems like
6 we need a sample size re-estimation here.

7 DR. HARRINGTON: I've already written
8 myself a note that one of the key elements for this
9 afternoon in terms of what else is required to have
10 more confidence in this area will include exactly
11 that discussion.

12 Dr. Nelson? And then we'll move to the
13 FDA presentation.

14 DR. NELSON: One thought that came to
15 mind when Emil was talking was the history of the
16 liver and metal toxicity is pretty broad and pretty
17 bad. And I'm sure this came up in the deliberation
18 over approving this drug whatsoever and I'm not
19 sure it's really related to what we're talking
20 about today exactly.

21 But when it comes to copper and iron and
22 thorium and a lot of other metals, when you start

1 putting large amounts through the liver, you start
2 to bring on whole new sets of syndromes, toxic
3 syndromes that are concerning.

4 So I don't know if it's ever been studied
5 in this renal insufficiency group, this renal
6 failure group, what happens when you start putting
7 all this metal into the liver. But does the
8 gadolinium start to accumulate there and, again,
9 open up a whole new problem that we haven't even
10 addressed up until now?

11 So just a thought. Maybe you could bring
12 some of that, if you have data about that, when you
13 come back this afternoon.

14 DR. HARRINGTON: Okay. Fair enough. So
15 let's move to the FDA presentations. First up is
16 Dr. Place to discuss the chemistry considerations
17 of the gadolinium contrast agents.

18 DR. LEUTZINGER: Good morning. I'm Eldon
19 Leutzinger from the Office of New Drug Chemistry in
20 CDER. This is a joint presentation between Dr.
21 Place and myself. I want to give David much credit
22 for much of the information that is contained

1 herein.

2 In this presentation, we will review what
3 is known from the published literature about the
4 chemistry of gadolinium agents, their stability
5 under well defined in vitro conditions, and what we
6 don't know about the chemistry of these agents
7 under less well defined conditions existent in
8 renal impaired patients.

9 The outline of the presentation will
10 cover gadolinium agents approved by FDA, why
11 gadolinium, gadolinium coordination and structure,
12 classification of the gadolinium agents, stability
13 considerations, and gaps in knowledge.

14 Actually, quite a bit of this material
15 has already been presented this morning in some of
16 the presentations. So some of this is going to be
17 a review and, actually, I probably am going to be
18 able to make this a fairly short presentation. For
19 example, we have been dealing with all of these
20 agents here from Magnevist all the way to ProHance,
21 and so I'm not going to spend any time on this
22 slide.

1 Gadolinium has the highest number of
2 unpaired spins, and so it is very efficient at
3 relaxing excited hydrogen nuclei. And I think we
4 all know, of course, the results of all this. And
5 we know that free gadolinium, of course, is toxic,
6 but when it is combined with -- complexed with an
7 organic ligand, why, that toxicity is reduced to
8 levels that are acceptable for human
9 administration.

10 Gadolinium coordination is nine. I'm
11 just going to show a ligand here, a linear ligand,
12 DTPA, or open-chain ligand. You see the three
13 nitrogens and there are five acetate groups.

14 What happens is that during coordination,
15 in forming of the coordination compound, is the
16 nitrogens, three nitrogens and one oxygen, bind to
17 gadolinium and lies in one of the planes of the
18 pyramid that you see here on the right side. And
19 the other four oxygens of the acetates lie in the
20 plane of the upper pyramid, and water occupies the
21 ninth coordination site. And it is this water that
22 comes on and off at a very large rate of about

1 several million gadolinium per second, which, of
2 course, everyone knows is what imparts the
3 paramagnetic properties to the gadolinium.

4 Actually, I want to go back. If you take
5 this structure here on the right side and you turn
6 it on N and you look down through to the gadolinium
7 in the center, you'll get what is on this next
8 slide. This is the way we have represented all of
9 the structures in this particular presentation.

10 What is notable here is that the ligand
11 has completely engulfed the gadolinium ion. It is
12 the ligand that is linear. It is not the complex.
13 On the next slide, this becomes fairly evident.

14 If you just perform a little thought
15 experiment and remove the gadolinium and the oxygen
16 or the water from the structures, you could see
17 this clearly and this is a comparison of a linear
18 ligand with a macrocyclic.

19 I think the most important point of this
20 slide, though, really is that there is a gap here
21 in the complex that is formed between the linear
22 ligand and gadolinium. This really presents sort

1 of a theoretical weak link in the ring around
2 gadolinium. It opens up a possible open door for
3 greater access to the gadolinium and it really
4 could start a series of events which could lead to
5 unraveling, sequentially unraveling the ligand from
6 the gadolinium.

7 The stability is really dependent on the
8 strength of the bonds and it also depends,
9 obviously, on how tight gadolinium is held within
10 the cavity. In the case of the macrocyclic, it is
11 greater than, of course, the case of the linear
12 complex.

13 This has led to all of these various
14 structural differences among the compounds, had led
15 to the classification of the FDA-approved
16 gadolinium complexes into three classes, which
17 we've already heard this morning, linear nonionic
18 and linear ionic and the nonionic macrocyclic
19 complexes. I'm not going to spend any more time
20 with that.

21 Very briefly, I'm just going to go
22 through here. In the linear nonionic complexes,

1 the three acetate groups balance off the gadolinium
2 ion, the plus-three charge and so they become
3 nonionic.

4 I want to really just say that what we
5 have in these particular kinds of complexes is a
6 replacement of the acetate by the amide groups.
7 And that does two things, of course. The X defines
8 the members of the group, whether it will be
9 gadoversetamide or gadiamide. But it also does
10 another thing which is really important and that's
11 to note that when you place an assay by an amide,
12 that really changes the type of coordinate bond and
13 the strength. That really is what accounts, in
14 part, for the weaker complex in the case of linear
15 nonionic complexes.

16 Here are the linear ionic complexes. In
17 this case, we have all five acetates that are bound
18 to gadolinium. And so we have a net minus-2
19 charge. Here, I've indicated the arrows where we
20 have various substitutions into the ligand. And if
21 substitutions occur at X, we get gadobenate of
22 MultiHance. If we have substitutions at Y, we get

1 Eovist or gadofosveset of Ablavar.

2 This is the final classification that
3 we've all been talking about this morning. This is
4 a macrocyclic agent. In this case, the only one
5 which is approved, of course, in the United States
6 is ProHance. I won't spend any more time on that at
7 this time.

8 This brings us to the issue of stability.
9 Complex stability is basically defined in terms of
10 an equilibrium reaction which exists between the
11 complex and the components that react to form the
12 complex. And you'll see that it's the position of
13 this equilibrium that determines the stability
14 constant.

15 Now, there are two stability constants
16 that we use. One is thermodynamic. It is the
17 concentration of product to the concentration of
18 the reactants, and we have a conditional stability
19 constant which occurs at pH 7.4. It's determined
20 to see 7.4 and, basically, it is more realistic to
21 what occurs in physiological conditions.

22 Now, the point I wanted to really point

1 out here and what I'm pointing out is that all
2 these constants are very large, the Ks that you see
3 here in this definition. So we usually represent
4 them as log Ks. So a log K of 20 is, for example, a
5 K of one-times-ten-to-the-20th. That is the ratio
6 of the complex to the dissociated products at
7 equilibrium.

8 It's important to remember -- we're going
9 to go to the data. You've already seen this data
10 this morning, the stability in water. The classes
11 that I've just described and you've seen this
12 morning are represented here.

13 The first two, gadoversetamide and
14 gadodiamide are the two nonionic linears and the
15 next four, gadofosveset to gadoexetate, are the
16 ionic complexes, linear, and, of course, the
17 gadoteridol, ProHance, which is the macrocyclic.

18 Now, the important point, I think, in all
19 of this, and we've seen this and we've discussed
20 this quite a bit already this morning, is the fact
21 that all of these data, all of these constants are
22 very large. It's like 10-to-the-16th, 10-to-the-

1 22nd. When you do the calculations, you find out
2 that that really amounts to very small amounts of
3 free gadolinium ion.

4 However, you have to understand that this
5 is in water and that it is the ideal conditions for
6 determining stability constant. Now, this data
7 came from Thomas Frenzel and it's a paper from
8 Bayer. I just want to point that out. We've seen
9 this data before.

10 Now, what happens when we bring it into
11 serum? In this case -- and we've also seen this
12 data this morning, but I'll just go through it very
13 briefly. Here, this represents a 10 millimolar
14 phosphate solution and the linear nonionics rise to
15 the levels that are shown here in this graph.

16 We also have the corresponding drug
17 products, Optimark and Omniscan; a little bit less
18 rapid because of the presence of excess ligand in
19 their formulations. Those acted as scavengers and
20 picked up any free gadoliniums that might be
21 produced reforming the complex.

22 Here we have the linear ionics well down

1 at the bottom of the graph, Magnevist through
2 Eovist, and we have, of course, essentially no
3 generation of gadolinium ion, as represented here
4 on this graph. This graph, again, is taken
5 from a Bayer paper of Thomas Frenzel.

6 I think that the important point here
7 really is that when you move a gadolinium agent
8 from water to an in vivo environment, you really
9 change the environment a great deal. That changes
10 everything. But we don't know whether that really
11 changes the stability constant or whether it's some
12 non-equilibrium collapse of the complex due to some
13 reaction with some component that is in vivo, and
14 then you have loss of gadolinium. And we don't
15 know how that actually occurs, whether that's
16 transmetallation or whether that's trans-
17 complexation. We really don't know whether all of
18 this just occurs with the whole complex itself,
19 because, obviously, there's very much more to a
20 complex than just gadolinium. It has the whole
21 ligand that is attached to it in a very strong type
22 of bonding.

1 Okay. We have some gaps in knowledge.
2 There are differences in the blood composition
3 between renal impaired and normal patients. We
4 don't know what those differences are, but they
5 probably are important. We don't know how the
6 effect of these differences are on dissociation
7 trends seen in normal serum.

8 Basically, what we have is we don't have
9 a lot of data on stability constants except in
10 water and we really need to have them in whole
11 blood from healthy subjects or whole blood or
12 plasma from renally impaired subjects.

13 We don't know what the fate of the
14 complex is during its residence in the body of a
15 renal impaired patient and there's lots of other
16 reaction possibilities that I've just discussed.
17 And due to gaps, these various gaps in knowledge,
18 there are questions that remain on the
19 applicability of current models that are based on
20 stability constants, because those constants are
21 all performed in water and do not really represent
22 realistically what might be going on in vivo.

1 The conclusion I would bring to you would
2 be although there are some inconsistencies in the
3 in vitro data, clearly, there are gaps in knowledge
4 and additional data may be needed to strengthen the
5 hypothesis that there are differential risks which
6 are related to physical-chemical properties and
7 structure of the agents.

8 Thank you.

9 DR. HARRINGTON: Thank you. If I could
10 get the next FDA presenter.

11 DR. CHAI: Good morning. I'm Grace Chai
12 and I'm a drug utilization analyst in the Office of
13 Surveillance and Epidemiology. First, I will
14 provide an outline of the presentation by the
15 Office of Surveillance and Epidemiology, then
16 present the FDA's analysis of the utilization of
17 the gadolinium-based contrast agents.

18 Following my presentation, Dr. Julia Ju
19 will present the FDA's literature review. Dr.
20 James Kaiser will then discuss FDA's analysis of
21 the post-marketing adverse events and will conclude
22 with the FDA summary and conclusions.

1 I will now present the drug utilization
2 analysis of the selected GBCA products from years
3 2005 to 2008.

4 The following is an outline of my
5 presentation. Today, I will present the extent and
6 scope of GBCA product use in terms of sales and use
7 data from data sources available to the FDA. The
8 drug use data will be provided in order to put
9 context for the literature findings and the adverse
10 events to presented later.

11 In this analysis, I will present sales
12 data from IMS and hospital discharge data from
13 Premier. After presenting these results, I will
14 provide the limitations of our findings and
15 conclude with the presentation.

16 First, I will present sales data in order
17 to provide the best estimate of national use.
18 Sales data was obtained from IMS Health, IMS
19 National Sales Perspective. This database provides
20 the amounts in viles and millliliters of drug
21 products sold nationally from the manufacturers to
22 retail and non-retail pharmacy settings.

1 The sales data was obtained as a
2 surrogate for use and estimation of number of doses
3 sold was calculated based upon the sales of the
4 gadolinium products in milliliters. The data of
5 actual use in patients will be presented later on
6 using hospital discharge data.

7 The total sales of the selected
8 gadolinium contrast agents decreased from
9 approximately 8.5 million to approximately 7.7
10 million vials from year 2005 to 2008. The majority
11 of these sales were for Magnevist at approximately
12 3.9 million vials, which represents approximately
13 50 percent of the gadolinium market in year 2008.

14 Omniscan was second in sales, but has
15 decreased from approximately 3.4 to approximately
16 1.5 million vials from year 2006 to year 2008.
17 MultiHance has increased in sales from
18 approximately 98,000 to one million vials from 2005
19 to 2008, while Optimark and ProHance have remained
20 relatively consistent in sales.

21 Understanding that some vials may have
22 multiple administrations, we estimated the number

1 of doses based upon the number of milliliters sold.
2 We calculated the estimated doses sold using the
3 average standard dose of 0.2 mls per kilo, which is
4 equivalent to 0.1 millimoles per kilo from product
5 labeling multiplied by an average adult patient
6 weight of 70 kilos.

7 Trends in the gadolinium in estimated
8 doses were found to be similar to the vial sales
9 trends. In year 2008, Magnevist had the highest
10 number of estimated doses administered at
11 approximately 6 million doses, followed by Omniscan
12 at approximately 2 million, but that has also
13 decreased since year 2006, while MultiHance has
14 increased and Optimark and ProHance have remained
15 relatively consistent.

16 It was found that the majority of sales
17 were sold to the hospital setting. Therefore,
18 additional analysis in this presentation is focused
19 on hospital discharge data. This data is provided
20 as the best estimate of actual use.

21 Premier RX Market Advisor is a large
22 hospital drug utilization database with information

1 from over 590 facilities. However, during this
2 analysis, we discovered that not all of these
3 hospitals reported the use of gadolinium by
4 specific brand. The number of hospitals reporting
5 by brand varied from 101 hospitals in 2005 to 182
6 in 2008.

7 This graph shows the absolute number of
8 inpatient discharges billed for a gadolinium
9 product from years 2005 to 2008 based on the sample
10 of the Premier hospitals. Approximately 55 percent
11 of the discharges were for unspecified brand of
12 gadolinium.

13 However, excluding for the unspecified
14 gadolinium, it was found that the individual
15 product trends were more reflective of the sales
16 data trends, although the proportion of use of
17 Magnevist was much higher in terms of hospital
18 discharges than sales.

19 As mentioned before, the discharge
20 billing of gadolinium varied over time and by
21 facility. In the past, gadolinium may have been
22 billed often under procedure codes such as MRI and

1 not billed separately for gadolinium.

2 When gadolinium was billed for, it was
3 often billed simply as gadolinium, resulting in use
4 data for this unspecified brand of gadolinium.
5 Although more hospitals are billing for specific
6 gadolinium products in recent years, a large
7 proportion of gadolinium billing is still
8 unspecified.

9 Earlier today, you heard utilization data
10 presented by the sponsor which varied in terms of
11 data sources used and reporting metrics, such as
12 number of procedures, number of patients, number of
13 vials sold, and administrations. However, in the
14 last two columns, the number of administrations
15 data was reported for all the products by Bayer
16 from AMR data.

17 This data reflects the trends seen in the
18 overall use of the products, with Magnevist having
19 the highest number of administrations, followed by
20 Omniscan. Unfortunately, the FDA does not have
21 access to all the sources used by the sponsors nor
22 can we validate these sources.

1 Before I conclude, I would like to
2 summarize the limitations of this analysis. Sales
3 data is not a direct estimate of use, but was
4 presented as a surrogate for use. In actual use
5 data, there were inconsistencies in the reporting
6 of inefficient gadolinium use in billing by
7 product-specific gadolinium over time and by
8 facility.

9 In conclusion, despite all these
10 limitations, we have provided the scope of
11 gadolinium use in the U.S. using sales data as the
12 best estimate of national use and inpatient data as
13 the best estimate of actual use in order to provide
14 context for other data to be presented, such as the
15 literature findings and the adverse event reports.

16 Furthermore, it was found that Magnevist
17 had the majority of sales and discharges, followed
18 by Omniscan, which was second in sales and
19 discharges, but has had a decrease in use since
20 year 2006. MultiHance has been increasing in sales
21 and discharges, while the trends in use for
22 Optimark and ProHance have remained relatively

1 consistent.

2 Dr. Julia Ju will now provide the FDA's
3 analysis of the literature findings.

4 DR. HARRINGTON: Thank you.

5 DR. JU: Thank you, Grace. Good
6 afternoon. My name is Julia Ju, from the Office of
7 Surveillance and Epidemiology. Today, I will be
8 presenting the epidemiological literature review of
9 GBCAs and the risk of NSF.

10 The following is my presentation outline.
11 The objective of this review is to evaluate whether
12 there is a differential risk of NSF across GBCAs
13 based on evidence from the literature. The method
14 used for this review will be presented in the next
15 slide.

16 Later, I will focus on the results of
17 estimated prevalence and odds ratio of NSF among
18 GBCAs. A summary of findings will be provided,
19 followed by detailed information from studies that
20 we reviewed. At the end, I will discuss the study
21 limitations and present the conclusions based on
22 the literature findings.

1 Our literature search was conducted in
2 PubMed from year 2000 to November 16, 2009. The
3 following are the keywords used in the literature
4 search. A total of 212 relevant studies were
5 identified. After exclusions, 23 studies with the
6 product-specific NSF prevalence or risk estimates
7 were included in the final review on differential
8 risk.

9 Among them, 10 studies examined and
10 compared the prevalence and the risk of NSF among
11 multiple GBCAs and 13 studies examined a single
12 GBCA product.

13 This slide presents our summary findings
14 of this review. The proportions of multi-agent
15 studies with a higher prevalence or odds ratio of
16 NSF are not equally distributed across GBCAs. Nine
17 out of 12 studies reported that Omniscan was
18 associated with a higher prevalence or odds ratio
19 of NSF than its comparators. In contrast,
20 Magnevist and ProHance were associated with a
21 higher prevalence of NSF in one out of 11 and one
22 out of five studies, respectively. There was only

1 one study on Optimark and ProHance each. Neither
2 of them were associated with a higher prevalence of
3 NSF than its comparators.

4 Since many studies had significant
5 limitations, no firm conclusion can be made to rank
6 other GBCAs for risk of NSF. However, this review
7 identified a potential dose response relationship
8 that will be discussed in more detail later.

9 To illustrate what the literature data
10 looks like and how we interpreted the study
11 results, this slide shows the detailed information
12 from studies with multiple GBCAs in patients with
13 Stage 5 CKD who are at high risk of NSF.

14 Also, in the study design, study period,
15 follow-up time in month, GBCA exposures, GBCA
16 dosages in millimole per kilogram, number of
17 patients exposed, prevalence and odds ratio of NSF
18 were captured in this table.

19 Among those six studies, five studies
20 reported that Omniscan was associated with a higher
21 prevalence and odds ratio for NSF than its
22 comparators. In one study, Magnevist was associated

1 with a higher prevalence of NSF. However, many
2 studies did not provide the confidence intervals
3 for the crude estimates. Therefore, we cannot
4 determine whether the differences in the estimates
5 among comparison groups were significant or not.

6 Our ability to interpret on the use of
7 study results were further constrained by the study
8 limitations. For example, the study period, we
9 notice for this study and this study and this one,
10 too, we see the exposure groups, they have a
11 different exposure period; because NSF awareness
12 increased over time, the different exposure periods
13 may lead to detection bias.

14 We also see that we're actually in the
15 fallout time, which could lead to detection bias,
16 as well, especially that lower, shorter lapse time
17 may leave some NSF cases to be diagnosed
18 afterwards.

19 The dosages were in study by the
20 comparison groups and, also, across studies. We
21 also see some studies did not report the study
22 dosage. We also found many studies to have a very

1 limited sample size, which limited the study power
2 to detect NSF cases.

3 In multi-agent studies, compared to
4 studies in CKD-5 patients that I just presented in
5 the previous slide, a similar trend has been
6 observed in patients with diverse renal functions
7 that include patients with CKD Stage 1 to 5 and
8 some patients with normal renal function.

9 In four out of six studies, Omniscan was
10 associated with a higher prevalence or odds ratio
11 of NSF than its comparators, while MultiHance was
12 associated with a higher prevalence of NSF in one
13 study. We also notice that the prevalence
14 estimates in this patient group are lower than
15 those in the Stage 5 CKD patients.

16 In single-agent studies, for patients
17 with CKD-5, the prevalence estimates ranged from 24
18 percent to 29.6 percent in three studies on
19 Magnevist. There were no NSF cases identified in
20 one ProHance study and the prevalence ranged from
21 0.8 percent to 18 percent in eight studies on
22 Omniscan. And for patients without significant

1 renal insufficiency, no NSF case has been
2 identified in four studies on Omniscan and one
3 study on MultiHance.

4 Now, I will move on to the potential dose
5 response relationship. There is evidence in the
6 literature suggesting that high cumulative dose of
7 GBCAs increases the risk of NSF.

8 One study reported that the prevalence
9 with one exposure to Omniscan was 12 percent and 36
10 percent with two exposures, 25 percent with three
11 exposures, however, noticing that the sample sizes
12 on the three exposures are extremely small.

13 Another study reported a prevalence of
14 2.7 percent for patients with one to two exposures
15 and 4.6 percent for patients with three to four
16 exposures. Compared to a patient without GBCA
17 exposures, one study said that the odds ratio of
18 developing NSF increased from 6.7 for having one
19 exposure to Omniscan to 44.5 for having multiple
20 exposures. And Kallen described that the odds
21 ratio increased in a stepwise fashion from 4.4 for
22 having one exposure to 14.1 for having two to three

1 exposures and 21.5 for having four or more
2 exposures.

3 Besides a high cumulative dose, high
4 single dose for GBCA use may also be associated
5 with higher prevalence of NSF compared to standard
6 dose. In the Prince study, a high dose of Omniscan
7 and the MultiHance use was associated with 0.2
8 percent and 0.6 percent prevalence of NSF.

9 In contrast, no NSF cases were identified
10 in users of standard dose for these two agents.
11 However, for Magnevist and ProHance, no differences
12 in the prevalence of NSF were identified between
13 users of a high single dose and the users of a
14 standard dose.

15 Other observations from the literature,
16 all NSF cases identified in this review have a
17 Stage 4 to 5 CKD or acute renal failure. The
18 latency of NSF development varies from days to
19 years after gadolinium exposure. Besides the
20 indication of MRI use, GBCAs have been used off-
21 label at the higher dose for MRA and MRV, et
22 cetera.

1 The study limitations identified in this
2 review will be summarized in the next several
3 slides. Because the latency of NSF development
4 varies, multiple exposures to different types of
5 GBCAs and observed GBCA exposures beyond the study
6 time or outside the study institution may lead to
7 misclassification bias.

8 It is uncertain which agent caused NSF.
9 Also, the risk estimates may be confounded by the
10 high cumulative dose. As we noted before, many
11 studies had a very small sample size that limited
12 the power to capture cases. It can also result in
13 wild confidence intervals around estimates.
14 Particularly, unequal sample size among comparison
15 groups will require additional interpretation of
16 the study results. Another limitation is that the
17 prevalence and the risk of NSF may be
18 underestimated in the current literature, because
19 some NSF cases may be under-diagnosed, undiagnosed
20 or misdiagnosed.

21 Although the current literature provided
22 some comparison in the prevalence or risk of NSF

1 for several GBCAs, no clinical trials or a single
2 observational study has directly compared the risk
3 of NSF across all five agents that we discussed
4 today.

5 Unfortunately, a quantitative comparison
6 of estimates across studies cannot be done either
7 because of the following reasons. Since the NSF
8 risk varies by patients' renal function, the study
9 results cannot be directly compared unless the
10 study population's renal function is comparable.
11 Because of the potential dose response
12 relationship, studies with unequal or incomplete
13 GBCA dosages may not be directly compared.

14 Lastly, the differences in the study
15 calendar time and the differences in the length of
16 follow-up time may lead to detection bias if the
17 results were compared unadjusted.

18 So in summary, the vulnerable patient
19 group identified in this literature review is
20 consistent with the high risk group classified in
21 the current label for GBCAs.

22 A restriction on high dose and off-label

1 use of GBCAs may be warranted because of the
2 potential dose response relationship. Although
3 this review observed that a larger proportion of
4 the studies reported a higher prevalence or odds
5 ratio of NSF for Omniscan than other GBCAs, future
6 studies, including the post-marketing safety
7 trials, are needed to overcome the limitations and
8 to provide a better picture on the differential
9 risk of NSF. Accordingly, no firm conclusion can
10 be made to rank other GBCAs for risk of NSF based
11 on the current epidemiology literature alone.

12 This concludes my presentation. Thank
13 you. The next presenter is Dr. James Kaiser.

14 DR. HARRINGTON: Thank you, Dr. Ju, for
15 that nice review of the literature. As you said,
16 next is Dr. Kaiser to speak on post-marketing AEs.

17 DR. KAISER: Thank you, Dr. Ju.

18 I'd like to conclude the OSE analysis by
19 discussing post-marketing adverse events reports.
20 For the analyses I present, I would like to
21 acknowledge the help of Allen Brinker and Susan Lu
22 of OSE.

1 Post-marketing adverse events reports are
2 submitted to FDA from various sources, patients,
3 physicians, lawyers, companies. Their primary
4 purpose is to discern rare serious events. Once a
5 product is marketed, it may expose large numbers of
6 patients, who, as a population, are more diverse
7 than the population studied in clinical trials. No
8 cases of NSF were reported in clinical trials. NSF
9 is a rare disease, sometimes with a long latency of
10 development. Without these, post-marketing data
11 are the only clinical data.

12 What I will show you on the next slide is
13 an illustration of when reports came in regarding
14 NSF and dates for these events. This figure is an
15 illustration of when post-marketing reports were
16 submitted to FDA, which is the report date, in
17 orange, and when an event was recorded, which is
18 the event date, through September 3rd, 2009. Not
19 all reports had event dates. This curve, which is
20 the one in blue, represents 59 percent of reports
21 and does not reach the same height as the report
22 dates.

1 The cumulative number of reports of NSF
2 is shown on the Y-axis and calendar years on the X-
3 axis. Since these curves are cumulative, the
4 numbers of reports in a given year are seen as the
5 difference in report counts on the Y-axis between
6 successive plot points.

7 As you can see by the orange curve,
8 reports started coming to FDA in 2006. Seventy
9 reports were received in 2006, 268 in 2007, 557 in
10 2008, and 223 to the date of this analysis in 2009.

11 Even date, shown in blue, may be the date
12 of first administration of a GBCA or the date of
13 receipt of the diagnosis of NSF. No event date was
14 earlier than 1994. The flattening of the curve
15 since 2008 indicates that very few reports with
16 recent event dates are now being received.

17 One hundred and ninety-four event dates
18 of 2006 were recorded, 128 event dates in 2007, 55
19 in 2008, and six in 2009, to the date of this
20 analysis. This probably reflects awareness of the
21 medical community about the potential connection
22 between GBCA administration and NSF and changes in

1 radiologic practice.

2 Numerous NSF adverse events reports were
3 reported to be associated with more than one
4 gadolinium contrast agent, as you've heard before.
5 What this table shows is a summary of reports in
6 which only one brand or chemical name of agent was
7 specified. These cases may have occurred after one
8 or more administrations of that single agent.

9 This table shows, at the top, the various
10 agents and the total numbers of single-agent
11 reports received for each. There were no domestic
12 cases from this analysis associated with ProHance
13 administration, so there is no column for that
14 agent.

15 Data are shown for sex, age and event
16 date. In italics are shown the numbers of reports
17 with those data. The key points to take from this
18 slide are there was no tendency for NSF to affect
19 one sex preferentially. The median age of patients
20 was not remarkably different among the various
21 products. Cases occurred in patients with a wide
22 range of ages.

1 Three, the median event date was somewhat
2 earlier for Omniscan than for Magnevist or
3 Optimark. The meaning of this is unclear, as all
4 of these medians were before changes in practice
5 based on the public health announcements could have
6 occurred. The one case in this series for
7 MultiHance had an event date after the initial PHA.

8 I would like to add an observation
9 regarding renal function about these single-event
10 cases. Narratives of these reports were searched
11 for mention of glomerular filtration rate. There
12 were only four reports, one for Omniscan and three
13 for Magnevist, in which a glomerular filtration
14 rate of greater than or equal to 30 was reported
15 and in only one of these cases was such a GFR 33 to
16 40 reported at the time of administration of a
17 GBCA. Whether this last GFR estimate is precisely
18 correct or not, the point is that the post-
19 marketing analysis was consistent with the
20 literature in showing that most, if not all cases
21 had had severe renal dysfunction.

22 This slide shows a comparison of the

1 numbers of domestic single-agent reports to doses
2 as estimated from sales data shown previously. The
3 single-agent reports were cumulative through
4 September 2009. The estimated doses are from 2005
5 to 2008 from data shown previously by FDA.

6 Precise risk cannot be determined by the
7 data that we have. Post-marketing data are
8 typically underreported and utilization is also
9 frequently and, in this case, only approximate.
10 You can see that the greatest numbers of cases were
11 associated with the top three agents, Omniscan and
12 Magnevist, followed by Optimark. Although there
13 were smaller numbers of single-agent reports
14 associated with Optimark, sales were lower, too.

15 One single-agent case was associated with
16 MultiHance, as I said before, and there were no
17 domestic cases associated with ProHance, although
18 FDA has also received a Swiss case. Information
19 earlier presented by Bracco would only change the
20 numbers for MultiHance and ProHance by one domestic
21 case each.

22 In summary, from 2005 to the present, use

1 of Magnevist was greater than those of the other
2 GBCAs, followed by Omniscan, whose use decreased
3 starting in 2006. Current epidemiological studies
4 in the literature were inadequately designed to
5 provide data to evaluate if the risk of NSF varied
6 across GBCA products. However, the data from these
7 studies do not exclude the possibility of
8 differential risk among these products. The
9 literature also suggests that a high cumulative
10 dose and a high single dose of certain GBCAs may
11 result in a greater risk of NSF.

12 NSF started to be reported to FDA in
13 2006. The numbers of new events have tapered
14 dramatically, probably due to public awareness of
15 the association of NSF with GBCA administration.
16 In conjunction with estimated use data, the risk
17 signals for the development of NSF after
18 administration of Omniscan, Magnevist and Optimark
19 are the highest. The signals for MultiHance and
20 ProHance are low.

21 In conclusion, there is a difference in
22 risk of NSF among the gadolinium-based contrast

1 agents considered in the OSE review. Omniscan,
2 Magnevist and Optimark are associated with the
3 highest risk, while the risk associated with
4 MultiHance and ProHance is low. Finally, we cannot
5 assess the risk of newly approved GBCAs without
6 sufficient post-marketing data.

7 This concludes the presentation. Thank
8 you.

9 DR. HARRINGTON: Thank you.

10 Dr. Kaiser, maybe you could stay there in
11 case -- we have about eight or nine minutes left --
12 if there are questions for you.

13 DR. BURLINGTON: Dr. Kaiser, in terms of
14 your conclusions, you did show us data that
15 indicated the very sparse reporting in the last
16 couple years. So are these conclusions really
17 relevant to practice patterns before the 2006
18 relabeling and educational exercise that went on in
19 conjunction with that?

20 DR. KAISER: I think that there were
21 reports from 2006 through 2008 and I think that you
22 couldn't make very good conclusions based on the

1 recent data. There are just too few reports.

2 DR. HARRINGTON: Let's go to Dr. Morrato,
3 Dr. Fogel, Dr. Kaul, Dr. Krantz, Dr. Wolfe.

4 DR. MORRATO: Thank you. I was also
5 struck by the rapid change or decline in the cases
6 that are being reported over the last couple of
7 years and, in essence, this might represent a
8 natural experiment that's occurring in the market,
9 based on what we're hearing in terms of we've seen
10 changes in treatment patterns, dosing, in practice,
11 contraindications or reduced usage in high risk
12 patients.

13 I'm wondering if the FDA has done any
14 root cause analysis that's really looking at sort
15 of what are practice patterns that are changing in
16 a systematic way as opposed to a more anecdotal
17 way.

18 The reason that I ask that is that we're
19 being asked to, what I might say, institutionalize
20 some of these changes that have been already
21 implemented in practice and we want to make sure we
22 understand what has been happening in a way such

1 that we don't introduce any unintended consequences
2 in actions that we might suggest.

3 DR. KAISER: That's right. I think the
4 data that you saw today from the utilization review
5 analyst and from the epidemiological review was an
6 approximation of an analysis of use -- of practice
7 patterns. We've seen that the use of Omniscan has
8 dropped. Magnevist use has stayed about the same.
9 The use of the other agents has stayed about the
10 same.

11 I don't know, in particular, I don't
12 think that we know, in particular, why the use of
13 Omniscan has dropped. People can draw conclusions
14 from that, but we haven't done a formal analysis of
15 that. And with regard to the epidemiological
16 literature, it shows that there was potentially
17 some use that was above the recommended use.

18 DR. MORRATO: A very quick follow-up. I
19 notice that the literature review focused on PubMed
20 searches.

21 Were there any other data sets? I'm
22 thinking that -- did the EMEA see any other

1 evidence or data that maybe isn't appearing in the
2 PubMed searches?

3 DR. KAISER: Well, I can't address that
4 directly. I could ask Dr. Ju to address that. And
5 as far as the EMEA information, I would have to
6 defer to anybody else who knows about what other
7 sources they may have used. I'm not aware.

8 DR. JU: My name is Julia Ju. In terms
9 of the literature search, PubMed is the only
10 database we have used.

11 DR. HARRINGTON: Dr. Fogel?

12 DR. FOGEL: Yes. We see a lot of data
13 that's being presented in terms of the reports of
14 NSF and then we see a lot of data that's presented
15 in terms of general use throughout the United
16 States and the world. But since nearly all the
17 cases occur in patients with chronic renal failure
18 or low GFRs, I guess the data that we really need
19 is not general use. We need the data on each
20 individual agent for its use in patients with GFRs
21 less than 60.

22 So my question is, is there anything out

1 there that gives us that data, because the general
2 use data is fine and good, but if we're trying to
3 assess the risk in the patient with a GFR less than
4 60, it really doesn't do us very much good.

5 DR. KAISER: I agree with your concern.
6 I would defer to Dr. Chai, but my sense is that
7 those data are not available to us.

8 DR. FOGEL: Dr. Chai?

9 DR. CHAI: The data presented today was
10 the extent of what we have available to us at the
11 FDA. As you can see from the hospital discharge
12 billing data, which was the closest we could get to
13 actual use, that was very spotty. So it'll be even
14 harder to get what you're asking for.

15 DR. HARRINGTON: So we're keeping a list
16 of the recommendations that we might want to make
17 for people going forward. So we'll keep track of
18 that, Dr. Fogel.

19 Sanjay?

20 DR. KAUL: Thank you, Bob.

21 I'm concerned about whether we are
22 trading one risk for another. So perhaps a more

1 systematic approach to estimating competing risks
2 would be informative. And to that extent, what I
3 would like is a breakdown of gadolinium contrast-
4 associated risk of NSF, non-NSF adverse events, and
5 the iodinated contrast-associated adverse events
6 rates.

7 So has that been done? And a follow-up
8 question would be I would like to see a similar
9 temporal trend in the adverse event profile related
10 to the non-NSF risk of these agents. We saw a
11 drop-down in the NSF reports. Was that
12 counterbalanced by an increase in the adverse
13 events? Because as you pointed out, the use of
14 Omniscan has gone down by 20 percent, which may
15 have contributed to the NSF reports going down, but
16 the MultiHance use had gone up by almost a million.

17 Did the risk of non-NSF adverse events go
18 up?

19 DR. HARRINGTON: Sanjay, several of the
20 sponsors made that point about the non-NSF side
21 effects and I have it listed as a topic I want to
22 get to this afternoon. But let's see if FDA has

1 actually done the analysis, which I think would be
2 nicely displayed the way you describe it.

3 DR. BOUCHER: I can answer that question.
4 The FDA hasn't formally done the analysis that Dr.
5 Kaul is thinking of. It would be a very, very
6 exhaustive analysis, as you might imagine, given
7 the range of products that are available, the
8 varying indications, the different populations they
9 would be used in. So we haven't tackled that yet.

10 I would make one observation, though,
11 since this subject came up with gadolinium agents
12 and anaphylaxis. One thing to bear in mind is that
13 the use of these products in patients with severe
14 renal dysfunction represents a fairly small exposed
15 population when you look at the population
16 nationwide.

17 So that should be borne in mind, as well.
18 For instance, for any productd that might be
19 contraindicated, in the way that EMEA has for use
20 in patients with severe chronic kidney disease, the
21 products could still be used in most everybody else
22 in the population. So I think that should be borne

1 in mind when considering this potential unintended
2 consequences of use with the gadolinium agents,
3 which may or may not be associated with less
4 anaphylaxis.

5 DR. HARRINGTON: Sanjay, are you happy
6 with that answer?

7 DR. KAUL: I'd like to see a crude
8 estimate, if feasible.

9 DR. HARRINGTON: So let's go to Dr.
10 Krantz.

11 DR. KRANTZ: Just a quick clarifying
12 question for Dr. Kaiser.

13 What is the case definition for this
14 entity? In other words, were almost all the cases
15 biopsy proven? Did that vary from data set to data
16 set, for example, in AERs versus your legal cases
17 or what have you?

18 DR. KAISER: The case definition was
19 where the case was called nephrogenic systemic
20 fibrosis and one database was used, the AERS
21 database.

22 DR. HARRINGTON: Dr. Wolfe?

1 DR. WOLFE: There seems to be a
2 discrepancy between the data that you showed and, I
3 guess, slide 5, where you use this as a basis for
4 concluding that the three riskiest products are
5 Optimark, Omniscan and Magnevist.

6 DR. KAISER: Can I go back through this
7 and go backwards to mine or does it have to go
8 forward? My slide 5.

9 DR. WOLFE: Your slide 5.

10 DR. KAISER: This one?

11 DR. WOLFE: No. Two more, I think. It's
12 a slide entitled "Domestic Post-Marketing Adverse
13 Events" and you've got single-agent reports. Yes,
14 that's it.

15 Anyway, that, I assume, is the basis for
16 your concluding that the three riskiest products
17 are Omniscan, Magnevist and Optimar.

18 DR. KAISER: That's the basis of the
19 post-marketing part.

20 DR. WOLFE: Right. But based, also, on
21 part-marketing data in, I guess, slide 14 of the
22 Bayer presentation on Magnevist, they have Omniscan

1 and Optimark standing out in both proportional
2 reporting ratio and relative reporting ratio, which
3 are things that the FDA had also concluded. In
4 that analysis, Omniscan and Optimark are way higher
5 in both of those than Magnevist.

6 So I guess the question is, what is the
7 difference? Is it this business of confounded
8 versus nonconfounded?

9 DR. KAISER: Remind me if they were
10 single-agent cases.

11 DR. WOLFE: Pardon?

12 DR. KAISER: Remind me of slide 14.

13 DR. WOLFE: I think the difference is
14 exactly what you're saying. These may be the
15 confounded and yours in this slide are single-
16 agent. But it is a huge difference.

17 DR. KAISER: I'm looking at the Bayer
18 slide.

19 DR. WOLFE: It's on page 14 or on page 7
20 of their presentation.

21 DR. KAISER: I see page 14. Maybe Bayer
22 can help me with this. This is the analysis of

1 single agent reports. We are not attempting to
2 make a precise risk ratio.

3 DR. WOLFE: I understand that, but
4 there's a huge difference between the two sets of
5 data. There were a couple of presentations this
6 morning that seemed to focus on Omniscan and
7 Optimark as being more risky.

8 DR. KAISER: If you're talking about what
9 I take to be slide 14, which is proportional
10 reporting ratios --

11 DR. WOLFE: And relative reporting
12 ratios.

13 DR. KAISER: -- and relative reporting
14 ratios.

15 DR. WOLFE: All those, right.

16 DR. KAISER: We do have our expert in
17 reporting ratios, but I will tell you my
18 understanding of the reporting ratio.

19 The reporting ratio is based on comparing
20 numbers of reports within a product to that same
21 event within other products. It is subject to many
22 assumptions about reports and the numbers of

1 reports that occur that are not NSF. And the
2 reporting ratios are mainly exploratory. They rely
3 on some assumptions and calculations that take you
4 a little bit further from the actual data. So we
5 use them in an exploratory fashion.

6 DR. BOUCHER: If I could add to that,
7 also.

8 DR. WOLFE: Just one quick thing. You
9 had said in the briefing materials that the
10 assumption was that the range of other adverse
11 reports within this category were similar.

12 DR. KAISER: That is true.

13 DR. WOLFE: Therefore, that would
14 diminish the --

15 DR. KAISER: Right. I take your comment
16 seriously, but as far as the other adverse events,
17 yes, you would expect them to be about the same.
18 You would expect them, you wouldn't know for sure.
19 But the other aspects of this in terms of its
20 exploratory nature and comparing events within a
21 product to the same event within other products
22 within an entire database are difficult.

1 DR. HARRINGTON: Jim, are you going to
2 clarify some of the quantitative issues?

3 DR. NEATON: I just wanted to kind of --
4 this was a point I was going to raise, too,
5 related, I think, to Dr. Kaul's question, I think,
6 but maybe you can explain it for us.

7 In the briefing document, when you looked
8 at, on page 15, the relative reporting ratio and
9 the proportional reporting ratio, you come to a
10 little bit different conclusion. And I wonder if
11 this relates to difference in the number of adverse
12 events other than NSF, which are being reported for
13 these products, because you do get a very different
14 picture when you look at this slide, I admit, than
15 when you look at the table in your report.

16 DR. KAISER: The table showing that
17 Omniscan and Optimark are --

18 DR. NEATON: They are clearly different
19 in the table you generated in the report, whereas
20 they separate quite a bit from Magnevist. I wonder
21 if that relates to other adverse events, a
22 differential number of other adverse events which

1 are being reported for these products.

2 If I'm understanding how these statistics
3 are being computed, I think that's the explanation.

4 DR. BOUCHER: I think the other way to
5 look at this, too, if I could comment, is that
6 we're looking at an apples and oranges comparison.
7 So Jim's slide, which is presented here, is single-
8 agent reports and the proportional reporting ratios
9 have to do with all reports.

10 The thing to bear in mind is that a
11 substantial proportion of the reports to FDA
12 include the names of multiple agents. So I think
13 that's why it's a somewhat different analysis. And
14 the goal in looking and doing this review in such a
15 way was that there's no clinical data from clinical
16 trials. So we were trying to look at the data
17 every which way possible and every data stream, and
18 that's why both these things were presented.

19 DR. NEATON: I understood the table in
20 the report. These were single-agent reports, as
21 well. That's the way the table is labeled. This
22 is a single agent. And so, the difference is just

1 in terms of how the statistics are being computed,
2 I believe, what the denominators are.

3 DR. FRANCIS: Well, one thing to keep in
4 mind is that there really is no good denominator
5 for this particular slide. But what we can do is
6 review the table and I can talk with you
7 individually about that.

8 But there is no rate that should be
9 construed from this particular slide. This is just
10 to give you a feel for the number of cases in a
11 particular group of patients, but cannot report a
12 rate. So it's a qualitative feel, but not a
13 quantitative one.

14 DR. NEATON: I know and I think we
15 understand that, except that a conclusion was
16 reached here that was different than the way I
17 would have -- I read the conclusion in the briefing
18 document.

19 DR. KAISER: I would put more stock in
20 the data that we have here than in the data from an
21 exploratory analysis that we presented.

22 DR. HARRINGTON: Okay. Final question

1 before we break for lunch from Dr. Gross.

2 DR. GROSS: I think I see what the
3 problem is. If you look at the Eovist
4 presentation, on page 7, I think it refers to a
5 slide that says page 13. For Optimark, it shows 35
6 cases that are not confounded, and they say that
7 there are more than 2.5 million doses given that
8 are both confounded and not confounded.

9 On this slide, rather than a figure less
10 than 2.5 million, the estimated doses are 4.7
11 million. So I'm not sure which number is correct,
12 but they're both not correct, if you see what I'm
13 saying.

14 DR. HARRINGTON: Yes. There's a
15 discrepancy between the two and only one of them
16 can be correct.

17 DR. GROSS: Right, because by one
18 estimate, the Optimark and Omniscan, as Dr. Wolfe
19 said, looks roughly the same and Magnevist looks as
20 though it has many fewer cases. But on this
21 particular slide, Optimark looks better than
22 Magnevist.

1 DR. KAISER: The perspective that we're
2 trying to show you here is not to determine risk
3 within a factor of one, two or three, but to look
4 at magnitudes of risk. I think the data sets are
5 not conducive to precise risk estimates that go in
6 factors of one, two or three.

7 DR. GROSS: I realize they're not
8 precise, but the magnitude of risk in the two
9 different slides are enormously different.

10 DR. BOUCHER: Well, the denominator is
11 different, as well, because one has to do with
12 administrations, where the other has to do with
13 sales. So there is a significant difference
14 potentially in the denominator.

15 DR. HARRINGTON: So these are the issues
16 we are going to grapple with after lunch. I would
17 like to break until 1:45. Precisely at 1:45, we're
18 going to start the open public hearing. We have a
19 full open public hearing.

20 I'll just remind the committee members
21 that there should be no discussion of the meeting
22 during lunch. There are tables reserved for the

1 committee in the restaurant of the hotel.

2 (Whereupon, at 12:55 p.m., a lunch recess
3 was taken.)

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15 A F T E R N O O N S E S S I O N

16 DR. HARRINGTON: Again, if we can go
17 ahead and take our seats, so we can begin.

18 Why don't we go ahead and begin with the
19 open public hearing? I'm required to read the
20 following remarks.

21 Both the FDA and the public believe in a
22 transparent process for information-gathering and

1 decision-making. To ensure such transparency at
2 the open public hearing of the advisory committee
3 meeting, FDA believes it is important to understand
4 the context of an individual's presentation.

5 For this reason, FDA encourages you, the
6 open public hearing speaker, at the beginning of
7 your written or oral statement, to advise the
8 committee of any financial relationships that you
9 may have with the sponsor or, in this case,
10 sponsors, their products, and, if known, the direct
11 competitors. For example, this financial
12 information may include a sponsor's payment of your
13 travel, lodging or other expenses in connection
14 with your attendance at this meeting.

15 Likewise, FDA encourages you, at the
16 beginning of your statement, to advise the
17 committee if you do not have any such financial
18 relationships. If you choose not to address this
19 issue of financial relationships at the beginning
20 of your statement, it will not preclude you from
21 speaking.

22 The FDA and this committee place great

1 importance in the open public hearing process. The
2 insights and comments provided can help the agency
3 and this committee in the considerations of the
4 issues before us.

5 That said, in many instances and for many
6 topics, there will be a variety of opinions. One
7 of our goals today is for this open public hearing
8 to be conducted in a fair and open way, where every
9 participant is listened to carefully and treated
10 with dignity, courtesy and respect. Therefore,
11 speak only when recognized by the chair. And thank
12 you very much.

13 As just sort of a rule of order, all the
14 speakers have been informed that they have a
15 limited period of time, at which point the
16 microphone will cease to work. So try to get your
17 remarks in in the seven minutes allotted. Thank
18 you.

19 The first speaker is Dr. Kanal.

20 DR. KANAL: I'd like to thank you for the
21 opportunity to be here. I am, as you correctly
22 listed, the chair of the Safety Committee for

1 Magnetic Resonance for the American College of
2 Radiology. But it's important that you recognize I
3 am not here today representing the ACR and this is
4 simply representing myself and my Department of
5 Radiology.

6 Seven minutes and seven requests. The
7 first is cumulative dose -- in no particular order
8 -- cumulative dose issues. The data is pretty
9 overwhelming at this point in the peer-reviewed
10 literature and, as you've heard several times this
11 morning, that NSF incidence and NSF potentially
12 even severity seems to scale with the total dose
13 and perhaps even total lifetime accumulative dose
14 that the patient may have received.

15 Increasing gadolinium concentrations have
16 also been reported in the peer-reviewed literature
17 in biopsy specimens. The patient does not continue
18 to get additional gadolinium doses, and, yet,
19 serially biopsied over time, increasing
20 concentrations of gadolinium have been reported.

21 These are just some of the articles that
22 have documented increasing doses or cumulative

1 doses and the relationship to NSF. So my first
2 request is a recommendation that you consider
3 having the advice that practitioners record,
4 monitor and review the total GBCA dose already
5 administered to patients with significant renal
6 disease before we re-dose them in subsequent
7 studies.

8 Neonates and infants, you will find that
9 in Europe and in other locations, some have
10 provided guidance that these should be precluded or
11 at least we should have warnings or caution about
12 this population.

13 As Dr. Cowper documented this morning,
14 there are no known patients less than six years of
15 age. Thousands, if not more, of neonates and
16 infants have already undergone contrast-enhanced MR
17 studies over the past 20 years for congenital heart
18 disease and many other such indications, with no
19 known cases.

20 We clearly recognize that NSF cannot
21 possibly be a GFR-only issue. We have many
22 patients with low GFR who get high concentration,

1 high doses and don't get NSF. There are certainly
2 other factors we're not yet aware of. It's not
3 just a GFR issue.

4 Also, especially with neonates and
5 infants, I am extremely concerned that we might be
6 inappropriately perhaps sending them to other
7 studies, such as those that may involve ionizing
8 radiation, where the risk in this age group may be
9 even worse than for adults.

10 Therefore, for neonates and infants, the
11 recommendation I would like to ask you to consider
12 is against any special wording or warning for this
13 age group, despite what EMEA might have come up
14 with.

15 In a similar fashion, hepatic disease, I
16 have no idea how this made it to our warnings. We
17 have no cases, as Dr. Cowper, again, reported this
18 morning, of patients without renal disease who have
19 NSF. And yet, you will find in the FDA and in many
20 other locations, they have wording that has warned
21 about patients with hepatic disease or hepatorenal
22 disease. There are no known cases, as I've said,

1 of NSF in patients without renal disease.

2 Furthermore, I grant you that there is a
3 reputation that patients with severe hepatic
4 disease may have labile renal function or
5 dysfunction and acute kidney injury incidents may
6 be high in them. However, in this study from 2007,
7 Dr. Ali was able to point out that, first of all,
8 the incidence of acute renal failure and acute
9 unchronic renal failure was much higher than
10 previously published. But nevertheless, when you
11 look at the co-morbidities, renal disease -- liver
12 disease -- excuse me -- liver disease was a small
13 percentage of all acute kidney failure or acute
14 unchronic patients with renal failure.

15 Therefore, I would suggest that you might
16 consider recommending against any special wording
17 for patients with hepatic disease, per se, and
18 let's stay focused on the ball, which seems to be
19 renal disease.

20 We also have specific GFR and CKD levels
21 that have been discussed to the point where we no
22 longer believe us and the track record from the

1 Food and Drug Agency, we have June 8, 2006, the
2 first public health advisory had against GFRs less
3 than or equal to 15 is what it said.

4 December 22nd, they changed that to be
5 careful if it's less than 60. May 23rd, 2007, be
6 careful if it's less than 30. Now, we do know that
7 the vast majority are in Stage 5. Maybe, ballpark,
8 10 percent or so may be in those that are Stage 4,
9 if not fewer. And there are definitely now
10 confirmed cases in the literature and in the FDA's
11 own databases where biopsy prove even Stage 3.

12 So I think using stages is going to be a
13 bit problematic. Furthermore, they underestimate
14 the amount that are attributable to acute kidney
15 failure, where the GFR is essentially meaningless.
16 The moving target is confusing and the italics is
17 one of the most important take-homes people are
18 going to be concerned that they see. If it's 30 or
19 above, it's okay for me to give them contrast, as
20 I've seen from so many sites.

21 Also, unrelated to NSF entirely,
22 nephrologists are considering redefining Stage 3A

1 and B at this stage, and somewhere about one in
2 five to one in eight of all cases of NSF were in
3 acute kidney failure at the time of administration.
4 So, therefore, I suggest you might consider
5 removing any reference to a specific GFR that
6 suggests or connotes safety above that threshold
7 and perhaps replace it with patients with
8 significant renal disease. Provide the facts to
9 the physicians that are going to be administering
10 these agents and allow them to act as physicians
11 and use their judgment. Also, I would recommend
12 that we continue to increase the emphasis on
13 patients with acute kidney failure, that they be
14 warned.

15 Number five, high dose agents, it's
16 important that you recognize the present labeling
17 is contradictory. The labeling now says that when
18 administering a gadolinium-based agent, don't
19 exceed the recommended dose and allow time for re-
20 administration. But for both Omniscan and
21 ProHance, after 20 or 30 minutes, you're allowed to
22 give double dose additionally, which certainly is

1 not enough time for re-administration. So this is
2 directly contradictory in today's product labeling.
3 So the recommendation is we should work on
4 rewording our labeling.

5 Further, I'd like to ask you something
6 novel and that's that you consider reassessing
7 whether or not we wish to have approval for high
8 dose administration for any of the especially
9 linear agents or the linear nonionic agents.

10 Assume that these agents were being
11 introduced for the first time today to the FDA.
12 Knowing what we know today, would we approve this
13 particular agent for high dose, yes or no? And
14 that's how I'd like to see the labeling be re-
15 approached.

16 Second to last, minimal dosing
17 requirements. It's important to recognize that
18 there have been innumerable references in the
19 literature and throughout the world today that have
20 documented that the dose relationship, which seems
21 so strong with this disease and these drugs, the
22 dose relationship is such that everyone is out

1 there suggesting give as little as necessary to
2 make the diagnosis, even if that's less than
3 standard dose. In fact, to my knowledge, the only
4 agency or individual or group out there
5 internationally today that does not make that as a
6 formal recommendation --

7 [Microphone times out.]

8 DR. HARRINGTON: Thank you very much, Dr.
9 Kanal.

10 Next is Dr. Martin Prince.

11 DR. PRINCE: Thank you very much for this
12 opportunity to address the committee. And I have
13 to say I pretty much agree with everything that Dr.
14 Kanal just said.

15 I think we're all enormously thankful at
16 the effort that the FDA has made to intervene with
17 this entity, to change practice patterns and reach
18 the point now where we've practically eradicated
19 NSF. I want to also disclose that I have financial
20 relationships with all of the companies in this
21 room, and these are my own personal comments, and I
22 paid my own way down to Washington, D.C.

1 Now, NSF warnings, now that NSF has been
2 virtually eliminated, there are still a few cases,
3 but we have to start thinking about the unintended
4 consequences that occur from the warning, such as
5 patients being switched to less accurate tests or
6 unproven tests, tests with other risks, x-ray and
7 nephrotoxicity, patients treated empirically
8 without a diagnosis, and the tendency for NSF risk
9 to trump all other risks in the assessment of what
10 to do in patients. And this excessive focus on NSF
11 has the potential to reduce patient safety.

12 Now, we actually switched, at one of our
13 hospitals, to using an agent that had very few
14 cases of NSF, which was gadobenate dimeglumine, and
15 we thought that we were seeing more adverse events.
16 So we wanted to figure out how to put this in
17 perspective to see, actually, in the big picture,
18 what effect we were having. And I'd like to just
19 share some data on that and I don't really have
20 conclusions.

21 So we looked at the PubMed database for
22 NSF papers, peer-reviewed publications, all biopsy-

1 confirmed cases, where there was sufficient detail
2 about each individual case so that they could all
3 be combined into a spreadsheet, like a meta
4 analysis.

5 We had 80 papers with 292 cases, 64
6 describing the relationship between gadolinium and
7 NSF in 243 patients, for which 220 had a history of
8 gadolinium exposure and, in 23, no exposure to
9 gadolinium was found. And then there were 49
10 mainly published before 2006 that did not even
11 discuss gadolinium.

12 The main risk factor in these papers was
13 dose, with 23 patients receiving standard dose and
14 the overwhelming majority receiving high dose. We
15 tried to look at whether multiple dosing conferred
16 increased risk. And there were 63 cases described
17 as having multiple doses, but in 55 of those, at
18 least one of those multiple doses was a high dose.
19 So we were not able to establish that multiple
20 standard doses seemed to be greater risk than a
21 single dose.

22 Now, the typical presentation, as has

1 been mentioned previously, is a patient on
2 dialysis, 71 percent. Another common presentation
3 of renal transplant patients, 20 percent, and more
4 than half of those were failing renal transplant
5 patients, 12 percent.

6 The gender distribution was equal. About
7 a third had contractions. And this is the key
8 point here. Death was reported in 47 of these
9 cases, but, actually, this patient population has a
10 very short life expectancy, because it's mostly
11 dialysis patients.

12 In these articles, we were able to find
13 evidence death hastened by NSF in two of the cases.
14 And I've heard Shawn Cowper talking about three
15 patients who terminated dialysis early due to the
16 miserable condition of the disease, and so that
17 sort of mirrors what we've discovered.

18 Now, for the death rate of two deaths, we
19 now want to sort of look at what is the death rate
20 from other kinds of adverse events, and to do that,
21 we looked at the AERS database, which sometimes we
22 refer to that as MedWatch, which is available to

1 download from the Web. And we looked only at the
2 U.S. events, excluding NSF/NFD events.

3 Now, there's a lot of criticism of data
4 in the MedWatch database. Because it's self-
5 reported data, sometimes the reporters are not
6 familiar with what agent is being utilized and they
7 report the same agent. There may be duplicate
8 reporting of agents. So it's really not data upon
9 which conclusions can be derived. It's only signal
10 data.

11 You can see the total adverse events are
12 actually, over that five-year period, more than the
13 number of cases of NSF. So non-NSF is more adverse
14 events than NSF. And when we look at the deaths,
15 there are more deaths from non-NSF than from NSF.

16 Now, it's very hard to get sort of a
17 rate, but there are databases that indicate market
18 share and you have to kind of estimate what's the
19 average dose, and you can come up with some
20 estimates, which are certainly not precise. And
21 like I said, it's just signal data.

22 But if we're trying to maximize overall

1 patient safety, it's not clear to me what is the
2 best compound to use in every situation, because we
3 don't yet have enough information about all of the
4 risks. And this data in the MedWatch database
5 suggests that the pattern of NSF risk is different
6 from the pattern of other event risk.

7 Until we figure out a way to combine all
8 that, it's a little tricky to create optimum
9 warnings. Thank you very much.

10 DR. HARRINGTON: Thank you, Dr. Prince.

11 Our next presenter will be on behalf of
12 the Society for Cardiovascular Magnetic Resonance,
13 Dr. Fuisz.

14 DR. FUISZ: Thank you, Committee. I'm
15 here today representing the Society of
16 Cardiovascular Magnetic Resonance and appreciate
17 the opportunity to speak with you. I have no
18 financial adverse reactions to tell you about.

19 [Laughter.]

20 DR. FUISZ: The Society of Cardiovascular
21 Magnetic Resonance, or SCMR, is the recognized
22 representative and advocate for physicians,

1 scientists and technologists who work in the field
2 of cardiovascular magnetic resonance, or CMR.

3 The SCMR, comprised of both cardiologists
4 and radiologists, is the principal independent
5 organization committed to the further development
6 of CMR through education, quality control, research
7 and training.

8 We are pleased to submit the following
9 comments to the FDA as you conduct important
10 discussions concerning gadolinium-based contrast
11 agents. We're a community of dedicated physicians
12 seeking to provide optimal imaging services that
13 are in the best interests of our patients.

14 Changes in practice patterns and cost
15 associated with efforts to understand and prevent
16 nephrogenic systemic fibrosis, or NSF, have
17 enormously impacted our patients. It is
18 encouraging to report the universal observation
19 that the rapid worldwide implementation of changes
20 in the use of GBCAs toward less use in renal
21 failure patients, less use of high dose protocols
22 in all patients, careful selection of GBCA for

1 patients with a GFR or less than 30 mls a minute,
2 and the use of prompt dialysis following GBCA
3 administration in dialysis patients, have resulted
4 in a virtual elimination of new cases of NSF. The
5 actions of the FDA deserve much of the credit for
6 this success.

7 It is also apparent that NSF has not
8 become the pandemic that some initially feared.
9 Deciding how many cases have actually occurred
10 remains complicated because of the variability in
11 defining this disease, the symptoms of which
12 overlap with other clinical conditions that can
13 occur in patients with renal failure.

14 Although the FDA has received reports of
15 1,128 cases and the EMEA, in August, indicated 900
16 cases, the total number of cases reported in the
17 peer-reviewed literature is about 400, plus or
18 minus 50, depending on the diagnostic criteria used
19 and whether or not a biopsy was used for
20 confirmation. The total number reported in the
21 leading registry, the International Center for
22 Nephrogenic Systemic Fibrosis Research, was greater

1 than 335 as of October 25th, 2009.

2 Although not every case is reported,
3 there is a wide spectrum of symptoms and only a
4 handful of deaths attributed to NSF, because,
5 thankfully, only approximately 5 percent of cases
6 have the rapidly progressive or fulminant course.

7 By comparison, approximately 100 patients
8 have died from allergic reactions to GBCAs since
9 their introduction. A number extrapolated from the
10 17 deaths in 45 million GBCA doses reported in
11 Investigative Radiology in 2006.

12 Although all physicians are heartened by
13 the success in containing this debilitating
14 disease, many are concerned that changes in
15 practice patterns toward alternative tests, like
16 catheterization, CT and SPECT imaging expose
17 patients to different, but measurable risks, and
18 that these tests may be significantly less
19 accurate.

20 The substitution of other exams for those
21 requiring GBCA, because of concerns about NSF,
22 raises the question as to whether these patients

1 are ultimately better off. Based on current
2 knowledge, MRI protocols which utilize a maximum of
3 0.1 millimole per kilo seem to have negligible risk
4 of NSF, including for liver disease patients, where
5 the risk appears to have been overstated.

6 The high rate of legal activity
7 surrounding cases of NSF have led to an
8 overemphasis on prevention of NSF, with a possible
9 unintended consequence of steering patients toward
10 riskier tests that have paradoxically less
11 litigation risk in the event of a complication.

12 It is important that any warnings or
13 regulations continue to acknowledge that there may
14 be clinical situations in which the benefit to the
15 patient of using a GBCA greatly exceeds the NSF
16 risk, even if the GFR is less than 30 mls per
17 minute.

18 To the extent that some agents with a
19 favorable safety profile and certain patient
20 classes are available outside the U.S., but not
21 available in the U.S., there is enthusiasm to
22 encourage the FDA to find a way to facilitate

1 bringing these compounds to the U.S. market, while
2 still following the FDA's rigorous safety and
3 efficacy requirements.

4 In addition, there may be MR contrast
5 agents that may not be based upon gadolinium that
6 can substitute for GBCA in those applications that
7 still require high doses, such as MR angiography.

8 Finally, we would like to encourage the
9 FDA to lend its support towards an RFA for NIH-
10 funded research to help resolve the remaining
11 questions surrounding the mechanisms by which NSF
12 occurs, as well as methods for prevention and
13 treatment.

14 I thank you for your consideration.

15 DR. HARRINGTON: Thank you.

16 Our next speaker is on behalf of the
17 Guerbet Group.

18 DR. DESCHE: Good afternoon. My name is
19 Pierre Desche and I am Vice President at Guerbet
20 and the head of Medical and Regulatory Affairs.
21 And together with Dr. Sophie Gaillard, head of Drug
22 Safety, we are going to give you a brief overview

1 of Dotarem.

2 First, a few words about Guerbet. It's
3 an international pharmaceutical company based in
4 Paris and dedicated to medical imaging since the
5 beginning of the last century. Two compounds are
6 approved and marketed in the U.S., Oxilan and
7 Hexabrix, and now we are investigating Dotarem for
8 U.S. markets. Dotarem is the only macrocyclic and
9 ionic gadolinium-based contrast agent. It has been
10 classified as a low risk agent for NSF by the EMEA.

11 Currently, it's in phase 3 clinical
12 studies in the U.S. and we are still actively
13 recruiting for subjects to expedite the clinical
14 studies. Our planning is to have the NDA filing in
15 2012.

16 Dotarem has been marketed internationally
17 since 1989 and it's now available in 65 countries.
18 So far, a total of 50 million doses have been
19 injected and the approved indications of the
20 following: CNS imaging, whole body MRI, and
21 angiography. Dotarem is registered for adult use,
22 as well as children and infants, and the usual dose

1 is 0.1 millimole per kilogram.

2 You have seen this slide so many times
3 this morning. So, again, Dotarem is the only
4 macocyclic and ionic GBCA and is highly stable, as
5 shown by the thermodynamic constant, as well as the
6 very long dissociation of life. And this has been
7 measured in vitro, but, also, in vitro in
8 physiological conditions.

9 Its efficacy and safety have been
10 demonstrated in 41 European studies, confirmed by
11 post-marketing studies in more than 64,000
12 patients. And so far, there is a low and stable
13 reporting rate of adverse reactions in post-
14 marketing settings. This rate is 1.1 for 10,000
15 patients and the most common adverse reactions are
16 those usually observed with contrast agents, either
17 iodinated or gadolinium-based.

18 Regarding the NSF, in the Guerbet
19 pharmacovigilance database, there are no single-
20 agent cases. There are nine multiple-agent cases.
21 One case is still under investigation with many
22 missing information and one case where Dotarem was

1 administered after the disease onset and before the
2 disease worsening. Please remember that so far, 50
3 million doses have been injected.

4 There was also a French academic study
5 performed in nine nephrology centers. The study is
6 called the FINEST study, in more than 300 patients,
7 with a follow-up period of four months. Among
8 them, 234 patients received Dotarem and, among
9 them, 77 percent had severe renal impairment, and
10 no cases of NSF were reported in that study.

11 When we look at the number of single-
12 agent NSF reports and the number of doses injected,
13 it's quite clear that there is a difference between
14 different products and this may be linked to the
15 structure and stability issue, linear versus
16 macrocyclic compounds, nonionic compounds versus
17 ionic compounds.

18 In summary, Dotarem is the only
19 macrocyclic and ionic GBCA. It's well in use
20 outside the U.S., has an excellent safety profile
21 for all patients, including severely renally
22 impaired patients, and I would say, also, in

1 children. And for us, we recommend to not go
2 towards the class labeling. The Guerbet mission is
3 to complete the clinical trials in the U.S. to
4 support a priority FDA review and approval, and we
5 are still actively recruiting subjects for trials.

6 Thank you very much for your attention.

7 DR. HARRINGTON: Thank you very much.

8 DR. ABU-ALFA: Good afternoon. I would
9 like to thank the FDA for the opportunity and
10 privilege to address the committee. My objective
11 today is to present two pieces of work we're
12 involved in at Yale University. One is to present
13 a model for risk of NSF by CKD stage based on the
14 literature reported cases, not the registry, and,
15 also, to present data on our screening at the point
16 of care at the hospital.

17 Our review is done every six months.
18 This letter is from May 2nd, '09, and we update it
19 periodically. I included cases that are biopsy-
20 proven, as stated in the paper. So there are
21 different thresholds for this compared to the
22 registry, but it's taken as is.

1 Many unique cases. Many cases have
2 preceded the association with GBCA, but this is not
3 important for this review, as far as we were
4 concerned. But there are many re-reporting of
5 cases and we did the best we can to identify unique
6 cases.

7 There are a total of 519 cases. About
8 479 are biopsy-proven from 20 countries at the time
9 of the review. Many of them come in large series.
10 We focused on the GFR and the CKD stage for this
11 review. Eighty-one percent were dialysis
12 dependent, very similar numbers to Dr. Cowper's
13 registry data; about 9 percent on peritoneal
14 dialysis, highlighting the potential risk for PD.
15 About 8 percent had CKD. All of them had CKD
16 Stages 4 and 5. And we excluded acute kidney
17 injury estimate of GFR, which should not be in this
18 group. The mean eGFR was 12.2. When it was not
19 provided, it was clearly less than 15 and, in five
20 cases, it was less than 30. Eight cases had
21 unknown stage, but the clinical description
22 suggested a very advanced stage. We contacted the

1 authors and we received partial responses for the
2 exact GFR. Again, it's worth noting that 11
3 percent had acute kidney injury, a very significant
4 group in terms of risk and need to be identified.

5 So NSF does occur in non-dialysis
6 patients. It has occurred in AKI patients, as I
7 mentioned, and mistakenly reported as CKD. So this
8 is something that has been corrected in the
9 literature.

10 Dr. Prince's letter is very helpful in
11 showing that patients who are suffering from acute
12 kidney injury were not dialyzed for two days, with
13 rising creatinine, seems to present the highest
14 risk we have seen so far in the literature.

15 How about CKD Stage 3, which is very
16 important. This is a series of reports that show
17 no cases of NSF in the experience, one from
18 Denmark, one from the treatment HALT trials of
19 polycystic kidney disease. One is an estimated
20 cohort of 600 from South Carolina. About 50
21 patients were deliberately exposed to high dose
22 gadodiamide as part of a CT procedure, not MRI,

1 and, in 168 cases, followed for -- about 100 were
2 followed for about six months, no cases in CKD-3.

3 This is the FDA recent cases of CKD Stage
4 3 from the material made available. I did my best
5 here to summarize them. As you can see, in two
6 cases, or maybe three, there was no data on the GFR
7 at the time of administration and the other two
8 were clustering around 30 GFR. Not all were
9 biopsy-confirmed.

10 So this is what I want to show you as a
11 model of risk. So it has some certain assumptions.
12 Based on the literature review, we seem to see 80
13 percent or so in dialysis versus 8 percent in CKD-4
14 and 5. If we take the highest risk, it's 2.4
15 percent per exposure, or 1 in 42, in ESRD, to
16 represent the true risk. This risk is very hard to
17 find in the literature. It varies anywhere between
18 1 and 2.4 percent. The 2.4 percent comes from the
19 dialysis population in Bridgeport, Connecticut,
20 where the exposures were to gadodiamide and to
21 Magnevist.

22 If we assume the utilization rate of GBCA

1 is the same across all stages, and that's something
2 that may need to be flushed out a little bit more,
3 the higher the use, the less the risk. And if we
4 use the enhanced prevalence data of CKD per stage,
5 we come up with this information that the risk
6 would be, at most, 1 in 900 exposed patients in CKD
7 Stage 4 or 5, not on dialysis.

8 As the cluster of patients is towards a
9 GFR below 15, it's not surprising that we see a
10 significantly higher risk in CKD-5, not on
11 dialysis. This is a particularly high risk
12 population, in my opinion, with a risk of 1 in 218
13 versus CKD-4, the risk is 1 in 2,500 or so.

14 If we assume five cases of CKD Stage 3
15 and we take that as an assumption, the risk will be
16 anywhere between 1 in 700,000 to as low as 1 in
17 137,000 exposed patients. This needs to be placed
18 in the context of contrast-induced injury in this
19 particular population with radiocontrast.

20 I want to switch gears now and talk to
21 you about screening that we have been doing at
22 Yale-New Haven Hospital for the past two years.

1 This is data that was recently published at our
2 scientific meeting and the American Society of
3 Nephrology.

4 We screened about 8,300 patients. I
5 cannot see very well from here, so excuse me if I
6 can't tell the exact numbers. But about half of
7 them get their creatinine checked with a machine
8 called E-Z-EM, which gives you an eGFR at the point
9 of care. About 50 percent ended up getting GBCA.
10 A few slipped through. About 1.8 percent get GBCA
11 without their creatinine documented, but may have
12 been checked.

13 What did we find? Very few people are
14 coming in with CKD. As you can see, out of the
15 4,700 patients, only about 113 had CKD Stages 3, 4
16 or 5, not on dialysis. Not even two dialysis
17 patients showed up during this outpatient
18 experiment. This is not inpatient.

19 All the CKD patients, 4 and 5, knew about
20 the disease on the questionnaire we administered at
21 the point of care, but only 20 percent, as you can
22 see, knew about their CKD when asked at the point

1 of care. So it is not helpful to ask patients do
2 you have kidney disease.

3 When we looked at the multivariate
4 analysis, you could see that the usual factors are
5 showing up, age, diabetes, hypertension, kidney
6 problem, single kidney, as risk factors for
7 identifying CKD.

8 This was, again, mentioned by Dr. Weinreb
9 earlier today. A joint effort within the National
10 Kidney Foundation and the American College of
11 Radiology from 2008, this has not been completed
12 yet. The work is in progress and the
13 recommendations are what have been discussed
14 earlier, so I will skip that.

15 I want to thank all my colleagues. And
16 our symposium is held every May and this year, it
17 will be in New York City. Thank you very much.

18 DR. HARRINGTON: Thank you very much.

19 Our last speaker, Celeste Lee.

20 MS. LEE: Thank you very much for having
21 me, allowing the opportunity to speak with you
22 today in this combined committee.

1 As you can see, my name is Celeste
2 Castillo Lee and I define myself in a myriad of
3 ways, I guess, a myriad of labels. As an advocate,
4 I'm the chair of the National Kidney Foundation's
5 Patient and Family Council. I'm also on the Public
6 Policy Committee for the National Kidney Foundation
7 and for the Carolina Donor Services. I'm also the
8 Chief of Staff of the President and CEO of Duke
9 University Health System. However, today, I'm here
10 to join you as a private citizen, because I'm very,
11 very dedicated to not having anyone else contract
12 NSF, which I have contracted.

13 So why are you all here today? Well,
14 you're here to look at the safety considerations,
15 right? The safety considerations for the FDA to
16 approve gadolinium-based contrast agents with MRI
17 scans, risk factors, exposure to GBCA, what effects
18 are, the eGFR level, the risk-benefit, et cetera.

19 Unfortunately, I'm not going to be
20 helping you with that here today. What I'm here to
21 do is just to humanize for you the 0.4 percent, I
22 think that's the risk, of being exposed to GBCA and

1 contacting NSF, which I have.

2 So let me tell you a little bit about my
3 story, and I'll be brief. January of 2006 is when
4 I had undergone an MRI to check to see if I had a
5 blood clot. In fact, I didn't. It was just scar
6 tissue. But, unfortunately, four days later, I
7 started to get a myriad of symptoms.

8 So let me go back really quickly. My
9 story is long. It's 27 years in the making. I
10 will say it's one filled with many, many benefits,
11 that I received clinical trial drugs and drugs
12 approved by the FDA in their clinical trials and I
13 appreciate that. It has been life-saving.

14 In 1982, when I was 17, I was diagnosed
15 with Wegener's granulomatosis. I had a cadaveric
16 transplant at the age of 21, which worked
17 beautifully for about 10 years, and then I
18 chronically rejected; have been on hemodialysis
19 since 1995 and currently still on dialysis.

20 So let's fast-forward to 2006, as I said,
21 when I was exposed to gadolinium. Four days later,
22 I had swollen ankles and incredible pain, and I

1 can't even tell you the type of bone pain that it
2 was. It was as if it was in a vice.

3 I had bone pain in my legs and the
4 tightening of the skin and it started to progress.
5 It progressed up my calves to my knees, to my
6 thighs. Almost 12-13 hours I could feel it getting
7 higher and higher. I would be crying. I went to
8 my nephrologist. I said, "What's going on? What's
9 happening?" He said, "I don't know, but it's not
10 dialysis related."

11 So then it kept getting higher and higher
12 and it went up to my upper trunk. It was very
13 tight and it was very painful. Finally, I was seen
14 by a dermatologist who did a punch biopsy and said,
15 "I believe you have NSF."

16 I went online and thank God for Dr.
17 Cowper, because he was actually beating the drum
18 back in early 2006, making the correlation between
19 gadolinium, NSF and people with chronic renal
20 disease.

21 At that point, it became my motivation
22 within the NKF to actually ask them to get involved

1 and saying we've got to make sure that no other
2 patient in CKD-4 or 5 is exposed to gadolinium,
3 even if the risk is very small.

4 The thing I find very interesting here is
5 people are talking about death, equivocating death
6 to NSF and the worry about NSF. And I have to tell
7 you, in some instances and then some times of my
8 day, death would be welcome. NSF, out of all the
9 experiences that I've had, is the worst thing I've
10 ever had.

11 It is very painful. It is very
12 debilitating. I actually can walk. I'm here to
13 speak for those 75 percent of us who are in
14 wheelchairs. Contractures is an easy word to say,
15 but until you actually have contractures behind
16 your legs, behind your knees, where you can't move,
17 you can't walk, you are being mummified by masking
18 tape around your legs, it's actually a torture.

19 So I want that to be known, that it's not
20 only death that is the way of not having NSF affect
21 a patient. It's the manmade disability. And what
22 happens when you're exposed to gadolinium with NSF

1 is that it's not like you can get a drug to
2 actually take away the adverse effect. Right?
3 This is a train you get on and once it leaves the
4 station, it's gone. It's an immunological response
5 that there is no treatment, there is no cure, and
6 it is progressive. And so I just want you all to
7 know that.

8 One other thing that I wanted to talk to
9 you about was that, as I said, there are a number
10 of patients who actually are in wheelchairs, who
11 actually have functional kidney transplants, who
12 received -- when they were doing renal mapping or
13 getting worked up for a transplant, were exposed to
14 gadolinium. The irony is they have a beautifully
15 functioning kidney now, yet they're not able to get
16 to the bathroom without being aided by someone else
17 to actually use that kidney.

18 On a lighter note, though, I do want to
19 say that NSF is not my only challenge. I actually
20 live in a house that's divided with Duke and UNC
21 and it is basketball season. So I can handle
22 challenges very well.

1 Again, thank you for this opportunity. I
2 really appreciate being able to let you know. One
3 thing I do have to say is I am so, so happy to hear
4 that it's pretty much accepted that those patients
5 with kidney disease between Stages 4 and 5 are
6 really not being exposed and that you see that
7 trend going right down. I can't tell you how I
8 feel very blessed that that's happening, because I
9 do not want to see another patient get exposed to
10 this disease, if we can help it.

11 Thank you very much.

12 DR. HARRINGTON: Thank you, Ms. Lee.

13 So now I'm required to read the
14 following. The open public hearing portion of this
15 meeting has now concluded and we will no longer
16 take comments from the audience. The committee
17 will now turn its attention to address the task at
18 hand, which is the careful consideration of the
19 data before the committee, as well as considering
20 the public comments.

21 So we now have about two and a half hours
22 to, I think, do a series of things. The FDA has

1 set out three objectives this morning that you
2 heard and they have also provided us two broadly
3 worded questions to help guide our conversation.
4 There will be no voting this afternoon, but the FDA
5 would like to hear all the opinions from the
6 various stakeholders and constituencies represented
7 on this committee this afternoon.

8 I'd like to do the following. First, we
9 have some questions from this morning that sponsors
10 have told us that over lunch they have put together
11 some information and they would like to make that
12 available. So I will ask the Bayer group to speak
13 first. They have some follow-up information on Dr.
14 Paganini's question.

15 Then the GE group will speak second.
16 They have some information on the epidemiology.
17 And then I'll go to the committee for questions,
18 and I believe Dr. Kramer will be first up, since
19 she was waiting before lunch.

20 So why don't we proceed with the Bayer
21 group?

22 DR. PERING: Thank you, Mr. Chairman. We

1 were asked to provide some information whether we
2 have investigated the elimination of Eovist in
3 special populations and I can provide you with
4 information that we, indeed, investigated the
5 pharmacokinetics of Eovist in special populations.
6 Among other, we investigated the use in a group of
7 patients with moderate renal impairment and in a
8 group with end stage renal failure. And we were
9 able to demonstrate that the fraction of the
10 administered dose, which is eliminated by the
11 liver, does increase. It increases only slightly
12 in patients with moderate renal impairment and
13 increases by about 20 percent in patients with end
14 stage renal failure.

15 The sample size is small, but this is the
16 information we were able to provide or collected
17 during the lunch break. And if more details are
18 needed, we'll be happy to provide it after the
19 meeting. Thank you.

20 DR. HARRINGTON: Thank you.

21 Emil, you had asked for this information.
22 Does this provide you some insight? Are there more

1 things you'd like?

2 DR. PAGANINI: No. Basically, I think
3 it's just the obvious that when your kidneys aren't
4 working, you don't put as much out in your urine.
5 That's not what I really asked.

6 Here is the question, I guess. As a
7 nephrologist, we're asked by radiologists
8 frequently, if someone has any type of renal
9 disease, specifically CKD-3 or higher, in many
10 programs, to dialyze these people within an hour or
11 two of exposure to the drug.

12 So I'm not sure that dialysis has
13 anything to do with removing this stuff. I don't
14 know of any data that tells me that this drug is
15 dialyzable, any one of these drugs are dialyzable.

16 So what I asked for were basic concepts
17 of drugs so you can put that information into some
18 sort of a formula to see whether or not it is
19 dialyzable. And the reason why I do this is
20 because a CKD-3 patient exposed to the rigors of
21 dialysis may, in fact, be given a higher risk of
22 faster progression than the risk that's proposed by

1 the drug that they've received.

2 So I'm very concerned that we're sort of
3 doing something that perhaps has not shown any
4 benefit at all and without any data. So I'm asking
5 for data is what I'm doing.

6 I would ask that the FDA, if there is
7 data forthcoming from the group, which is fine,
8 that they get dialyzability of drugs here, because
9 we're talking about longevity exposure of higher
10 doses, half-lives much longer, et cetera, et
11 cetera, et cetera. And if we don't know how this
12 stuff is handled, that's a problem.

13 DR. HARRINGTON: Well, your comment is
14 well taken. I think I noted during the public
15 hearing session that the cardiovascular MRI group
16 actually recommends that -- I think they said that
17 -- that they recommend that certain patients get
18 dialyzed as part of the algorithm to reduce the
19 risk of NSF, and what you're asking for is the data
20 that actually supports that recommendation.

21 Larry, do you have a comment? And then
22 we'll go to Mori.

1 DR. HUNSICKER: Just very briefly. I
2 think that Emil got to where I was at the end of
3 his comment, which is it is clear that there are no
4 data. As the old saying goes, absence of proof
5 doesn't mean proof of absence. We have no idea
6 what the role of dialysis is here and, clearly,
7 there is a good rationale why dialysis might be
8 useful, but we don't know. That should be
9 answered, but we can't answer it today and I think
10 that this should just be put on the shelf as
11 something that's got to be found out in the future.

12 DR. HARRINGTON: Mori? And then I'll go
13 to Jim.

14 DR. KRANTZ: I was just under the
15 impression that dialysis was only given, Emil, to
16 those who were already dialysis-dependent. Is that
17 not the case, then, that this is being used in a
18 more open and widespread manner for those that are
19 not even dialysis-dependent?

20 DR. PAGANINI: Again, this depends on the
21 program and the radiologists that are there. But
22 in our institution, there is a period where they

1 would not perform this therapy unless there was a
2 scheduled dialysis afterwards within an hour or two
3 of giving the drug.

4 I'm not sure how pervasive that is, but
5 I've heard around the country that's pretty common,
6 and there's no real data to support that. And I
7 think in the FDA briefing document, they also
8 mention that there was no data to support dialytic
9 support for removal of drug. So I'm just looking
10 for data.

11 DR. HARRINGTON: FDA, did you want to
12 comment?

13 DR. KREFTING: Yes. Dr. Paganini, I just
14 wanted to confirm your statement. We did say that
15 there was no data.

16 DR. HARRINGTON: Thank you.

17 I'm going to go now and ask the group
18 from GE who wanted to make some comments on
19 questions that Dr. Gross and others were bringing
20 up about discrepancy in incident rates, if I
21 recall.

22 DR. CANTOR: No, you're exactly right.

1 Thank you. I thought, just based upon the previous
2 conversation and what you had asked, this is the
3 information that we can share. And we agree with
4 the discussion that although dialysis,
5 hemodialysis, specifically, will remove Omniscan,
6 there is no evidence that it decreases the
7 incidence of disease or decreases morbidity
8 associated with it, should NSF occur.

9 That being said, we have a
10 pharmacoepidemiologist with us and a public safety
11 expert, Dr. Wendy Stephenson, who wanted to make a
12 couple of comments regarding some of the previous
13 debate before lunch regarding surveillance and
14 epidemiology and some conflicting data.

15 DR. STEPHENSON: Good afternoon. I'm
16 Wendy Stephenson. I'm a consultant in drug safety
17 and epidemiology, and, obviously, today I'm here
18 with GE Healthcare.

19 There was a lot of discussion about one
20 of FDA's slides earlier and I wanted to make a few
21 comments about that in light of the importance of
22 exercising caution and drawing conclusions about

1 relative risk from spontaneous reports.

2 It was slide number 5, I believe, if it's
3 possible to put that up.

4 DR. CANTOR: Not our slide.

5 DR. STEPHENSON: Not our slide. It was
6 FDA's slide.

7 While you're getting that, I think FDA
8 noted that you can't really calculate rates here.
9 Obviously, from spontaneous reports, we're unable
10 to calculate incidence rates in order to get an
11 actual relative risk, because we don't really have
12 a complete numerator and it's often difficult to
13 really know the denominator.

14 In this case, we can't. It really can't
15 even calculate a reporting rate. And the one thing
16 I thought was important to point out was that while
17 the adverse event reports are cumulative, the
18 exposure data is limited to 2005 to 2008. I think
19 that's what might explain the difference between
20 this slide and the slide that Bayer showed, where
21 the exposure was cumulative exposure to each
22 product.

1 So, for example, we know that Omniscan
2 has had over 25 million doses administered. So the
3 older products would not have a complete picture
4 here. So your denominator is really not applicable
5 to your numerator. You can't really calculate a
6 reporting rate.

7 Even if we had the appropriate
8 denominator in terms of overall exposure, I think
9 one of the questions earlier from the panel was
10 alluding to the importance of knowing what the
11 denominator would be in terms of the patients at
12 risk. And that is really the important
13 denominator, since I think everyone would agree
14 that this is an issue for patients with severe
15 renal failure and not an issue for patients with
16 normal renal function.

17 So the appropriate denominator would be
18 patients at risk for NSF. If products are being
19 used differentially in those patients -- so if some
20 products are more likely to be used for MRA, for
21 example, with high doses, then it would not be
22 surprising that you would have more cases for those

1 products than the other products; not because the
2 product itself has a higher risk, but because more
3 patients at risk are being exposed to that
4 particular product.

5 DR. HARRINGTON: Thank you, Dr.
6 Stephenson.

7 Is there a follow-up question? I think,
8 Peter, you and Sid had both brought this up.

9 Does that explanation help you at all?

10 DR. GROSS: Well, before I say yes or no,
11 I need to know the slide that came from Bayer that
12 showed greater than 2.5 million administrations of
13 Optimark.

14 Does that cover the same time period or a
15 longer time period?

16 DR. PERING: The same estimates we used
17 covered the entire time period since the launch of
18 the products. And I pointed out, when talking
19 about the denominators or the usage rates, that
20 there are certain times periods you can look at
21 and, as we've heard, the FDA used a cutoff 2005 to
22 2008.

1 If you look at the entire number of NSF
2 reports, I concur with the colleagues from GE that
3 you need to also look at that respective time
4 period of usage and, in particular, the
5 longstanding agents will have a higher usage rate.
6 But our numbers reflect the total number of
7 administrations since launch based on sales data
8 similar to what the FDA has used.

9 DR. GROSS: So there's still a
10 discrepancy, because the 2.5 million covers a
11 longer time period than the 4.7 million. It
12 doesn't make sense, but I understand the comments
13 about not being able to assess risk. But I'm just
14 talking about that that number still doesn't make
15 sense.

16 DR. HARRINGTON: Sid?

17 DR. WOLFE: I agree with Peter. The
18 point I was raising was that in one analysis,
19 namely, the one Bayer showed, it appeared that both
20 Omniscan and Optimark were way ahead of everything
21 else and in the FDA's analysis, Magnevist came in
22 there. And in their recommendations, they have, in

1 fact, put those three together, similar to what the
2 EMEA did, as the high risk products.

3 DR. HARRINGTON: So that's still an
4 unresolved discrepancy.

5 Dr. Kaiser? Could you go to the
6 microphone?

7 DR. KAISER: I wanted to raise the issue
8 of when most of the cases' event dates were
9 reported to us. And given the fact that there were
10 60 percent of the event dates and not all of them,
11 based on the curve that I showed, most of the cases
12 started to be reported around -- or the event dates
13 were around 2005.

14 So 2005 through 2008 were the lion's
15 share of all the event dates. And I think that it
16 is a disadvantage of the analysis that it didn't
17 include all of the time period for all the agents.
18 But I think if you look at the curve that I showed
19 on dates of event dates, most of the cases occurred
20 during that time period.

21 DR. HARRINGTON: Dr. Kramer, you were
22 going to be up next.

1 DR. KRAMER: Yes. This is a question I
2 had had earlier. When I'm considering the
3 questions the FDA poses, I like to understand
4 actually from FDA what the driver was for you to
5 have this convening of the meeting at this point in
6 time.

7 I know the incidence rate of NSF is --
8 reporting rates are declining and I wondered how
9 much it was driven by EMEA having now a different
10 recommendation. If you could just explain that to
11 us, I think it would help the discussion.

12 DR. RIEVES: Well, as you can tell, we
13 struggled back in 2006 and then, ultimately, in
14 2007 as to the best form of labeling. It was
15 nearly a year after we received reports of NSF that
16 this action took place. So we felt compelled to
17 act relatively promptly there. But it's such a
18 challenge. It's just such a challenge with the
19 post-marketing database, the limitations, coming to
20 some definitive conclusions. We did not want to
21 give inappropriate safety claims, if you will, from
22 misinterpretation of the labeling.

1 At that time, we felt that the data could
2 not rule out some risk for all the agents. So we
3 took that approach of class labeling. But, also,
4 we're very cognizant these are not generic drugs.
5 They're unique. They have differences.

6 In the pharmaceutical world, I think
7 that's very well recognized. In the medical
8 practice world, I'm not so sure it's as readily
9 recognized when we talk about class labeling,
10 because class labeling is very conducive to
11 misinterpretation. It can be interpreted as
12 meaning that FDA is saying the risk is the same for
13 all agents. That's not what we were trying to say.
14 In fact, we spelled out very specifically that the
15 risk may differ, there were limitations within the
16 data set. But at the time we made that labeling
17 change, we knew that the insight would hopefully
18 improve over the subsequent years and we actually
19 started planning this committee even at that time
20 in one form, giving some thought. The actual
21 logistical planning started about a year ago for
22 this committee, actually, to get opinion as to

1 whether or not we've done all that we should.

2 Like you say, Dr. Kramer, we're glad to
3 see that the reports or the events have really
4 seemed to taper off, which we're proud to see that.
5 But still, we want to know have we done enough.

6 As you've heard today, there are many
7 opinions that we have not done enough, in fact. So
8 that's actually where we're coming from. We want
9 to hear. Have we done enough? Should we do more?
10 Any advice for the companies.

11 We have a number of agents actually under
12 development. Such thoughts as should class
13 labeling continue to apply to all these agents;
14 independent perspectives, if you will. So I think
15 you see where we're coming from.

16 DR. HARRINGTON: Judy, does that answer
17 your question?

18 [Dr. Kramer nods affirmatively.]

19 DR. HARRINGTON: Let's go to Dr. Tatum.
20 I'm sorry. Go ahead, Dr. Krefting.

21 DR. KREFTING: I think it's very
22 heartening that, as you just heard from my

1 colleague, that the incidence of NSF has gone down
2 dramatically with the 2006 recommendations. We're
3 all very heartened about that. But one of the
4 major drivers for this committee meeting is the
5 newer agents coming down the road and how we should
6 interpret them. You brought up the issue of the
7 EMEA, another well respected regulatory agency I've
8 heard of.

9 How do we deal with the classification or
10 continuation of class labeling when we don't have
11 post-marketing data? How do we best advise the
12 practicing community in the absence of post-
13 marketing data and with a classification system
14 that may be subject to discussion and further
15 interpretation at bodies like this? So we look to
16 you for all that information.

17 DR. HARRINGTON: Thank you.

18 Let's go to Dr. Tatum.

19 DR. TATUM: So we're heading down the
20 path I wanted to go down, which is the class. The
21 class issue came up several times from
22 presentations, some people wanting class labeling,

1 others, I think, trying to separate themselves from
2 class labeling. It's nuanced enough to talk about
3 class labeling in therapeutics, but this one really
4 gets to be quite interesting.

5 So it would be helpful, I think, number
6 one, to have further discussion from the FDA as to
7 how they actually define class labeling in this
8 particular situation and I think I just heard part
9 of that, because now there's a problem, because
10 clearly you're getting products that don't fit
11 under that classification so easily anymore; and,
12 second, to begin a discussion whether we think this
13 is a class label issue or not.

14 That really goes to Question 1A, to get
15 to that recommendation or whatever this is going to
16 be. So I'd like to start with more clarification
17 on class labeling and what it constitutes.

18 DR. HARRINGTON: You're absolutely right,
19 Dr. Tatum. We are going to have the discussion
20 about class labeling and whether or not there are
21 differential -- the specific question we've been
22 asked is, are there differential risks amongst the

1 agents.

2 Dr. Rieves, do you want to further
3 clarify your comments on what class labeling means
4 to help
5 Dr. Tatum understand that?

6 DR. RIEVES: Well, I can offer a few
7 comments. We've got a number of great folks from
8 the FDA here, so please correct me if I get it
9 wrong.

10 In my mind, class labeling is more of a
11 colloquial regulatory term. I'm not aware of any
12 guidances, any regulations that specifically define
13 class. Now, we have developed the concept of
14 pharmacologic class as part of our new labeling
15 initiative, but the concept of class labeling, I
16 think, has evolved over many, many years in more of
17 a colloquial sort of aspect instead of having a
18 solid regulatory definition, if you will.

19 It integrates not only the pharmacologic
20 class, but, also, some of the clinical
21 considerations; for example, the NSAID, the ACE.
22 The list goes on and on of what might be called

1 class labeling, if you will. So in my mind, it's
2 more of a colloquial type term.

3 DR. HARRINGTON: Other comments from FDA?
4 No.

5 So let's go Susan, then Larry, and then
6 Dr. McGuire.

7 DR. HECKBERT: Yes. I have a question
8 for the FDA regarding this concept of class
9 labeling. I noticed in the handout for Dr.
10 Krefting's presentation, slide 6, the language --
11 and I believe this is part of the label and that's
12 what I wanted you to confirm, that this is part of
13 the label currently.

14 "Where a specific agent was identified,
15 the most commonly reported agent was Omniscan,
16 followed by Magnevist and Optimark. The extent of
17 risk for NSF following exposure to any specific
18 gadolinium-based contrast agent is unknown and may
19 vary among the agents."

20 So is that part of the label and where is
21 it in the label?

22 DR. KREFTING: Yes, you are correct.

1 That was taken directly from the label. It's in
2 the warning section, somewhere in the middle of the
3 paperwork there.

4 DR. HECKBERT: Okay. It's not in the
5 black box, I guess.

6 DR. KREFTING: No. The boxed warning
7 stands for itself at the beginning and that was
8 perhaps the earlier slide.

9 DR. HECKBERT: So even though this is a
10 class warning, we are actually getting some mention
11 of the available data on particular agents, even
12 though it is a class warning.

13 DR. RIEVES: That's exactly right. When
14 we developed this labeling, part of the intent was
15 to just present the data. It is in the label, if
16 one reads the entire label.

17 DR. HARRINGTON: So I think, Susan, one
18 of the places you're going was actually one of Dr.
19 Krefting's second objectives for this meeting,
20 which was if you believe that there is a difference
21 amongst the agents, how best should the FDA
22 communicate that to patients and providers. I

1 think that's the path that you're going down, that
2 perhaps there is inadequacy in the current method
3 of communication if it's in the middle of a lot of
4 other words.

5 DR. HECKBERT: We may be able to improve
6 the way that it's communicated. Actually, I think
7 what it says, though, is quite good. That's what
8 the data are and I don't think, actually, that the
9 data we heard today take us much beyond what it
10 says right here in terms of what the data actually
11 show that we can feel confident about.

12 DR. HARRINGTON: So we're going to be
13 coming back to that.

14 Larry and then Dr. McGuire.

15 DR. HUNSICKER: Well, perhaps I'm going
16 down the same road. What I'm interested from the
17 FDA to hear is what evidentiary standard do you
18 want for what we talk about today. Now, let me put
19 this into a context.

20 I think that there is a reasonable
21 hypothesis that the toxicity of these agents are
22 related to transmetallation. This is quite

1 plausible. It's consistent with the majority of
2 the data. But it is not the level of evidence that
3 would be required for approval of a new agent.

4 I sit on an advisory board where we
5 typically are dealing with approval of new agents
6 and this just wouldn't get anywhere there, and yet
7 we're dealing with a safety issue. And I've never
8 sat on a safety board before, so I don't know quite
9 what the evidentiary standard is or where the FDA
10 should get involved.

11 We know that there are recommendations
12 that have been made by any number of authoritative,
13 well qualified groups that are speaking to their
14 professionals, presumably, I think not
15 communicating, apparently, very well to the public.
16 I'm not sure what the role of the FDA is before
17 there is solid evidence.

18 So that's my question. What's the
19 evidentiary standard?

20 DR. FRANCIS: In terms of determining
21 what are the particular safety signals that we'd
22 need to act on, the standards probably will not be

1 as stringent -- or can be as stringent as they are
2 in the preapproval, because you have a sort of like
3 defined clinical trial in order to get certain
4 parameters you're looking for.

5 In the safety signals, we're looking for
6 rare events to occur in very large populations.
7 And one thing that's been very striking is our
8 experience that a lot of the signals that might
9 represent a significant problem occur in various
10 unusual forms and different ways. So we have to
11 use the best data that's available within a
12 reporting system that's, as you've found, very
13 inaccurate. We have a self-reporting system where
14 we have to define certain kinds of outcomes based
15 on our experience, as well as that of signal
16 detection.

17 So to answer your question specifically,
18 we may not always get the exact answer we want, but
19 one of the reasons we bring the questions to the
20 committee is that the combination of clinical
21 experience and what we see in our reporting
22 systems, the combination of things can get, at

1 best, intelligent estimation of what the risk is
2 and how to act upon it.

3 DR. HUNSICKER: Well, if I am free to ask
4 or to extend this, we already have a black box
5 warning that, so far as we are able to see, has
6 taken care of the problem now. That is to say, the
7 frequency of NSF is very low.

8 So the evidence that we're looking for is
9 not really evidence that we should be recommending
10 against use of something. We seem to have dealt
11 with that. The question is have we overdone it and
12 that seems, to me, to be much closer to the issue.

13 I mean, you could put it this way. I put
14 it down in my comments to myself here, that if you
15 take Dr. Kanal's point that we may have gotten to
16 the point where we are now actually doing the wrong
17 test, because we're not using the best agent in
18 order to delineate the anatomy, or we are using
19 agents which actually have a higher total
20 complication rate, because of our concern for NSF,
21 then what we're really looking at is whether there
22 is evidence that some agents are safer than others.

1 That really is much closer to being like finding a
2 new indication and we don't have the data for that.

3 DR. HARRINGTON: Go ahead, Dr. Rieves,
4 and then Dr. Wolfe.

5 DR. RIEVES: Well, Dr. Hunsicker, that
6 understanding is consistent with my understanding
7 and that's one reason we're here today. You're
8 right. Substantial evidence of efficacy, the
9 evidentiary standard is different compared to the
10 safety considerations.

11 But when one does get into the realm of
12 differential safety, it is tantamount to almost
13 making an efficacy claim. So making that sort of
14 claim is a very important consideration, because
15 it's close to an evidentiary efficacy claim almost.

16 DR. HARRINGTON: Go ahead, Sid.

17 DR. WOLFE: Many people, I guess I'm one
18 of them, think that rather than having a P less
19 than 0.05 to randomized control trials as the
20 standard for efficacy, that, in fact, one needs to
21 be a little more relaxed or safety conscious when
22 you look at safety issues.

1 For example, the addition of a black box
2 warning is often based on a case series where there
3 is no other explanation; sort of this drug looks
4 like there are 50 cases of toxic epidermal
5 necrolysis and it's not any kind of randomized
6 study.

7 Here, one could argue, I suppose, that by
8 doing the class labeling, which is what was done in
9 2006 and 2007, that you may have scared some people
10 away and had them take other diagnostic tests. But
11 I think you could flip that around and say -- which
12 is, I think, the basis of what the EMEA did and
13 later in this discussion, I can read what their
14 advice was to patients two weeks ago when they put
15 this out.

16 But you could almost say that by saying
17 these are the high risk agents and the others are
18 low risk -- or they have three different groups,
19 but let's just say high risk and lower risk, or not
20 high risk, you might be encouraging people who are
21 not at high risk, which is the majority of people
22 getting these drugs, to use those drugs that are

1 not high risk.

2 So I think a problem, in a way, with the
3 class labeling is something that may cause more
4 problems than if you actually distinguish between
5 the drugs as best as you can -- we all agree it's
6 not perfect data -- on the basis of the risk for
7 this small subgroup of patients.

8 These overall figures about people
9 getting anaphylactic reactions or whatever else,
10 most of those people don't have severe kidney
11 disease. The phrase that Britain used, which Dr.
12 Kanal, I'm sure, is happy with, is not GFR under
13 30, it's severe kidney disease.

14 So if you've got severe kidney disease,
15 maybe you should stay away from these drugs, the
16 high risk ones, and go, if you need to have an
17 enhanced MRI, have the other one. So I think that,
18 yes, it's difficult. It's a very different issue
19 in many ways, a little bit the same in terms of
20 efficacy. But I think that by distinguishing in
21 terms of risk, you can actually go in a better
22 direction.

1 DR. HARRINGTON: So let's go to Dr.

2 McGuire, Dr. Fogel, Dr. Nelson.

3 DR. MCGUIRE: Just to take advantage of
4 the microphone, I'm going to make two editorial
5 comments and then ask my question. So first is I'm
6 a little concerned about using words "high risk"
7 and "low risk." These are extremely rare events.
8 So I think we may want to discuss, in the context,
9 putting these in qualitative terms, perhaps "more
10 or less" or "higher or lower" instead of "high
11 risk." "High risk" has the unintended consequence
12 of abandoning the entire procedure, which it has
13 done at our institution, where it is presently
14 impossible to get a contrast MRI in these patients.

15 The second editorial is I share the same
16 concerns voiced by Drs. Neaton and Kaul about the
17 potential power limitations of the plans, as I
18 understand them, in the present ongoing studies
19 assessing this and have some uncertain ethical
20 issues, as well, and that may be food for further
21 conversation.

22 My question is this. I'm struck by the

1 complete absence of data. We're paralyzed here not
2 being able to detect contribution or attribution of
3 individual agents or dosing among the agents. And
4 I'm struck, as a physician, every time I write a
5 prescription, I have to designate an agent, a route
6 and a dose.

7 It strikes me -- and help me understand -
8 - how we're able to administer this intravenous
9 contrast agent without a physician or healthcare
10 provider somewhere documenting in the medical
11 record the agent, the dose and the frequency.

12 I understand this is not a drug, but I've
13 never thought through this process. I just cannot
14 believe that it's possible that hospitals
15 administer these agents without a prescription or
16 order of some sort.

17 DR. HARRINGTON: Well, you've heard,
18 Darren, from I think it was Dr. Kanal, from the
19 American College of Radiology, although he did not
20 he was speaking on behalf of himself, that one of
21 his recommendations was that your comment be
22 actually put forward as a recommendation. I took

1 that to mean that the radiologists acknowledge that
2 they don't do that and that he's asking us to think
3 perhaps about pushing the community to do that. I
4 don't want to speak for Dr. Kanal, but that's how I
5 interpret it.

6 Okay. He's giving me the thumbs-up.

7 So I interpreted his remark right along
8 the line that you said. So I think when we come to
9 the questions, Darren, the FDA has given us two
10 questions that have a sort of series of sub-
11 questions to them, and I've added to my own notes a
12 third question, which is what other data can we
13 recommend that FDA push the sponsors to consider in
14 terms of supporting some of the remarks that we
15 make today. So I share your comment.

16 Did you have another question?

17 DR. MCGUIRE: No. I guess my question
18 is, is this under the FDA purview or is it a DEA
19 issue or is it simply responsible practice driven
20 by societal recommendations, the administration of
21 adjuncts to imaging?

22 DR. FRANCIS: It's a practice of medicine

1 issue. As you recall from all the
2 pharmacovigilance systems, it's based on voluntary
3 reporting and what the companies provide us, and
4 our limitations are based on what information is in
5 there. We don't have the right necessarily to
6 mandate all the things that are required, as you
7 specify. So it's a combination of issues that have
8 to force that issue to fore.

9 DR. HARRINGTON: This gets into issues
10 of, for example, the professional societies making
11 recommendations to their membership and perhaps
12 those recommendations being taken up by people who
13 pay for the tests, that that becomes a quality
14 indicator. So those sorts of things are largely
15 driven by the profession and not driven by the
16 agency.

17 I think we had you next, Mark.

18 DR. FOGEL: I know that we're here to
19 assess the risk of the individual agents, but I'm
20 still struggling with the actual patient population
21 that's reporting NSF. We've heard a lot about
22 patients with chronic kidney disease and low GFRs.

1 I'm not a nephrologist, but I know that
2 there are a lot of reasons why one can have a low
3 GFR. And we really haven't heard anything with
4 regard to the type of chronic kidney disease and
5 are there patients who are at greater risk because
6 of the different types of kidney disease versus
7 not.

8 On the flipside, why don't patients who
9 are neonates get it? Obviously, we've heard that.
10 And these patients have decreased renal function,
11 and yet they apparently appear to be immune.

12 So I guess besides the actual agent
13 itself, I think we need to know a little bit more
14 about the patient population at risk, and I was
15 wondering if there was anybody who had any
16 information regarding the patients who have had
17 NSF, what types of kidney disease they have and is
18 there a preponderance of one type of kidney disease
19 that has the expression of NSF versus others that
20 don't.

21 DR. HARRINGTON: So why don't we
22 start -- we have a couple of nephrologists on the

1 panel to see if they can help us. If not, we can
2 ask the sponsors.

3 DR. HUNSICKER: With respect to chronic
4 kidney disease, I'm not aware of any evidence that
5 suggests that there is a particular population. It
6 is clear that not everybody gets this. You know
7 that the incidence of NSF, even amongst people on
8 dialysis, is certainly less than 20 percent,
9 perhaps less than 10 percent. And so, it's not
10 everybody who gets it, but I don't know of any
11 evidence that says that it's diabetes or
12 glomerulonephritis.

13 The one caution I would make is in your
14 looking at the data about acute kidney failure,
15 please be aware of the fact that a person who has
16 onset today of AKI, acute kidney injury, may have a
17 creatinine of 2 and a GFR of zero. So the
18 creatinine is a remarkably bad measure of kidney
19 function in people with acute kidney injury, and I
20 think that should be put together in your thoughts
21 about this acute kidney injury, which is, clearly,
22 those people have much worse renal function than is

1 apparent from their creatinines.

2 DR. HARRINGTON: I think Dr. Kanal made
3 that point, as well, and hence his comments on
4 significant kidney disease.

5 Emil, do you want to comment on this, on
6 whether you're aware if there's a differentiation
7 amongst the types of chronic kidney diseases?

8 DR. PAGANINI: No. There was a fellow by
9 the name of Roger Rodby out of Rush who did a very
10 nice review of this last year at the American
11 Society of Nephrology, and in his review, he found
12 no predilection with any type of preexisting or
13 existing diagnostic reason for end stage renal
14 disease, glomerulonephritis, diabetes, things like
15 that, PKD disease. None of them were higher or
16 lower in the risk for NSF.

17 I would also like to point out that
18 Larry's comment on acute kidney injury and the use
19 of serum creatinine, especially early on, is very
20 bad. Serum creatinine is really not a very good
21 indicator of GFR in the acute setting.

22 DR. HARRINGTON: So are you and Larry

1 supporting this notion that perhaps focusing on a
2 creatinine clearance or GFR is not appropriate,
3 that labeling should be, more broadly, significant
4 kidney disease? Do you want to comment on that
5 now?

6 DR. PAGANINI: That's a different
7 question. I think the question there is, do folks
8 that have renal dysfunction, are they posing a
9 higher risk, and it would apparently seem that they
10 do. The question is what level are you. So what
11 you do is, over the last four or five years, they
12 threw a series of gradations for GFR and we've
13 heard sponsors saying, "Gee whiz, will you guys
14 settle on a number so we can put it somewhere."
15 Even renal is now sort of varying on numbers.

16 If you do CKD-1 and CKD-2, I think those
17 are garbage numbers, because those are normal
18 people. So that's just to start off. It's sort of
19 like an introduction to a book or something.

20 Then after that, you get into CKD-3, 4
21 and 5 and with 3, now you're hearing an A and a B.
22 So it's a gradation of worsening kidney function

1 based on GFR. Now, GFRs are usually based on
2 creatinines or other issues, and if you get a true
3 GFR, creatinine sort of takes second place.

4 Without belaboring the answer, which I
5 already have, I'd say that severe kidney disease or
6 kidney dysfunction carries a bigger number. If you
7 want more specifics, it would be probably, as far
8 as I'm concerned, 4 and 5, which probably should be
9 restricted as it's currently classified. I don't
10 think 3 should be restricted at all. And as
11 another caveat, I would certainly look at who needs
12 to be dialyzed after these things. Please,
13 children --

14 DR. HARRINGTON: We're going to come back
15 to that.

16 Larry, do you want to ask your question?

17 DR. HUNSICKER: Yes. I think you are
18 asking a slightly different question, which is
19 should we use creatinine or creatinine clearance.
20 Creatinine is a reasonable number to get in order
21 to evaluate the GFR of a person with chronic renal
22 failure. You have to translate it into one of

1 these equations, so that you don't equate the
2 football player with the tea-and-toast lady.

3 What you're really asking is can we get a
4 measure of renal function in a person with acute
5 kidney failure, and you suggested or you at least
6 used the words "creatinine clearance" or other
7 clearance.

8 The problem that you have is, typically,
9 the time at which you want to do your studies is
10 when these people come in acutely ill. You don't
11 want to wait four hours for a study to tell you
12 that the clearance is okay, and even if you did,
13 I'm not sure how good it would be, because to get
14 an accurate measure of clearance, you need some
15 period of time. So I think that it is impractical
16 to try to use a clearance measurement as a gateway
17 to getting an MRI with gadolinium. I think it
18 flies in the face of good medicine.

19 What do you use? The community has had
20 lots of fun trying to decide how we should make a
21 diagnosis of acute kidney injury and we've come up
22 with all sorts of scales and one most recently --

1 what do they call the scale that we use nowadays?

2 DR. HARRINGTON: There's a Rifle score.

3 DR. HUNSICKER: Yes, the Rifle score. A
4 large number of nephrologists who -- the Rifle
5 score comes from nephrology. A batch of
6 nephrologists were asked did they use the Rifle
7 score and it was remarkable that almost none of us
8 did, because they are just really not practical.
9 You've got to look at the patient and you know
10 whether they're in kidney failure or not.

11 DR. HARRINGTON: Mark, before I let you
12 follow up, let me make sure that the other question
13 was answered.

14 Maybe answer Mark's question, Emil or
15 Larry, about why no NSF in the neonates. Is GFR
16 different in neonates? Is there something about
17 the whole neonatal physiology that might be
18 protective?

19 DR. HUNSICKER: The answer to that is
20 empirical. That is to say, gadolinium-based agents
21 have been used in large numbers in pediatric
22 patients and there hasn't been a description of

1 NSF.

2 I haven't the faintest idea why these
3 children, who really do have less GFR per mass of
4 body than we do, why they don't get it. That's not
5 my problem. They just don't seem to get it.

6 DR. HARRINGTON: Mark?

7 DR. FOGEL: Yes, I think it is. But I
8 guess I'm wondering two things. One is if that's
9 the particular case, then in the boxed warning,
10 should there be an exception made, as was suggested
11 in the public comment, in neonates and children who
12 are very young in terms of their NSF risk.

13 Then the other thing I just wanted to
14 mention was if transmetallation is, indeed, the
15 mechanism by which we're hypothesizing this occurs,
16 then, in theory, you would think that patients, for
17 example, with sickle cell disease, who have kidney
18 failure and who have iron overload, you would
19 expect that there would at least be a predominance
20 of those particular patients to have NSF, because
21 you would think that the iron would displace the
22 gadolinium and then give you NSF.

1 So I guess if that's what we're
2 theorizing, that that should be the case, is there
3 a predominance or, I should say, is there a higher
4 than expected number of patients with sickle cell
5 disease, for example, who can get kidney failure or
6 the Phase 3 or higher. Is there a predominance or
7 is there more than expected in those particular
8 patients?

9 DR. KREFTING: I just wanted to speak to
10 the first part of your question and to remind the
11 committee, in general, that in the labeling, the
12 U.S. labeling of these products, they are not
13 indicated for children under two years of age.

14 There are, from some of the sponsors,
15 proposals for pediatric studies in younger
16 children, which are now going through the review
17 process, et cetera. But in terms of USA data,
18 information, general practice of the use of these
19 agents, they're just not indicated in that age
20 group and we don't have all that information.

21 Additionally, as I understand it, the
22 decreased renal function is truly in the real

1 infantile, newly born, neonate phase up to about
2 approximately three months or so. So there is a
3 rapid improvement in renal function. But as I
4 said, all of that data in its use is not U.S.
5 available at this time.

6 I didn't get the other part fully of your
7 question. But I believe there are some warnings in
8 the label concerning use in sickle cell disease,
9 but perhaps not relevant to NSF, in general,
10 though.

11 DR. HUNSICKER: A specific answer to your
12 question is that this is a matter of the absence of
13 proof rather than the proof of absence. I don't
14 think that there are any data whatsoever that talk
15 about the relative prevalence of NSF in people who
16 have renal failure sickle disease.

17 DR. HARRINGTON: We have Dr. Nelson,
18 Dr. Gross, Dr. Tatum, and Dr. Choyke.

19 So let's go with Dr. Nelson.

20 DR. NELSON: Thank you.

21 Just a question for FDA. Again, going
22 back to this class effect issue, my understanding

1 of class effect is that it's typically mechanism-
2 based or maybe, to some extent, structurally-based.
3 Same thing when you think about opioids, for
4 example, working through a typical receptor.

5 Obviously, within the classes of opioids,
6 there are all kinds of safety issues that don't
7 transcend the class, QT in some, and you don't
8 really look at them and classify things that are
9 respiratory depressants as a class, but opioids
10 would fall into that class, but usually it's a
11 therapeutic efficacy issue.

12 So here, we're obviously here to talk
13 about risk. And I guess, from what I understand
14 and where I'm going with this is when you set the
15 warning out in '06 or '07, the intent was to come
16 back and relook at the safety issues. We've
17 accumulated some data. There are a lot of problems
18 with the data, obviously, we've heard about. And
19 you have to act on the data that we have, or not.

20 But I guess what I'm trying to find out
21 is, is the interest at this point in strengthening
22 the warnings if certain drugs look more dangerous

1 or relaxing the warnings and moving some of the
2 members of the class out of the warning for those
3 that appear to be more safe, or is just to stratify
4 within the class and not do either of those? Does
5 that make sense?

6 DR. RIEVES: Yes. Your point is well
7 taken. The initial impetus was to decipher as to
8 whether we've gone far enough in terms of labeling
9 in the recommendation, meaning are there agents
10 that are riskier such that our labeling should be
11 strengthened, if you will, or intensified in some
12 manner.

13 But the other aspects that you're
14 bringing up, have we inappropriately made
15 statements that shouldn't be made statements, are,
16 obviously, on the table. But the initial impetus
17 was have we done enough.

18 DR. HARRINGTON: Dr. Nelson, I think that
19 when you see the questions get posed, we're going
20 to ask if you have an opinion on your own question
21 about whether or not they should be further
22 categorized by risk or by perceived risk.

1 We have Dr. Gross, then Dr. Tatum, then
2 Dr. Choyke.

3 DR. GROSS: Looking over the questions
4 we're going to have to address, it appears as
5 though you want us to make some risk assessment,
6 but we've been told by several speakers don't use
7 these numbers to assess risk or determine relative
8 risk.

9 So how do we answer the questions?

10 DR. HARRINGTON: Your point is well
11 taken. When we get to the questions, the first
12 part of it will be do you believe that there is
13 differential risk and if so, based upon what body
14 of evidence. And you may well say, "I can't
15 determine that there is a differentiation of risk
16 because I don't believe that the evidence is
17 adequate. And one of the reasons the evidence
18 might not be adequate is the discrepancies in the
19 evidence. "

20 That would be a perfectly acceptable
21 answer for the FDA to hear, because that would lead
22 them down a certain path of requiring more clarity

1 in the quality of the evidence. So I think your
2 comment is not a nuance, but is actually an
3 important element of what we're going to talk
4 about.

5 Dr. Tatum?

6 DR. TATUM: Going back to this issue of
7 no data or difficult data, I want to point out, on
8 the other side, because this came up in the risk-
9 benefit thing, there have been statements made that
10 maybe by what we're doing with the safety side,
11 that we may be changing practice in such a way that
12 an inferior type of technique is being used. We
13 don't have any evidentiary data for that either.
14 So you can't do a risk-benefit on that one and go
15 down that particular track.

16 The last question, have we done enough,
17 for the FDA, I think we may broaden that more past
18 the FDA. We don't understand what's going on here.
19 So we have not done enough until we figure out
20 what's going on, because it, as I said earlier
21 today, may be the tip of the iceberg or something
22 else we really need to understand, and that goes to

1 that class effect at the same time.

2 So to get to my last point on data, and
3 I'll ask this, actually, of the sponsors, because I
4 know it's in their vested interest to know this,
5 that they've got it, is there any other biomarker -
6 - let's get past renal function. Maybe it's
7 immunoregulatory or something else. Is there any
8 other biomarker out there that looks like it could
9 be predictive in a research study that anybody has
10 come across or has knowledge of or do we need to go
11 looking for one?

12 DR. HARRINGTON: Are you asking any
13 sponsor in particular?

14 DR. TATUM: Anybody.

15 DR. HARRINGTON: Again, in the fairness
16 of getting everyone involved, next up would be
17 Covidien, if you wanted to answer. Then it would
18 go to Lantheus or then I'll open it up to anybody.
19 I just want to be fair.

20 Okay. The group from Lantheus? No.

21 Any of the sponsors want to take a shot
22 at this?

1 DR. YUCEL: I wish I had the answer to
2 that. But along the lines of perhaps what we, as
3 industry and others, need to do to answer some of
4 these questions, I can let Dr. Ben Newton know
5 where we're going, that may help to answer that
6 question, at least in part.

7 DR. NEWTON: I think one of the major
8 concerns we have, and it's been alluded to several
9 times today, is that a very small minority of
10 patients with end stage disease actually develop
11 NSF. And I think some of the estimates that have
12 been proposed today vary between 1 percent and
13 maybe 6 percent of patients with end stage renal
14 disease develop NSF.

15 So that suggests -- and this is a
16 direction of our research -- that there are other
17 factors -- sorry -- other than the properties of
18 GBCAs -- that are important.

19 In that regard, what we intended to do
20 was to try to bridge the gap between some of these
21 studies on the kinetics, on the stability
22 properties of contrast agents in the case reports.

1 We tried to look at the effect of contrast agents
2 directly on cells.

3 Now, I know these are in vitro studies,
4 but they are human cells and they are cells that we
5 know to be important in the development of
6 fibrosis. So although nephrogenic systemic
7 fibrosis is a comparatively young disease,
8 fibrosis, per se, is well recognized and we do
9 understand the cell types which drive that process.

10 Now, to our surprise, when we did those
11 studies, we found that the gadolinium chelates all
12 appear to stimulate cells and stimulate those cells
13 to induce responses that are reminiscent of
14 nephrogenic systemic fibrosis. So pro-inflammatory
15 cytokines are released and pro-fibrotic mediators
16 are released by those cells, particularly
17 fibroblast monocytes, fibrocytes, and fibroblasts.

18 Now, what is more interesting, and this
19 is the direction that our research is taking, is
20 that not all donor cells actually respond to
21 gadolinium contrast agents. In fact, quite a small
22 proportion of donor cells respond to gadolinium

1 contrast agents.

2 So what we've been able to do is to look
3 at the profile of mediators of the responding
4 cells, and we're now looking at biopsy samples from
5 end stage renal disease patients and we're looking
6 for those same biomarkers that we see being
7 released or regulated in cells that respond. That
8 work is ongoing, but I think it's important to
9 point out that this is important and time-consuming
10 work and it's not completed yet.

11 The interesting point, I should say, that
12 I really wanted to emphasize, is that the
13 gadolinium chelate may be different between
14 products, of course, and the gadolinium chelate may
15 confer different properties, particularly at low pH
16 with respect to thermodynamic stability or kinetic
17 stability at very high pH and so on.

18 Although there are differences in the
19 stabilities in these different conditions,
20 actually, the behavior and effect of these contrast
21 agents is very, very similar across the cells. So
22 the same kind of responses are elicited.

1 So one of the things that we've observed
2 is that gadolinium chelates themselves are
3 bioactive and, in fact, induce an effect within
4 minutes of application, especially at high
5 concentrations. And, of course, does, as we've
6 seen throughout the presentations today, is an
7 important factor in the development of NSF.

8 DR. YUCEL: So I think that the answer to
9 the question is that we hope, in the future, based
10 upon some of these research, that we will identify
11 certain elements that differentiate why certain
12 patients with receiving high dose and certain
13 patients that have renal failure that are exposed
14 to and have all these risk factors, and others that
15 are mentioned, why do only certain ones of them get
16 this disease and there may be genetic differences
17 that we'll be able to elucidate in the future.

18 DR. HARRINGTON: Great.

19 Dr. Choyke?

20 DR. CHOYKE: So the recurrent theme of
21 today has been how bad the available data is. But
22 we have a very compelling piece of information from

1 the fact that a couple years ago, radiologists in
2 the United States decided not to give contrast to
3 patients with end stage renal failure and,
4 remarkably, we have essentially eliminated this
5 disease.

6 So that's very compelling. The data from
7 the chemical composition, from the animal
8 experiments, and from the human experiments show
9 that there are three agents, two or three agents,
10 depending on who you want to talk to, that are
11 definitely associated with risk of NSF. And one of
12 those manufacturers actually voluntarily put in a
13 contraindication to using it.

14 So I think we need to just look at what
15 we've accomplished here by changing the practice
16 patterns so that we're more careful. The practice
17 is way ahead of the label right now and we need to
18 get these two matched up. So I feel I needed to
19 say that.

20 DR. HARRINGTON: We might be able to skip
21 the next hour or so having you just summarized
22 that.

1 Dr. Jones?

2 DR. JONES: Yes. I wanted to echo that.
3 In fact, I think we did the same thing where the
4 alternative is not any longer do a non-contrast MR
5 or do some alternative study. But in practice,
6 what happened is radiologists looked at some data,
7 even though it isn't perfect, the chemistry, and,
8 also, the epidemiologic data and just went ahead
9 and changed their own practice by giving a
10 macrocyclic.

11 I think that maybe we do need to consider
12 that in what we say. That did change and it's not
13 reflected, because, unfortunately, radiologists
14 don't track everything we do. We already heard how
15 we're not too good at documenting exactly which
16 agent, but we're getting better at that. Like all
17 physicians, we're doing better at computerized
18 order entry. And, unfortunately, there isn't
19 really good data from the radiologists on this and
20 there should be in the future. I think we did make
21 that change and we really should try to measure
22 that more so than we have.

1 DR. HARRINGTON: Dr. Kramer?

2 DR. KRAMER: I'm very glad to hear the
3 last two comments, because that's the line that my
4 brain was working in all day. But I would like to
5 point out that those comments really raise this
6 question of what the evidentiary basis is for these
7 sorts of discussions.

8 If you look back, if the FDA had required
9 definitive causal relationship before anything was
10 done back in 2006, we'd be in bad shape right now.
11 And I do think that when we're dealing with safety,
12 we can't wait until there's causative, definitive
13 proof before we act on an accumulation of data.

14 I think that's really what's at hand
15 here, because I do think that we wouldn't be
16 fulfilling our responsibility if we didn't address
17 the question of what about these new agents that
18 aren't -- we're not sure where they fit in this
19 whole pattern. I do think we do need to look at
20 not perfect data, but there's some -- when you put
21 it all together, there is an impression that is
22 different than if you now say is it proof perfect.

1 The other thing is I -- this is my own
2 naivete about what the Division of Imaging can do
3 in terms of controlling the recording of prescribed
4 regulated drugs. But these contrast agents are
5 regulated. You have a label.

6 I was struck by Darren's comment about
7 usually you have to write a prescription and
8 specify the agent. Is it just a practice of
9 medicine issue? Can the agency say, "How can I
10 continue to assess safety of agents if the practice
11 is not to record the agent that was administered?"

12 It seems to me that it is within the
13 purview of the Food and Drug Administration to
14 actually consider the implications of leaving it to
15 the practice of medicine to record what's
16 administered. How can you ever expect to interpret
17 an adverse event report?

18 DR. HARRINGTON: Before I go to FDA, I
19 think Dr. Jones wants to get in here, Dr. Neaton
20 wants to get in here, and then I'll let the FDA
21 maybe give one answer.

22 DR. JONES: Well, it's not just a

1 practice of medicine matter. The Joint Commission
2 reclassified the contrast agents as a drug and so
3 now we are all recording it. Prior to a couple of
4 years ago, that wasn't the case and so people would
5 typically just say MR contrast agent was
6 administered. So now, in practice, everybody is
7 doing that, but we are looking at data back from
8 2005 and before and it wasn't done then.

9 DR. HARRINGTON: Dr. Jones, have the
10 radiologists also taken the step that Dr. Kanal has
11 recommended, which is to keep track of the
12 cumulative dosing, as best one can?

13 DR. JONES: Right. But maybe individual
14 centers are doing that, but I think it would be
15 more useful, because these are infrequent cases,
16 for people to be able to do that on a broader
17 scale.

18 Also, when patients go from hospital to
19 hospital, they don't bring -- they're starting to,
20 but they don't bring all their data and that will
21 be very useful when people keep their own
22 electronic medical records for people to be able to

1 do that, so the next radiologist or physician who
2 is asking for an MR will know whether they had it
3 before.

4 DR. HARRINGTON: It's analogous to the
5 radiation exposure issue.

6 DR. JONES: Yes, exactly.

7 DR. HARRINGTON: Let's go to Dr. Neaton.
8 Then I'll ask the FDA to comment on Dr. Kramer's
9 original question.

10 DR. NEATON: I may be off base here a
11 bit. I was impressed by the observation that the
12 number of cases is so low in the last two years.
13 But isn't this, confounded with dose, potentially
14 changing to a different drug, as well as not
15 scanning people with advanced renal disease? I
16 have not seen any data to sort out what it is
17 today.

18 Then the other point was that relative to
19 the different agents and kind of their different
20 effects -- I don't have to repeat what everybody
21 else has said, that the data is pretty limited, but
22 one thing that I'm concerned about that I heard

1 today that perhaps is not in the warning is the
2 cumulative dose issue.

3 If you have a progressive disease and --
4 and we also heard from the two speakers this
5 morning, both of them, that they're concerned that
6 there are many cases that are diagnosed late, that
7 it's under-diagnosed. I worry that by just
8 singling out a few drugs and not the whole class,
9 we may be kind of putting some people at risk,
10 feeling some comfort that they can get one of the
11 other drugs, by not carefully accounting for the
12 cumulative doses that they've had to date.

13 DR. HARRINGTON: So you're bringing up
14 several issues that others have brought up that,
15 when we go through the specific questions, Jim, I
16 think we're going to get to.

17 Is it the same topic, Dr. Nelson? Okay.

18 DR. NELSON: I was just going to add one
19 other thought. When an adverse effect becomes
20 fairly well known, people stop reporting it. So
21 based on your experiences, just to tag onto Dr.
22 Neaton's question, would this be following that

1 pattern?

2 Nobody reports anaphylaxis to penicillin,
3 because you just don't do it. It just happens. So
4 is this at that stage now that maybe the reporting
5 fell off, not for any other reason than people --
6 it's been so widely publicized, everybody knows
7 about it?

8 DR. HARRINGTON: So two questions for the
9 FDA. One, getting back to Dr. Kramer's about the
10 FDA's oversight of dosing, is there some mechanism
11 by which you can insist upon dose collection. I
12 think that was Judy's question. Then the second,
13 from Dr. Nelson, has to do with is there any sense
14 that there is now an underreporting because people
15 accept this as a rare, but known side effect.

16 DR. FRANCIS: Well, to answer Dr.
17 Kramer's question, the tool that the FDA would use
18 would be the risk management programs, and we have
19 several different ways, using what they call
20 elements of safe use, to balance between not
21 interfering with clinical practice, but make sure
22 that the agent, whatever it is, is being used

1 properly. And now that the comment has been made,
2 we'll take it under advisement of whether that tool
3 should be the appropriate one to use.

4 For the second question from Dr. Nelson,
5 the phenomena of stimulated reported, as you know,
6 has several streams of impact on clinical practice.
7 First, like you've noticed, in 2006, you had the
8 reports coming out of Denmark, and you had this
9 tremendous surge in cases of people being aware of
10 what happened. Even though they may not
11 understand the pathophysiology of what happened,
12 they do know the association.

13 The after-effect is twofold. What we'll
14 see within the pharmacovigilance system is what you
15 saw, sort of like tapering off of reporting,
16 because, okay, we now know what it is, we're not
17 going to report anymore. So, yes, there may be
18 some underreporting, but it doesn't represent
19 necessarily a bad clinical practice, because people
20 are aware of the problem.

21 The second effect is because people are
22 aware of what happened, they're changing their

1 practice. And part of what we saw, without any
2 formal intervention from the FDA, was people saw
3 the association and began changing clinical
4 practice, even though we hadn't made formal
5 announcements of what to do.

6 DR. NELSON: That was Jim's question and
7 my tag onto it.

8 Is there any sense from you which of
9 these phenomenon it might be? Did the number of
10 cases really fall? I mean, based on other similar
11 previous adverse effects that had been reported,
12 that maybe there's been a systems change that has
13 reduced the incidence of disease, or has just
14 reporting fallen off in those cases, which would be
15 more likely reflecting this case?

16 DR. FRANCIS: I think it's a combination
17 of the two. There's no easy way to separate the
18 two and I think it would probably vary in the
19 different drugs that's being announced. In this
20 particular case, I think you had reporting a large
21 response and a very focused clinical response
22 within the practicing community of what needs to be

1 done, because you had a circumscribed side effect.

2 DR. HARRINGTON: Dr. Kramer?

3 DR. KRAMER: I'm not clear on the answer
4 to my question.

5 Are you saying that the only way -- if
6 this has been reclassified as a drug, you're saying
7 the only way that you can regulate whether people
8 actually order a specific drug and dose is through
9 a risk management program? You're saying it can't
10 be a requirement to actually specify when you order
11 it?

12 DR. FRANCIS: I'm not quite sure I
13 understand your question, but at least in terms of
14 --

15 DR. KRAMER: If I understood the comment,
16 the radiologist at the other end of the table
17 specified that these are now considered drugs, not
18 just imaging agents.

19 So my question is, how does it happen
20 that they can be ordered and prescribed in an
21 institutional setting without specification of the
22 agent? And you're saying that the only way to do

1 that is through a risk management program.

2 Isn't it a prescribing issue?

3 DR. FRANCIS: As I understand, the
4 question is, what system would FDA use to assist in
5 that process. There's a couple things going on.

6 DR. KRAMER: No. What regulatory
7 requirement is there, is what I'm asking. I'm
8 talking about literally a regulatory requirement.

9 DR. FRANCIS: The requirement would be
10 that there is identification of a new safety
11 problem, in which case we'd have a number of
12 different responses, by our regulation, which we
13 are allowed to use to address that particular
14 issue.

15 DR. HARRINGTON: Yes?

16 DR. LESAR: Tim Lesar. Just to answer
17 those questions, those are usually regulated by
18 state department of health, as well as specific
19 practice legislation. To answer your question,
20 it's common to see drugs that don't, for instance,
21 go through the pharmacy that are handled strictly
22 by licensed individuals, practitioners, to be

1 ordered and often not recorded. They're not
2 ordered, but obtained and given and not recorded.

3 So I think that answers some of your
4 questions, that it's actually not regulated by the
5 FDA at all. It's either local decisions or
6 required by the Joint Commission, as previously
7 mentioned.

8 DR. HARRINGTON: Dr. Tatum?

9 DR. TATUM: I want to follow-up on
10 Dr. Neaton's comment that had to do with the total
11 dose over time and whether we make it a class or
12 not. I really think that the only way to do this
13 correctly is to have new agents actually get an
14 approval for use in severe renal disease. And
15 that's what I see in the original work for Dotarem
16 that's coming at the same time, which really
17 removes the whole class question at that point,
18 because you have then an indication that clearly
19 defines the population that this is safe to use in
20 and do the study to do that.

21 DR. HARRINGTON: So that may be on that
22 category of what other data this group might

1 recommend.

2 DR. HUNSICKER: I think it's a very
3 different thing for us to recommend to the FDA that
4 they collect some sort of ill-described information
5 on the so-called low risk things to see if that
6 satisfies people or to do what Dr. Tatum has just
7 said, which is we have said already that there is a
8 substantial risk for the use of these agents in
9 patients with advanced renal disease.

10 Now, if somebody wants to propose a new
11 drug application with the appropriate documentation
12 of safety in this group, that's fine. But that's a
13 new drug application, it's not a safety question.

14 DR. HARRINGTON: Agreed.

15 Sid?

16 DR. WOLFE: This is more along the lines
17 of existing post-market studies, which, as you know
18 from our briefing material, the FDA asked all these
19 companies to do post-market studies.

20 Between the comments that were made this
21 morning and some extensive things in the briefing
22 package by GE, the two products, the GE product and

1 Optimark, the other one, both of them are having
2 incredible difficulty recruiting patients for their
3 post-marketing studies. I think the GE one, a lot
4 of the centers decided they didn't want to do the
5 study.

6 So on the question of should a new drug
7 be tested in people with, quote, "severe renal
8 disease," 4 or 5, whatever, and approved, knowing
9 in advance that it's actually safe for those
10 people, I think that's a good idea. I don't think
11 that's really the stuff of what we're talking about
12 today.

13 On the other hand, the fact that in the
14 real world, such as it is, those two, Optimark and
15 Omniscan, are having incredible difficulty
16 recruiting patients says something about at least
17 the perception -- perception, and I think it's
18 based on some data, not perfect data -- that those
19 two products, and, according to Britain, Magnevist,
20 also, are in a high risk group.

21 I keep going back to this issue. The FDA
22 has three times, when we asked them, "Why did you

1 convene this meeting," "to see did we go far
2 enough." I think the answer is we probably didn't
3 go far enough and may have done some deviltry by
4 making it appear that the class is uniform.

5 DR. HARRINGTON: So that is almost the
6 perfect segue into our questions, which are going
7 to ask whether or not there are differences amongst
8 the agents. I think we've had a good discussion,
9 asked a lot of questions.

10 What I'd like to do now is have the panel
11 be able to give the FDA their comments. These are
12 not voting questions today and these are questions
13 where the FDA is looking for thoughts, ideas, what
14 all of you think after having viewed the data and
15 listened to the discussions all day.

16 We have a couple of members who will be
17 leaving a bit earlier, and so you'll have to grant
18 me some leeway in calling on them so that they can
19 make travel plans, et cetera.

20 We're scheduled for a break, but I'm
21 going to skip that in the hopes that we can move
22 along efficiently, but feel free to get up, get

1 some coffee, et cetera, if needed.

2 So the first question. I will go ahead
3 and read the question and then open up the
4 discussion. A lot of this we've done throughout
5 the day, as I think will be clear as I read it.

6 Discuss the strengths and limitations of
7 the presented data, particularly with respect to
8 any differential NSF risk among the gadolinium-
9 based contrast agents, including those with
10 relatively limited post-marketing data.

11 Specifically, what the FDA would like to
12 hear from us is do the available data establish a
13 higher NSF risk for certain agents. So, Sid, this
14 is getting to your last comment. And if so, going
15 into B, identify these agents and provide your
16 train of thought, your basis for those conclusions.

17 Then the question underneath that is,
18 should these high risk agents be contraindicated
19 for patients with severe renal insufficiency? Now,
20 here, they give a GFR. We can have some discussion
21 as to whether or not the comments of Dr. Kanal and
22 others really should be taken into consideration

1 here that GFR not be looked at as the sole measure
2 of renal insufficiency, but there be other
3 terminology considered.

4 So let's open up the first question and,
5 Sid, I'll start with you, since you led us into
6 this.

7 Do you believe that the available data
8 establish a higher NSF risk for certain agents and
9 if so, identify those agents that form that belief
10 for you and give us the train of thought?

11 DR. WOLFE: Well, two years ago, the
12 American College of Radiology essentially said
13 don't use one of these high risk agents, and two
14 years ago, the EMEA did. I just want to read one
15 sentence. I threatened to read this, I'll read it.
16 This is a very nice Q-and-A for patients and
17 doctors issued about 14 days ago by the EMEA. It's
18 sort of what do you do, what's the evaluation.

19 "To minimize the risk of NSF, the
20 committee recommended a number of changes to the
21 prescribing information of these medications,
22 depending on risk classification of the agents."

1 And again, the high risk that they chose were the
2 Optimark, the Omniscan and the Magnevist. They
3 said, "For high risk gadolinium-containing contrast
4 agents, the CHMP recommended that" -- and Dr. Kanal
5 will be happy about this, was happy -- "they must
6 not be used in patients with severe kidney
7 problems, in patients around the time of liver
8 transplantations, and in newborn babies less than
9 four weeks of age or known to have immature
10 kidneys."

11 Then they went on, in terms of other
12 groups of people, the dose should be restricted to
13 the minimum recommended dose in patients with
14 moderate kidney problems, 3 probably, and infants
15 up to one year of age and there should be at least
16 a period of seven days between scans.

17 Anyway, this seems like a reasonable kind
18 of suggestion and one can dispute, which is why
19 both Dr. Gross and I were wondering why there was a
20 difference between the one that said just Optimark
21 and Omniscan are high risk and the one that added
22 on Magnevist, also.

1 But whichever it is, the two or the
2 three, I think they agree, and I think others
3 agree, and we all have already talked about all the
4 imperfections in the data, that those are higher
5 risk than others. And we're talking about a tiny
6 fraction of users of all of these products and
7 we're just simply saying you should stay away if
8 you are in that fraction, severe renal disease,
9 from these products. I think the evidence is
10 enough to do that. Again, it's not the kind of
11 evidence you would need for approving a drug as
12 effective, randomized controlled trials, but it's
13 enough evidence.

14 DR. HARRINGTON: So let me push a little
15 bit before we go on.

16 DR. WOLFE: I don't like to be pushed, I
17 just want you to know.

18 [Laughter.]

19 DR. HARRINGTON: I know you better than
20 that. Two or three agents or are you not willing to
21 put your nickel down on whether it be three or
22 whether it be two?

1 DR. WOLFE: Well, Dr. Gross and I did not
2 get what I would call a satisfactory answer. The
3 FDA's answer was that the 2005 through '09 was okay
4 because most of the cases occurred during that
5 time. But that, of course, punts on the issue of
6 cumulative dose from people who got doses earlier
7 than 2005.

8 So I can't say whether it's two or three,
9 because --

10 DR. HARRINGTON: But in your mind, it's
11 at least two.

12 DR. WOLFE: It's at least two and
13 probably no more than three, because the others
14 pretty much fall away. Indeed, although the EMEA
15 categorized them in middle and low risk, the
16 recommendations are the same for the middle and the
17 low risk. So essentially, it's a dichotomizing,
18 high risk or not high risk.

19 So two or three, the FDA can fight that
20 out, because they really played it, in a sense, two
21 different ways in the briefing package.

22 DR. HARRINGTON: So let me not push you,

1 but ask you one more question.

2 Dr. Kaul and others have raised the
3 question of unintended consequences. By peeling
4 off two or three from the list, do you create a
5 dynamic in the market that suggests that the others
6 are, in fact, safe?

7 DR. WOLFE: Again, as I said before, I
8 think that by making it seem like they're all the
9 same, you may drive more people away. I was
10 looking at this chart on overall deaths and
11 anaphylaxis. I think it was in GE's presentation.

12 The risk of those events is two orders of
13 magnitude smaller than the risk of NSF, assuming
14 that the risk is the prevalence you see in the
15 kidney class 5 patients. It's 1 percent, 2
16 percent, 3 percent. These are 0.04, 0.004 percent,
17 these other events. So that is an offset, but it
18 is, I think, trumped by the NSF.

19 In terms of going to iodine-containing
20 compounds and switching people over to CT scans, I
21 don't know, because there aren't any data, and Dr.
22 Kaul was saying that those data should be

1 available.

2 But I think that we're now three years
3 since the Danish alarm and everything and there's
4 been, it looks like, about a 5 percent decrease in
5 the overall use of these compounds. So it's not
6 like they have fallen by the wayside. They may
7 fall some more, but, again, the fall is -- there's
8 a lot of fall in Omniscan and it looks like there's
9 beginning -- the numbers are too small for a fall
10 in Optimark.

11 So I am concerned about that, but I think
12 that we need to listen to the FDA. Did we go far
13 enough? The answer is no and this is what I think
14 we should be recommending to them.

15 DR. HARRINGTON: Okay. Larry, you had
16 your hand up. Then I'll go over to Dr. Morrato,
17 Dr. Gross, Dr. Kaul, Dr. Kramer.

18 DR. HUNSICKER: Well, I step forward
19 because I guess I'm almost at the other extreme
20 from Dr. Wolfe. And I want to start -- I wrote most
21 of these comments out that I'm going to refer to
22 here before I came, but I've appended them with

1 names as people have made these things so that I
2 don't appear to ignore that other people have made
3 these points.

4 First of all, there appears to be no
5 significant NSF risk for patients without kidney
6 disease or CKD at Stage 3 or less. For other
7 patients, it is likely that non-NSF risks are more
8 important than NSF risks.

9 The issue of relative risk to these
10 agents in other patients should not focus on NSF,
11 as Dr. Kaul said. And the reason I say this here
12 is that we are talking about risky or less risky
13 agents, and I think whenever we say this, we have
14 to put this in the context of less risky or more
15 risky for patients with severe kidney disease. It
16 doesn't relate to anybody else.

17 DR. WOLFE: I agree.

18 DR. HUNSICKER: The second thing is
19 transmetallation release of free gadolinium is, in
20 fact, a hypothesis consistent with the majority of
21 the data, but the data are not of the quality
22 usually needed for an FDA approval. Much of the

1 use of GBCA is technically off label and it would
2 be sort of odd for the FDA to make recommendations
3 about off-label use, and this makes me a little
4 uncomfortable, too.

5 This addresses the question of whether we
6 need to do more, which is why I'm leaping in right
7 now. The incidence of NSF right now is very low.
8 So I would argue the major safety concern now,
9 after the class-based black box warning, is more on
10 the side of not using the GBCAs when the contrast-
11 enhanced MRI would be the optimal approach, as has
12 been suggested by Drs. Prince and Fuisz, and I
13 actually take -- whatever the word is -- take
14 exception with your comment.

15 I think the data for a preference of
16 using gadolinium-based agents for head CT and for
17 spinal cord CT is pretty solid. I'm not a
18 radiologist, but I've been told it is. So you can
19 clarify that.

20 In addition, there is, as reported
21 elsewhere, not up there now, pretty clearly, lower
22 frequency of AEs and SAEs for the gadolinium-based

1 agents in the broad population than there is for
2 the iodinated ones. So we have to keep this
3 thing in proportion. We're talking about only the
4 patients with severe kidney disease.

5 So if, in fact, we have solved the
6 problem, in large measure, by the black box, Mark,
7 warning that's already out there, the major issue
8 before us, as far as I can see, is to determine the
9 safety of agents proposed to be safer with severe
10 kidney disease, and I would like to do that.

11 I'm a nephrologist. I would like to be
12 able to use these agents where they are perhaps
13 preferable to other agents. I don't like to use
14 radiocontrast substances in people with CKD Stage 5
15 who are not yet on dialysis. I'm a kidney doctor.
16 I want to save my patients. But this is, in
17 essence, equivalent to asking for a new indication
18 and that's what I've argued before. And I really
19 don't think that we have the basis for saying
20 anything is safer at this point.

21 So I wouldn't do that. I think that we
22 start with what we have, which has worked, and we

1 challenge the companies that want to suggest that
2 an agent that is perhaps -- I can't remember the
3 names right offhand, but the one that goes around
4 in circles or the ionic agents or whatever -- have
5 to demonstrate to us that they're safer and when
6 they demonstrate that they are safer --

7 DR. WOLFE: The macrocyclic.

8 DR. HUNSICKER: The macrocyclic, there we
9 go. And when they've demonstrated they are safer,
10 then they can come and get a new indication for the
11 use in patients with severe kidney disease. That's
12 the right way to go.

13 In the meantime, I would not want to
14 contraindicate it, because there may well be a
15 patient that I have for whom I am sure that I need
16 to get this information by -- the person just
17 cannot tolerate, for one reason or another, an
18 iodinated contrast material and I need the
19 information, and I'd just as soon not have it be
20 contraindicated in that population. It's clear
21 that it's risky there. We know that.

22 So I have, before I came here, sort of

1 envisioned two approaches that we could use. One
2 would be to leave things as they are now with black
3 box warnings, perhaps with modifications, as
4 suggested by Dr. Kanal, with respect to liver
5 failure in children. I'm not an expert in either
6 liver failure or children, so I'm not going to
7 suggest that that ought to be done, but I think
8 that ought to be reviewed. If in fact there are no
9 data suggesting that children or -- well, you said
10 it's not even approved for the young children. But
11 if there are no data that suggests this is a risk
12 in these populations, that ought not be in our
13 label.

14 Leave to the literature and
15 nongovernmental agencies -- God knows there are
16 enough people telling us how to practice medicine,
17 that the FDA doesn't have to add its opinion to
18 what's coming out from everybody else.

19 The alternative, and this is really off
20 the wall, which probably is going to be flushable
21 out, and that is to take what I've called here a
22 Subpart H type approach. If you believe that we do

1 need to distinguish between the levels of risk --
2 and I would agree that you're talking about the
3 linear nonionic compounds that seem to be the ones
4 probably at higher risk -- you would say that the
5 other agents are lower risk, possibly, in a
6 provisional kind of a thing, saying it appears
7 today -- it's sort of like saying the preponderance
8 of evidence suggests that, but you need to do a
9 trial to prove that.

10 If you're going to say that, then it has
11 to be followed up with hard data at a specified
12 time when you've controlled the trial so we know
13 whether that assumption is correct or not, and
14 that's the approach I'd take.

15 DR. HARRINGTON: So as I'm listening to
16 both of you, I'm actually sensing more agreement
17 than there is disagreement between the two of you,
18 despite the rather vigorous nature of the
19 discussion.

20 DR. HUNSICKER: Well, then, that just
21 means that the dimensions are narrow.

22 DR. HARRINGTON: So what I'm going to

1 throw out are at least two categories for the group
2 to think about and see if you want to add to this.
3 We have one approach from Dr. Wolfe, which is --
4 let me put out what I think you both agree on,
5 which I think are key issues for the committee,
6 first of which, we're talking about patients with
7 significant renal dysfunction. I don't think
8 anybody is disagreeing with that.

9 If anybody disagrees with that, have your
10 piece in a moment. But we're talking about
11 patients with significant renal dysfunction, and I
12 think we're all agreeing that perhaps a focus on
13 GFR alone is not good enough, that the broader
14 phrase probably is worthwhile.

15 DR. HUNSICKER: It's not that GFR is not
16 good enough. That is to say, what I want to be
17 clear about here is a drop in GFR is not the only
18 thing that is wrong with chronic renal disease.
19 But a drop in GFR is, I believe, what we're talking
20 about in terms of the increased risk of the
21 gadolinium-based contrast. But my problem with
22 measuring GFR is the practicalities of trying to

1 get a measurement in a timely fashion when you've
2 got a sick patient.

3 DR. HARRINGTON: Got it.

4 DR. HUNSICKER: I think we are talking
5 about GFR, but we can't ask the FDA.

6 DR. HARRINGTON: So if we all agree that
7 this is something that we're really confining to
8 the population with significant or severe kidney
9 disease, I'll jump to the other end, Larry, that
10 you brought up, which is that we all agree, I
11 think, that the quality of the evidence is not very
12 good to differentiate one agent from another.

13 Dr. Wolfe, though, is willing to take the
14 perspective that at least two, maybe three of the
15 agents, that the evidence is good enough to move
16 them away from the pack. You're a little less
17 certain of that and you're more willing to say that
18 if you really want to be separated from the pack,
19 prove it.

20 DR. TATUM: You've got it.

21 DR. HARRINGTON: Okay. Let's get some
22 other folks in here.

1 Sanjay, I'm going to go to you, because I
2 know that you do have to get on the road. Even
3 though you're not next, I'll go up to you.

4 DR. KAUL: Thank you, Bob. At the risk
5 of repeating what has already been articulated --

6 DR. HARRINGTON: And you don't have to do
7 that.

8 [Laughter.]

9 DR. KAUL: Since I took the time to sort
10 of -- I'm on my third version of my comments here.
11 Someone wise once said that it's hard to make steak
12 out of leather, and that's what we are doing here.

13 The evidence is remarkable for paucity of
14 high quality data to inform this debate, and yet we
15 are often called to draw inferences and make
16 decisions in the face of uncertainty and are
17 drawing upon our expertise, our experiences, and
18 our judgment regarding benefit-risk tradeoffs.

19 So not surprisingly, the results of our
20 decisions are not likely to be satisfactory to all,
21 no matter how well intentioned and diligent the
22 deliberation.

1 So in my opinion, the totality of data
2 drawn from several lines of evidence of varying
3 scientific rigor and quality might suggest the
4 possibility of a differential risk, but this
5 differential risk doesn't appear to be confined to
6 NSF.

7 On one hand, I find the recent decision
8 by one of the sponsors to contraindicate the use of
9 the agent to be a prudent strategy that could
10 potentially merit consideration for other agents at
11 higher than usual risk for NSF. But on the other
12 hand, it's important to understand the entire
13 spectrum of risk and particularly consider the
14 competing risks in assessing the overall benefit-
15 risk balance.

16 I think we will all agree that none of
17 the stakeholders will be well served if all we end
18 up doing is trading one risk for another. So I
19 think that's very important.

20 So my recommendation to the FDA and to
21 the sponsors, collectively, is to adopt a more
22 systematic approach, if possible, in estimating the

1 entire spectrum of risk and provide quantitative or
2 semi-quantitative information regarding competing
3 risks to inform the physician judgment and to guide
4 clinical practice on an individual case-by-case
5 basis.

6 Will we ever be able to do a better job
7 of separating signal from noise? In a way, I think
8 we have become victims of our own success in that
9 as the signal intensity is rapidly declining, it is
10 becoming even more difficult to discriminate it
11 from background noise.

12 Finally, I think it's important to put
13 things in perspective; that while the FDA put out a
14 boxed warning a couple of years ago to restrict the
15 use, the impact on clinical practice has been quite
16 different. Essentially, physicians and practices
17 and hospitals have contraindicated the use of these
18 agents for medical/legal reasons, amongst others.

19 So that's where I'll end. Thank you,
20 Bob.

21 DR. HARRINGTON: Great. Thanks, Sanjay.
22 I'm going to go over to Dr. Krantz, is that's okay,

1 Dr. Choyke, because he is also leaving us.

2 DR. KRANTZ: I'll be real brief. I agree
3 with everything Sanjay said. I think really my
4 only advice to the agency is that sometimes less is
5 more and I'm a big fan of being very declarative in
6 guidelines and in package inserts and other risk
7 mitigation tools. I think in this case, you may
8 end up falling into a trap if you're too
9 declarative in terms of differentiation amongst the
10 agents.

11 DR. HARRINGTON: Thank you, Dr. Krantz.

12 So my lineup right now is Dr. Gross,
13 Dr. Morrato, Drs. Kramer, McGuire and Choyke.

14 DR. GROSS: Okay. Well, our job as
15 committee members is to be comfortable with
16 discomfort and I think that's why the FDA gathers
17 these advisory committees, because the data is
18 never 100 percent clear. Otherwise, they wouldn't
19 need us.

20 So I'm going to agree with Dr. Wolfe and,
21 specifically, I'm going to recommend that Omniscan
22 and Optimark be contraindicated in patients with

1 significant kidney disease, which, in the
2 marketplace, in effect, will probably eliminate the
3 use of those two drugs.

4 I think the data for the others is less
5 compelling. I would be very comfortable with my
6 recommendation if the estimated dose of 4.7 for
7 Optimark turned out to be a typographical error and
8 it, in fact, is 1.7 instead of 4.7. That would
9 make it more consistent with the rest of the data
10 presented.

11 That's all I have to say.

12 DR. HARRINGTON: Thank you, Dr. Gross.

13 Dr. Morrato?

14 DR. MORRATO: I just wanted to say I also
15 concur with Dr. Wolfe's and Dr. Gross'
16 recommendations and just wanted to add the point
17 that in many ways, the market has already acted.
18 You asked the question around the unintended
19 consequences of the change. Optimark has already
20 proceeded with the contraindication. We can phrase
21 the wording such, if it's GFR versus a more generic
22 type of term, but it's already there.

1 In essence, Optiscan has had
2 difficulties, because IRBs and institutions aren't
3 using it in those patients. So I think in many
4 ways, the market has already moved towards that.
5 Large groups of physicians have responded to the
6 data, wrestled with it, and what we'd be
7 recommending here is that the -- I forget who
8 mentioned it -- but the labeling catches up with
9 what is sort of standard of practice.

10 DR. HARRINGTON: Okay.

11 Dr. Kramer?

12 DR. KRAMER: The advantage of waiting is
13 that other people say what you want to say. I
14 agree with what Dr. Gross and Dr. Wolfe have put
15 forward and several others.

16 I have to say that I'm looking at this
17 from a safety standpoint, with a reduced need for
18 evidentiary basis compared to efficacy. I'm
19 thinking about the patient's presentation here.
20 We're trying to prevent probable morbid conditions
21 in patients who have other alternatives. And for
22 that reason, I do think that we should reach out

1 and recognize that the preponderance of all the
2 lines of evidence do seem to indicate that the two
3 agents that have been mentioned have greater risk.

4 I think it's very interesting that the
5 manufacturer of Optimark voluntarily decided to
6 contraindicate it. I did find the nonclinical rat
7 data that was extended out to a year follow-up very
8 compelling in terms of the dose response and the
9 consistency with the transmetallation hypothesis.
10 Everything was really very consistent.

11 I think I'd feel better if those -- given
12 that there were studies conducted by the sponsor,
13 if they were validated by maybe an independent
14 pathologist or something like that. But I think
15 that I put that together with the reduction in
16 incidence that we've already attained by acting
17 quickly on the safety concern, and I think that we
18 should specify Omniscan and Optimark as
19 contraindicated.

20 My impression, at least from several
21 lines, is that Magnevist was -- at least some lines
22 of evidence indicated it wasn't as high risk.

1 Certainly, the disproportionality between it being
2 the most highly prescribed agent in the U.S., but
3 not having as many cases as Omniscan, was one of
4 the things that influenced me.

5 DR. HARRINGTON: Dr. Kramer, let me ask
6 you the same question I asked Dr. Wolfe and that
7 Larry jumped into in terms of answering.

8 How do we prevent the unintended
9 consequence of sending the message that the others
10 are, quote, "safe," end quote? Do you want to be
11 as firm as the comments you heard over here, that
12 if you want to really say that it's safe, it needs
13 to be proven?

14 DR. KRAMER: No. I actually think -- I
15 mean, we do this all the -- I think the FDA does
16 this all the time in labeling. It depends on how
17 you phrase it in the labeling. You can clearly say
18 that it appears there may be some differential risk
19 among these agents, but that there is no evidence
20 that any single agent is completely safe.

21 You can specify that specifically in the
22 label and you can very clearly highlight the other

1 risks in terms of anaphylaxis and things that
2 you're concerned about. I think it depends on how
3 you word it, but we need a communications expert to
4 work with the people who are writing the label.
5 But I don't think that it requires that we don't do
6 what we think is indicated.

7 DR. HARRINGTON: Okay.

8 Dr. McGuire?

9 DR. MCGUIRE: It's clearly complicated
10 decision-making, but I do think there is enough
11 data to differentiate in the product label. And
12 the reason I say that is it's damped harmonic
13 oscillation, where the pendulum has swung,
14 certainly, in my private practice and clinical
15 setting, where we are literally unable presently to
16 get a contrasted MRI scan. There are selected
17 patients where I think the clinical utility of the
18 scan is worth the low risk, acknowledged risk of
19 NSF.

20 Now, I don't equate NSF complications
21 with all these other anaphylactoid reactions and
22 interstitial nephropathy and other things with

1 imaging agents. This is a serious adverse
2 reaction. So I think it does warrant this
3 conversation and this weighted consideration for
4 the risk. But having said that, I think we do need
5 to still have the ability clinically to scan those
6 patients for whom there are no other imaging
7 alternatives available and clinical decision-making
8 is in the balance.

9 So in that regard, I think we have to
10 acknowledge that there is great uncertainty in this
11 field, that based on the best available evidence,
12 as bad as it may be, it does appear that there are
13 differential risks associated with the different
14 agents. Whether they're physical-chemical in
15 nature or other things, we don't have any
16 understanding, but I think the data support some
17 differential exposure risk.

18 So I would advocate considering high risk
19 with Optimark, Omniscan and Magnevist and recommend
20 designating as lower -- and I would avoid the words
21 "high risk" and "low risk." I don't think those
22 are relevant here. I think it's more or less or

1 higher or lower risk, one compared with the other.
2 But we should have the ability to use these agents
3 with caution and with deliberation with regards to
4 any other possible imaging modality available.

5 A couple other comments on that regard.
6 I don't think we have enough data to make any claim
7 about Eovist or Ablavar to date. The exposure just
8 isn't ample and it's been accumulated largely in
9 the context of clinical care, where we've abandoned
10 most of these agents in advanced renal disease. I
11 do advocate the use of a more general terminology
12 for severe renal disease, as we've heard a number
13 of people, as opposed to a specific threshold.

14 Then I will just throw another concept
15 out there that we have used occasionally in
16 cardiology for such cases and the consideration for
17 a recommendation for informed consent specifically
18 for this reason in this high risk population. We
19 have used informed consent for thrombolytic therapy
20 and we have occasionally used informed consent for
21 2b 3 antagonists until their safety was defined.

22 So there is clinical precedent to take a

1 unique patient population and a unique agent and
2 administration with unique, albeit low risk, but
3 very severe risk and specifically apply informed
4 consent in that setting. So at least the patient
5 is negotiating with their physician the risk.

6 DR. HARRINGTON: Darren, let me just ask
7 you. Dr. Wolfe started us off by saying at least
8 two of the agents, maybe three. Dr. Gross, Drs.
9 Kramer, Morrato and others have said that they've
10 specifically listed two of the agents. Now, you've
11 gone and just said three agents.

12 Are you in the Dr. Wolfe camp that it's
13 at least two, maybe three, or are you pretty clear,
14 the evidence is good enough for you to
15 differentiate that the three separate from the
16 pack?

17 It is an issue for the FDA, because they
18 may well decide to list agents differentially as
19 being of higher risk than the others.

20 DR. HUNSICKER: I'm saying that it's
21 probably a dead issue, since I think the third
22 agent, which either might or might not be included,

1 is the one that decided that it was contraindicated
2 anyway.

3 DR. MCGUIRE: No. It's Magnevist that's
4 on the line here. Even if that number is 4.7,
5 there's been a lot of conversation. I think the
6 explanation for that difference -- the 4.7 is
7 accurate. As we've seen, I don't remember the
8 slide, but it was in the OSE presentation, the
9 cases were reported 2005 to 2008, but there's that
10 long left-skewed tail of cases and the incidence of
11 the cases.

12 So there were a lot of cases reported
13 retrospectively that occurred in the preceding
14 probably 10 years, and probably the difference
15 between those two numbers, 2.7 and 4.7, is that 10-
16 year differential in time.

17 So I think the 4.7 number is accurate and
18 by that, that means the point estimate, if you can
19 make any kind of qualitative point estimate, is
20 lower than we would have been led to believe if it
21 was actually 2.7.

22 Despite that, I think the absolute signal

1 of risk and the severity of this risk in the
2 presence of at least two agents that really have
3 very little signal, if any, with, arguably,
4 somewhere between one and four total cases
5 reported, justifies, in my mind, the separation and
6 including Magnevist in the higher. I'm not
7 going to call it high risk, but I would call it
8 higher than ProHance and MultiHance.

9 DR. HARRINGTON: So more along the lines
10 specifically of what EMEA said.

11 DR. MCGUIRE: Partitioning into two
12 instead of three groups, yes.

13 DR. HARRINGTON: Okay. We've got Dr.
14 Choyke next and then we've got Dr. Paganini, Dr.
15 Nelson, Dr. Heckbert, and we'll go down here, as
16 well.

17 DR. CHOYKE: I'm in favor of limiting --
18 like Dr. Wolfe's team. I'm on Dr. Wolfe's team.
19 But their concern on the other side that endorsing
20 these -- in a sense, we're endorsing the other
21 agents by prohibiting the three or two.

22 I think it's really important, a critical

1 teaching point, that caution needs to be exercised
2 when using any gadolinium compound in end stage
3 renal disease. That just has to be the first line
4 of anything and then you can move on.

5 In terms of the problem of unintended
6 consequences that Dr. Kaul spoke to, it's been
7 absolutely remarkable that the concern over
8 gadolinium agents has led to technological
9 improvements that don't require contrast agents in
10 many people.

11 Dr. Weinreb showed examples of MRA that
12 don't require gadolinium. In fact, the unintended
13 consequences of this kind of labeling is probably
14 positive, that we're going to stimulate technology
15 to try to glean more information from scans without
16 requiring contrast media, and that may have
17 widespread benefits across the entire population.

18 So I don't think all unintended
19 consequences are bad and I'm really not that
20 concerned about the shifting risks of anaphylaxis
21 in this very small population. These patients have
22 all been exposed many times to many agents and I

1 think we know a lot about their allergies at the
2 time that we see them.

3 Finally, on the issue of GFR, whether we
4 should have a number in there or not, I'm very much
5 in favor of having a number. We're absolutely
6 talking about the clearance rates. Now, formal
7 GFRs are difficult to obtain, but estimated GFRs
8 from the equation, the Cockrell equations, et
9 cetera, are very easy to derive and very effective,
10 and they provide a level playing field for
11 communication.

12 I would say that we would defeat the
13 purpose almost of putting in these
14 contraindications if we don't specify what the
15 estimated GFR is, because it will open up into
16 debate what constitutes a problem in a particular
17 patient, and you could end up using an agent that
18 we know or we suspect is going to be very dangerous
19 in a patient.

20 So I'm very much in favor of leaving in
21 the at least eGFR estimate.

22 DR. HARRINGTON: As the sole measure of

1 defining significant kidney disease or as a
2 measure?

3 DR. CHOYKE: I think a measure. But to
4 be honest, as a practical matter, it will be the
5 measure.

6 DR. HARRINGTON: But you want it listed.

7 DR. CHOYKE: Yes.

8 DR. HARRINGTON: Go ahead, Larry.

9 DR. HUNSICKER: But with the proviso that
10 you can't use it to evaluate renal failure and
11 acute renal failure.

12 DR. HARRINGTON: Dr. Paganini?

13 DR. PAGANINI: I'm going to declare
14 myself one of Larry's legions as opposed to the
15 other camp. While I'm a special government agent
16 here, I feel as though I'm a government agent
17 looking for a still in a Louisiana bayou.

18 There has been a whole bunch of dose
19 changes over this time, new drugs that have come
20 in, new formulations that have come in, and we're
21 now asked to decide whether or not there's a
22 differential in a very changing and rapidly

1 changing area with data that has been presented
2 here that's not convincing that any one agent is
3 much safer head and shoulders above any other
4 agent, at least on the data that we're seeing.

5 I think there is some separation that
6 seems to be a signal, but nothing that's really
7 striking that would have me change label. I think
8 that we do need an absolute level and that's Stage
9 4/5. The whole purpose why nephrology went by and
10 classified this was to get away from the softness
11 of severe renal failure without really
12 understanding what that meant. And here, we at
13 least put it into some sort of cement type
14 framework that we can then use either prospectively
15 or retrospectively to find out the influence of
16 different agents.

17 I think that the risk labeling was very
18 positive in that it created maybe a review of
19 standard methods of looking at these people, which
20 created maybe a rebirth of is it really as bad as
21 what we thought it was initially. There were other
22 agents that came along. C02 is one, which, at

1 least in our hospital, has been used a lot. And
2 there are other agents that I understand are in the
3 pipeline, such as iron-based and things of that
4 nature that might be taking the place of
5 gadolinium. So that's a positive.

6 I think the level of practice has changed
7 and I think that the FDA, with the black box
8 warning and specific patient exposure concerns, did
9 that, but I also think that a tremendous amount of
10 TV ads and trial lawyers had a significant amount
11 of influence over practice, as well.

12 Finally, I think that if you're going to
13 have a drug, as they are now classified, to have a
14 lower risk in a specific subgroup or sub-
15 population -- which I think needs to be studied,
16 because that's the very population that you're
17 trying to preserve as much renal function as you
18 can, you don't want to give anything that will hurt
19 their renal function. So if your drug is
20 preserving renal function, but allowing MRIs or
21 MRAs or any other MR type of thing, then that has
22 to be proven, and I think for the company to come

1 forward and say, "We are a drug that can be used in
2 this subgroup of populations." That's what I've
3 got.

4 DR. HARRINGTON: Great. Thanks, Emil.

5 Jim, is that an indication that you have
6 to go soon?

7 DR. NEATON: That's an indication.

8 DR. HARRINGTON: Yes. So let's get your
9 comments in.

10 DR. NEATON: I think I'm somewhere
11 between the two camps on that corner of the table.

12 DR. HARRINGTON: Typical statistician.

13 DR. NEATON: Exactly. The black box
14 warning, the way it's set up, as I understand it,
15 with the other text below, where there is some
16 separation of the agents, I would leave the black
17 box warning more across the board; that in people
18 with serious renal disease, as defined, with the
19 appropriate wording that people have discussed
20 here.

21 The thing I would add to it is the -- and
22 the rationale would be the uncertainty about what

1 cumulative dose might mean. If you're going to put
2 more text in the label, it's really hard to discern
3 among these agents, based on the data. But if I
4 had to make a choice, I would choose Omniscan and
5 Optimark, based on the data that the FDA gave us in
6 the book and what we saw today. Magnevist is
7 somewhere in between. But at least by the material
8 that was given to us in advance, it's an order of
9 magnitude in terms of difference, in terms of the
10 risk.

11 So I might kind of separate them there,
12 but not in the black box, because it seems like
13 we'd be messing with something that's been
14 successful for uncertain reasons, as I mentioned
15 before, either across-the-board non-use or drop in
16 dose or kind of whatever. But I would leave it
17 across the board in the black box and add the
18 caveat about making certain we check about the
19 previous MRIs for the patients.

20 DR. HARRINGTON: Okay. Dr. Nelson,
21 you're up next.

22 DR. NELSON: I think you've heard a lot

1 already, but my general sense is it's probably
2 preferable to warn about something that's
3 potentially unsafe than it is to leave something
4 that's potentially unsafe on the market. Again,
5 that's your job, but I'd prefer to see you mandate
6 or request that any of these things that feel
7 they're safer than others, prove it. It just seems
8 like there's a nice baseline that we have already.

9 In terms of the warning, I guess the
10 crafting of this has to be such that there are many
11 that are concerned that we're going to be
12 suggesting one is safer than other and I think what
13 your job is going to have to be is to say that
14 while these are all, at least for now, unsafe, some
15 are less unsafe perhaps than others, not that
16 they're necessarily safe, at least when it comes to
17 the issues that we're talking about today.

18 It's going to be tough to do, but I
19 really think that the risk of -- I don't know if
20 it's a beta error or an alpha error, but the risk
21 of leaving something kind of in a limbo state where
22 it's used inappropriately is more dangerous than it

1 would be to inappropriately warn and require more
2 data.

3 DR. HARRINGTON: Okay. Again, I'll take
4 chair's liberty.

5 Dr. Halperin, you look like you're going,
6 and then I'll go to Dr. Heckbert next to you.

7 DR. HALPERIN: Thank you very much,
8 Dr. Harrington. Actually, I just want to make one
9 small point at this point, because so much has been
10 said. I prefer to think about this in terms of
11 quality of evidence, that we have well established
12 risk with particularly the linear nonionic agents,
13 Omniscan and Optimark, and less well established
14 risks for the other agents.

15 I think placing it in those terms may
16 avoid potentially some of the concerns about the
17 perception of safety by making it clear that the
18 potential for risk remains for all agents, it's
19 just well established by virtue mainly of lesser
20 exposure.

21 I also think it's worth just emphasizing,
22 with respect to the potential for labeling, that I

1 think laboratory assessment of renal function is
2 necessary in all patients subjected to exposure to
3 these agents. I think because of an uncertainty
4 regarding the risk stratification of the agents
5 themselves amongst the various agents, that it
6 should be assessed across the board. I think it's
7 important, furthermore, to recommend documentation
8 of the incident, as well as the cumulative dose and
9 type of gadolinium-based contrast agent that's
10 used.

11 I also think it's important to specify
12 the importance of avoiding high dose imaging
13 protocols unless other modalities would be less
14 safe or less accurate.

15 DR. HARRINGTON: Jonathan, before you
16 leave, because it is something I'm going to ask
17 particularly Larry and Emil to comment on, Larry
18 has said there's no way you can get a creatinine on
19 everybody and have it in time to actually do the
20 test.

21 DR. HUNSICKER: You can get a creatinine.
22 You can't get a GFR. You can get an eGFR, but the

1 eGFR is meaningless in the case of a person who is
2 in acute renal failure. All I'm trying to say is
3 you cannot use creatinine to assess renal failure
4 and acute renal failure.

5 DR. HARRINGTON: Got it.

6 Jonathan?

7 DR. HALPERIN: That's exactly why I use
8 an assessment of renal function rather than a
9 specific number.

10 DR. HARRINGTON: Perfect.

11 Susan?

12 DR. HECKBERT: Yes. My thinking is that
13 the studies and the data we reviewed today do not
14 provide a basis for saying that -- more than is
15 already stated in the label about certain
16 gadolinium-containing contrast agents versus
17 others.

18 The label already calls out Omniscan,
19 Magnevist and Optimark and says that where a
20 specific agent was identified, these were the ones
21 that were most commonly reported. I don't think
22 the quality of the data is beyond that now, even

1 though that label, I guess, was written in 2007.

2 I do feel that the current label is good
3 and that the FDA ought to be happy with the fact
4 that we've had a positive result apparently from
5 this label or it appears that we have, and that we
6 still can make good recommendations. I think the
7 current label makes a lot of good recommendations.
8 It could use a little tweaking. I would echo the
9 comments of others that some information ought to
10 be added regarding cumulative dose.

11 DR. HARRINGTON: Okay. Dr. Coukell?

12 Allan?

13 MR. COUKELL: Thank you, Mr. Chairman. I
14 fall into the two and maybe three category. And
15 without reiterating what others have said about the
16 limitations of the data, let me just say a word
17 about my thinking on Magnevist, which is it's very
18 clear there is an association of NSF with
19 Magnevist. It's impossible to quantify it.

20 I think it would be a different decision
21 were this class smaller, but given that you could
22 contraindicate that third drug in this specific

1 small population and still be left with a number of
2 treatment choices, it seems that that would be a
3 conservative thing that would not harm patients to
4 take that path.

5 Then the only other thing I'd say is just
6 to reiterate what others have said, which is the
7 importance of advocating the lowest effective dose
8 in all patients, which, again, seems conservative
9 and may also drive the science to new techniques
10 that, in the long term, will reduce total exposure
11 to these agents.

12 DR. HARRINGTON: Thank you.

13 Dr. O'Brien?

14 DR. O'BRIEN: I fall into the camp of the
15 two, also, and I think the idea of the lowest
16 effective dose is good to add.

17 Just another comment I was going to make
18 on the lack of data and the fact that it doesn't
19 appear to be getting resolved in the near future
20 and the comments about cumulative exposure and
21 different providers.

22 I don't know if the FDA is -- this whole

1 tracking of moving toward meaningful use of health
2 information and Medicare/Medicaid incentives and
3 the fact that HHS is really shaping what quality
4 and safety data is collected by every provider in
5 the United States.

6 I know there's a large focus on pharmacy
7 data being consistent and they're driving vendors
8 to change and be consistent and there will be a lot
9 of activity over the next few years. I didn't know
10 if you should look into contrast agents and see
11 where they fall, because it's a wet cement
12 opportunity to really shape the way data is
13 collected. And it's going to be easy, because
14 everyone is changing it right now.

15 By 2015, there's going to be decision
16 support attached to all this, which would be really
17 a natural link for all the imaging expansion that's
18 on the horizon.

19 Just a comment that with your parent
20 organization, maybe you have some influence.

21 DR. HARRINGTON: Perfect. Let's go to
22 Dr. Jones, then Dr. Tatum, then Dr. Fogel.

1 DR. JONES: Most of this is just
2 repeating what other people have said. But I don't
3 think we're ever going to get to a point where we
4 can't even get the case control trials for some of
5 these agents.

6 So I really don't think we can wait
7 around. I think you just have to loosen the
8 expectation for the evidence that you want when
9 it's a safety matter. So I guess I fall into the
10 camp of while I'm drawing a line, the only problem
11 is I don't know exactly where that line is. I've
12 got Optimark and Omniscan on one end and I've got
13 the cyclics on the other end, and I honestly don't
14 know where to put the agents in between. I agree
15 with what some other folks have already said about
16 not using the terms high and low risk and limiting
17 to this and keep it very focused on patients with
18 renal disease.

19 I want to reiterate something Dr. Kanal
20 said and others have echoed, to please stick with
21 what is on the label. For most of the drugs, it's
22 0.1 millimole per kg, but in two, I believe there

1 still is the re-dosing and we might want to address
2 whether re-dosing needs to stay in there on any of
3 the agents.

4 We've mentioned, I think, use the lowest
5 possible dose, but in those two drugs, it is still
6 on the label, I think.

7 DR. HARRINGTON: Dr. Tatum?

8 DR. TATUM: I'm in the Wolfe camp and I
9 take exception to everything that Dr. Hunsicker
10 said, and I would go with the one and two. One of
11 the things you might do, instead of calling
12 something low risk, is to say the risk of NSF has
13 not been established, that essentially there's not
14 enough data.

15 So you're not declaring it low risk, but
16 you're saying you're taking the risk of using this,
17 but we don't have the data, at the same time. So I
18 think that's one thing.

19 I am worried about a couple of other
20 things that came up that have been mentioned, which
21 is accumulated dose. I'm still a little concerned
22 about that and how we track that, the high dosing,

1 the repeat dosing.

2 I think it was GE, whoever is pursuing
3 the pharmacogenomic thing with the data, I think
4 that's really important and I really encourage them
5 to proceed with that.

6 DR. HARRINGTON: Dr. Fogel?

7 DR. FOGEL: Yes. Again, I'm not going to
8 repeat everybody else's comments, although I do
9 fall into the two category, one with Omniscan and
10 Optimark, and Magnevist being a middling risk
11 category.

12 But in terms of the question about
13 whether or not a high risk agent should be
14 contraindicated, I hear everybody talking about the
15 paucity of the data and the rigor of the science of
16 the data, which I totally agree with, but
17 contraindication sounds like it's too harsh of a
18 term. I mean, contraindication sounds like we've
19 done rigorous studies, we know for sure that this
20 is a really bad thing, and, therefore, this
21 particular gadolinium-based agent shouldn't be
22 used. It seems sort of counter to what everybody

1 is saying with having a paucity of data and paucity
2 of rigor in the science to then use the word
3 contraindicated. I would say something would be
4 less, a less rigid term than contraindicated,
5 should be shied away from or significant risk.

6 It just seems like there isn't enough
7 data for you to say contraindicated when we're all
8 saying here that there isn't the science here,
9 there isn't the rigor here to actually say, beyond
10 the shadow of a doubt, that the evidence says that
11 we shouldn't use it.

12 DR. HARRINGTON: I think, Mark, let me
13 see if I interpret some of the remarks from my
14 colleagues. I think people are saying that the
15 quality of the evidence is not what it usually is
16 in terms of being able to say we have established
17 proof. But in a case of a severe, debilitating
18 side effect like NSF, people are willing to say
19 that it's contraindicated unless you can prove
20 otherwise, unless there is some element of proof
21 otherwise --

22 DR. WOLFE: In this small group of

1 people.

2 DR. HARRINGTON: -- in this small group
3 of people.

4 DR. FOGEL: Well, one of the reasons why
5 it would be appear to be contraindicated is because
6 there are other agents that might be useful.

7 DR. HARRINGTON: I think Dr. Nelson used
8 a term which I liked, I wrote it down, less unsafe.

9 DR. HUNSICKER: Could not one say
10 something like -- first of all, leave, as -- I've
11 forgotten your name. But as she said, leave the
12 black box the way it is. I think you said that,
13 leave the black box the way it is.

14 But I would have no problem with the
15 discussion down there, just what you said. What
16 are the facts? Saying something along the line of
17 although there is uncertainty about the relative
18 safety of these things, prudence would suggest that
19 you avoid the use of nonionic linear agents.

20 If you say that in the labeling that you
21 have, nobody is going to use it in these people,
22 and that seems to me as though it describes what

1 the fact is. Prudence would suggest that you not
2 use linear nonionized agents.

3 DR. HARRINGTON: I have not asked Dr.
4 Lesar or Dr. Royal their opinion.

5 Do you want to weigh in here, Tim?

6 DR. LESAR: That's an interesting point.
7 I go back to the vast majority of patients who
8 we're talking about who get these drugs do not have
9 renal failure and I'll reiterate that point again.
10 I was surprised that we did not see more
11 information from the AERS about these drugs, other
12 than anaphylaxis, which was actually reported, the
13 non-NSF adverse event. So I was just curious now.
14 I understand the weakness of this one snapshot of
15 one adverse event report, but it would be very
16 useful to know what that data is right now in AERS
17 for all the agents, for other reports, for other
18 types of adverse events.

19 This would suggest, actually, for the
20 vast majority of patients, it's less safe to go to
21 other agents than the ones which we're saying we
22 should restrict.

1 So that's my concern. And the way the
2 world works is exactly as you said. You present
3 with a drug whose risk for NSF is lower and the way
4 contracting works and organizations wanted to
5 simplify, they only use one agent. So the movement
6 would be to the agents that have less NSF, which is
7 clearly the most severe adverse event, but it
8 doesn't impact the vast majority of patients.

9 But they do it because they don't have to
10 measure renal function, quote-unquote, or we don't
11 have to worry about it as much. But now you're
12 going to put this drug in which may not have had as
13 serious side effects in the vast majority, but
14 appears to have more or possibly more.

15 So that's my major concern. If you see
16 that shift occur, we actually may be exposing a
17 large number of patients to maybe less severe
18 adverse events, but nonetheless, they're adverse
19 events.

20 DR. HARRINGTON: I think that was Dr.
21 Kaul's point, that those risks should be quantified
22 in a better manner than they have been.

1 Dr. Royal, did you want to weigh in here?

2 DR. ROYAL: I primarily do nuclear
3 medicine. So this was a topic that I didn't know a
4 lot about. Having listened to the presentations, I
5 still don't know a lot about it. I'm impressed
6 with the fact that the data isn't at all very
7 clear.

8 There are certainly a lot of comments
9 that have been made that I agree with. Using the
10 terminology "high risk" I think isn't very
11 meaningful and to the extent that that could be
12 quantitated, it would be useful.

13 We heard about the use of prescriptions
14 and I think that's a step in the right direction.
15 But having some way of keeping track of that data,
16 I'm just struck by the fact that we have all these
17 people out there who are being injected with
18 contrast agents and there's really no way of
19 following up on them.

20 The last comment I'll make is on the call
21 for informed consent. It's hard to argue against
22 informed consent. On the other hand, it's actually

1 hard to get informed consent. This thing that we
2 call informed consent is usually a legal document
3 that protects the hospital against lawsuits. So if
4 that's what we mean by informed consent, I'm not
5 sure that I'm in favor of that.

6 DR. HARRINGTON: Fair comment.

7 Can we go to the next question? Then I'm
8 going to try to summarize. I think we've answered
9 a lot of this. In fact, I think we've answered
10 this question several times.

11 Dr. Rieves, let me see if I can summarize
12 the discussion and see if you agree that you have
13 gotten from the panel what you have wanted and then
14 ask us, if there is anything you didn't get.

15 I'll make eight quick comments, the first
16 of which is that I sense that the group feels that
17 you did your job the first time, that the initial
18 labeling was very positive, and that then the
19 professional societies really took that, ran with
20 it, and practice now is ahead of where the labeling
21 actually is. We've heard that from several people.

22 The second, which I've heard over and

1 over, is that please be very certain that this be
2 specified that these comments apply to the group of
3 patients with severe renal disease, which gets at
4 perhaps some of your comments, Tim.

5 The third point is that the majority of
6 the group feel that at least two of the agents do
7 appear to be different from the other agents. I'll
8 leave it as different from the other agents and let
9 you think about the wording. There was some sense
10 that a third agent might also fall into that
11 category, but there seemed to be less consensus
12 around that.

13 The fourth comment is that there was no
14 clear evidence that any one single agent was safe
15 in this population and, in fact, I heard
16 encouragement from at least two or three people
17 that that avenue of investigation should be pursued
18 specifically.

19 The fifth comment is that significant
20 renal disease is an important concept that cannot
21 be defined only using a creatinine or an estimated
22 GFR, and that, particularly, you need to point out

1 to the prescriber that the issue of acute kidney
2 injury is perhaps different than chronic kidney
3 disease in terms of how one assesses it.

4 The sixth point I've heard over and over
5 all day, which I think is an incredibly important
6 point, is this issue of cumulative dosing and that
7 somehow, I think you're hearing from the panel that
8 we'd like you to use your influence as a regulatory
9 agency or as a body within HHS to try to understand
10 better how we can capture cumulative dosing issues
11 not just perhaps around this imaging agent, but
12 amongst all imaging agents and perhaps even the
13 radiation issue.

14 The seventh issue I've heard is that all
15 members here seem to understand that you're
16 advocating the lowest possible dose for the
17 technique that is to be employed is really
18 important and that, as part of that, that you
19 reexamine some of the re-dosing issues.

20 Then the final point, which I think
21 Dr. Choyke made, is that all of these changes, in
22 fact, could spur on new innovation, new technology

1 developments, and that we would all be very much in
2 favor of looking at the positive consequences as
3 opposed to the unintended consequences.

4 So do people think I've captured what the
5 conversation has been? And, Dwaine, does that give
6 you some food for thought? I think the group has
7 done their job of listening and then responding to
8 you.

9 Yes, Larry, go ahead.

10 DR. HUNSICKER: One very specific thing.
11 I'm actually on Emil's team with respect to the GFR
12 limit. I want to be very precise so that -- I think
13 you understand what I've said, which is that
14 although it is certainly not the case that chronic
15 kidney disease is only a decrease in GFR, it is
16 almost certainly the decrease in GFR that is
17 relevant to the toxicity of these agents.

18 So I actually think that the data are
19 fairly solid that the highest risk is in Stage 5
20 and ESRD patients, with a modest or somewhat
21 reduced risk in 4, and very little risk below that,
22 and I don't see any reason we should ignore those

1 data.

2 The problem with saying severe kidney
3 disease is that my severe kidney disease is not
4 your severe kidney disease and, in fact, the data
5 already do speak to where that line is. And 30
6 GFR, not being absolute, is not a bad dividing
7 point.

8 So I personally would leave that 30
9 milliliters per minute in patients with chronic
10 kidney disease and the specific exception is that,
11 as you've already pointed out, you have to make the
12 point and get people to understand that a
13 creatinine taken in the course of acute kidney
14 failure doesn't tell you much about kidney
15 failure.

16 DR. HARRINGTON: Even as knuckle-
17 dragging, interventional cardiologist, I did get
18 that point. But I think Dr. Choyke made that quite
19 well, that for the practitioner, having that number
20 there is going to be important.

21 Dwaine, did we answer your questions and
22 provide you advice?

1 DR. RIEVES: That was very informative.

2 It was a very nice summary, actually. I was very
3 impressed that you could do that, articulate it so
4 nicely. But Dr. Krefting, Dr. Boucher, Dr. Cowper,
5 we have had so many on this team who have worked so
6 hard on this, I'm going to turn to them.

7 Do you all have any extra questions?

8 DR. KREFTING: I think that was a
9 terrific capture of a lot of disparate opinions and
10 you put it together very well. I think you've
11 given us a real direction and pathway to go here.
12 So I appreciate all that.

13 DR. BOUCHER: If I could comment, also.
14 I very much appreciate hearing all of the comments
15 made by the panel participants. It's been very
16 helpful. And just to make one comment about the
17 proof issue, I think two or three of the panelists
18 mentioned proving that one might be safer than the
19 other or something to that effect.

20 Just to acknowledge, we've heard some
21 discussion today that sponsors are having
22 difficulty enrolling patients in the PMRs which we

1 asked them to do, and there are, I think, several
2 reasons for that.

3 There probably are some ethical issues
4 when you look at the patients who get NSF and the
5 idea that we might want to give them something
6 which causes disease is, obviously, a problem and
7 is almost certainly one of the reasons why
8 enrollment is low.

9 The epi review today at least suggested
10 that the case control studies, which have been done
11 to date, are very, very limited and there are very
12 few new cases. So going forward, I think even a
13 case control design is going to have problems.

14 So my point is -- my sense, my personal
15 sense, is that this is going to come down to
16 developing an animal model or some such thing to
17 get the information that we need. So I'd throw
18 that out to the sponsors.

19 I'd be very interested in hearing that
20 from them. It doesn't have to be through this
21 forum; obviously, we'll be at the agency. But I
22 think that's a very reasonable thing to consider,

1 especially given that there is new product
2 development.

3 DR. HARRINGTON: So I've got Dr. Morrato,
4 Dr. Paganini.

5 DR. MORRATO: Real quick. I thought you
6 did an excellent summary, as well. I just wanted
7 to add that oftentimes, you don't see success
8 stories after black box warnings. What gets
9 reported is black box warnings are ineffective.

10 I think this may be an opportunity, if
11 there is time, to document it and get this kind of
12 case example out in the literature as to what
13 happened that made it work. Was it the fact that
14 there were alternatives? Was it the embracing of
15 the warning by the medical society? It's probably
16 a combination of factors, but I think it's
17 important that success stories get out and get
18 shared broadly so others can learn from this and
19 dealing with other kinds of warnings.

20 DR. HARRINGTON: Emil?

21 DR. PAGANINI: Just one, again, request
22 for dialyzability of the various drugs. I think

1 that would be something that would be important.

2 DR. HARRINGTON: Dr. Nelson, then Dr.

3 Rieves.

4 DR. NELSON: Thank you. My question, you

5 reminded me again, about the hepatic effects of

6 these metals was never really answered either, and

7 I just think it may turn out to be nothing.

8 The effect of gadolinium accumulation in

9 the liver, if the liver is able to metabolize this

10 compound and pull the gadolinium out and bio-

11 accumulate either to metallothionein or to whatever

12 metal-binding agent it has, we see this with other

13 organs, cadmium in the kidney, et cetera, it could

14 be an unintended consequence if we're not careful.

15 DR. HARRINGTON: Dr. Rieves?

16 DR. RIEVES: Dr. Harrington, not to put

17 you on the spot, but you were very articulate in

18 your word choice by saying that the majority of the

19 members felt that two agents were different from

20 the others. You did not say specifically that the

21 majority felt they should be contraindicated.

22 DR. HARRINGTON: I very specifically said

1 that, because as I was summarizing the discussions,
2 I heard comments from Dr. Wolfe -- I'll put them in
3 different camps.

4 The Dr. Wolfe camp was they should be
5 contraindicated, they're different enough that they
6 shouldn't be used. The Dr. Fogel camp was, yes,
7 they're different, but I'm not sure they should be
8 contraindicated.

9 So that's why I tried to give you the
10 nuanced discussions. One of the things I was told
11 at the beginning is because we weren't voting, you
12 were looking for not consensus, but to hear
13 different opinions.

14 DR. RIEVES: Right. So I guess since we
15 are not voting -- I don't want the panels to be
16 misinterpreted here. So I think you're comfortable
17 saying there is not a consensus regarding
18 contraindications; is that correct?

19 DR. HARRINGTON: I'll let the panel weigh
20 in. I'll put a straw man out there. I would say
21 that the majority of the panel, in their remarks,
22 suggest that there should be a contraindication for

1 at least two. But for the third agent, I would say
2 that there was not consensus or not a majority that
3 would include it. In fact, I would put that in the
4 McGuire camp, who had all three, similar to the
5 EMEA differentiation of risk. I thought that was a
6 minority opinion that it be three, but I'll leave
7 it up to my colleagues that I interpreted it
8 correctly.

9 Does that answer it?

10 DR. RIEVES: Actually, it does, right.
11 So I much appreciate you clarifying there, because
12 there will be quotes that come from this. So we
13 all understand, the majority felt that there should
14 be a contraindication for at least two of these
15 agents.

16 DR. HARRINGTON: That's my interpretation
17 of the discussion of today. That was my
18 interpretation of the discussion.

19 Susan?

20 DR. HECKBERT: I guess it seemed to me
21 that people were responding to the first question,
22 which was, is there a differential risk. There, I

1 believe there was consensus, even though I didn't
2 feel that the data supported that. But I agree
3 with you on that.

4 But I'm not sure that everybody spoke up
5 as to whether they felt that based on that, a
6 contraindication for people with severe renal
7 failure should be put in place by the agency.

8 DR. HARRINGTON: Okay.

9 DR. KREFTING: Since this also is a
10 communication advisory committee, we did want --
11 because as you heard, things coming out of here are
12 quoted, et cetera, we did want to clarify that.

13 You feel there is a difference, but is
14 that difference being communicated as a
15 contraindication for certain agents?

16 DR. HARRINGTON: Well, in the spirit of
17 Susan's comment, let me open it back up. I
18 specifically said it was different, but I did note
19 that there are different camps around the table.
20 So let's open it up.

21 DR. KREFTING: It's almost dichotomous,
22 either we say it's a contraindication or not.

1 DR. HARRINGTON: But you didn't ask us to
2 vote, because we could have voted.

3 Judy?

4 DR. KRAMER: Bob, you make a good point.
5 I don't think, after the fact, without a vote, you
6 can actually give the answer directly. But I would
7 comment that of the two agents we're talking about,
8 one of them has already voluntarily contraindicated
9 for severe renal disease.

10 So we're talking about one agent and even
11 though I said that I thought it should be
12 contraindicated, I don't know that I would
13 interpret all the comments around the table as
14 agreeing with that.

15 My concern about not contraindicating it
16 is that we know what behavior is, and if you just
17 say it might be increased risk, then you put it in
18 this never-never land where people either don't pay
19 attention or you have the lawyers driving what
20 people do.

21 It seems to me sometimes it's better to
22 just bite the bullet and if you think that that is

1 why things have gotten better, that you might
2 consider contraindicating in that small subset of
3 patients. That's just my opinion, not a summary of
4 everyone else's.

5 DR. RIEVES: If I could make one comment.
6 There actually is a regulatory definition of
7 contraindication, which has to do with the benefit
8 never outweighing the risk. So I think the panel
9 should take that into consideration.

10 DR. HARRINGTON: I think that was where
11 Dr. Fogel was going, if I interpreted your remarks,
12 that there will be times when you'd want the
13 option.

14 DR. FOGEL: That's absolutely correct. I
15 remember a few years ago, when I was listening to
16 Bob Temple talk at an FDA meeting, and he basically
17 said that there may be, in that particular
18 instance, an anti-hypertensive that may have severe
19 side effects; yet, if it's the only hypertensive
20 that would fit this patient's profile, he would
21 want to have the physician have the option to be
22 able to use it.

1 So for contraindication, for me,
2 contraindication and lack of data and rigor in
3 science seem like an oxymoron. So I would say
4 significantly high risk, very high risk, super-high
5 risk, but I don't know if contraindication I would
6 use.

7 DR. HARRINGTON: This is why you didn't
8 ask for the vote, Dwaine.

9 Let's go to Sid, then Larry.

10 DR. WOLFE: Just quickly. The situation
11 you just described, Mark, is one where there aren't
12 other alternatives. Here, we have several
13 alternatives. So to contraindicate one of these
14 two drugs or whatever is essentially to say use one
15 of these other three. So I think
16 contraindication is appropriate.

17 DR. HARRINGTON: Larry?

18 DR. HUNSICKER: I actually am going to
19 switch sides and say that I think that -- that, in
20 fact, I did keep track of the expressions as they
21 went around and I believe that it is a statement of
22 fact that the majority of the people who responded

1 said that they would favor contraindication. So I
2 believe that is a statement of fact.

3 I agree with the doctor across the way
4 there that if we say that there is serious concern,
5 or whatever you want to say, that a prudent man
6 would not use it or whatever, effectively, it will
7 become contraindicated and I think it's probably
8 just more straightforward to say that it's
9 contraindicated.

10 DR. HARRINGTON: Dwaine?

11 DR. RIEVES: Thank you very much. We
12 were very fortunate if we got a consensus. We're
13 very content with a preponderance. I think that's
14 an accomplishment. So we have a sense of the
15 preponderance of thought.

16 DR. HARRINGTON: I want to thank the
17 committee, thank the FDA, thank the sponsors, who
18 did such a terrific job in putting together the
19 materials, and travel safely.

20 (Whereupon, at 4:48 p.m., the meeting was
21 concluded.)

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