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DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

ORTHOPAEDICS AND REHABILITATION DEVICES

ADVISORY PANEL

OPEN SESSION

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Wednesday, August 8, 2001

9:32 a.m.

Walker/Whetstone Room
Gaithersburg Holiday Inn
2 Montgomery Village Avenue
Gaithersburg, Maryland 20879

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PARTICIPANTS:

Michael J. Yaszemski, M.D., Ph.D.,
Chairperson
Haney Demian, Executive Secretary

VOTING MEMBERS:

Albert J. Aboulafia, M.D.
Maurean Finnegan, M.D.
Kinley Larntz, Ph.D.
John Lyons, M.D.
Clayton Peimer, M.D.
Douglas Wright, M.D.

NONVOTING MEMBER:

Harry Skinner, M.D., Ph.D.

CONSULTANTS DEPUTIZED TO VOTE:

Edward Y. Cheng, M.D.
Stephen Li, Ph.D.

INDUSTRY REPRESENTATIVE:

Sally Maher, Esq.

CONSUMER REPRESENTATIVE:

Robert A. Dacey

FDA:

Celia Witten, M.D., Ph.D.
Daniel S. McGunagle, M.D.

P R O C E E D I N G S**Call to Order**

MR. DEMIAN: Good morning, everybody.

We are ready to begin this meeting of the Orthopaedics and Rehabilitation Devices Panel.

My name is Hane4y Demian, and I am the Executive Secretary of this panel; in addition to that, I am Acting Branch Chief for the Orthopaedics Devices Branch.

I would like to remind everybody that you are requested to sign in on the attendance sheet at the table by the door. You may also pick up an agenda and information about today's meeting, including how to find out about future meeting dates and how to obtain meeting minutes or transcripts.

I will now read two statements that are required to be read into the record--the Deputization of Temporary Voting Member Statement and the Conflict of Interest Statement.

"Appointment to Temporary Voting Status. Pursuant to the authority granted under the Medical Device Advisory Committee Charter dated October 27, 1990 and as amended August 18, 1999, I appoint the following individuals as voting members of the

1 Orthopaedics and Rehabilitation Devices Advisory
2 Panel for this meeting on August 8, 2001: John
3 Lyons, Doug Wright, Kinley Larntz, and Clayton
4 Peimer."

5 "For the record, these individuals are
6 Special Government Employees and consultants to
7 this panel. They have undergone customary conflict
8 of interest review and have reviewed the material
9 to be considered at this meeting."

10 This is signed by the Director of the
11 Center for Devices and Radiological Health, David
12 Feigal.

13 "Conflict of Interest Statement. The
14 following announcement addresses conflict of
15 interest issues associated with this meeting and is
16 made part of the record to preclude even the
17 appearance of any impropriety. To determine if any
18 conflict existed, the agency reviewed the submitted
19 agenda for this meeting and all financial interests
20 reported by the committee participants. The
21 conflict of interest statute prohibits Special
22 Government Employees from participating in matters
23 that could affect their or their employers'
24 financial interests. However, the agency has
25 determined that participation of certain members

1 and consultants, the needs for whose services
2 outweigh the potential conflict of interest
3 involved, is in the best interest of the
4 Government. Therefore, waivers have been granted
5 for Drs. Edward Cheng, Stephen Li, Kinley Larntz,
6 and Harry Skinner for their interest in firms that
7 could potentially be affected by the panel's
8 recommendations."

9 "The waivers permit Drs. Cheng, Li, and
10 Larntz to participate fully in matters before
11 today's panel. Dr. Skinner may participate in the
12 panel deliberations but not vote on the
13 reclassification petition."

14 "Copies of these waivers may be obtained
15 from the agency's Freedom of Information Office,
16 Room 12A-15 of the Parklawn Building."

17 "We would like to note for the record that
18 the agency also took into consideration other
19 matters regarding Drs. Li, Larntz, Finnegan, and
20 Lyons. Each of these panelists reported current or
21 recent interest in firms at issue, but in matters
22 that are not related to today's agenda. The agency
23 has determined, therefore, that they may
24 participate fully in all discussions."

25 "In the event that the discussions involve

1 any other products or firms not already on today's
2 agenda for which an FDA participant has a financial
3 interest, the participant should excuse him or
4 herself from such involvement, and the exclusion
5 will be noted for the record. With respect to all
6 other participants, we ask in the interest of
7 fairness that all persons making statements or
8 presentations disclose any current or previous
9 financial involvement with any firms whose products
10 they may wish to comment upon."

11 Before turning this meeting over to Dr.
12 Yaszemski, I would like to introduce our
13 distinguished panel members who are generously
14 giving their time to help FDA in matters being
15 discussed today and other FDA staff seated at the
16 table; so we will just go around the table and have
17 everybody give their name and their area of
18 interest.

19 Dr. Yaszemski?

20 DR. YASZEMSKI: Michael Yaszemski. I am
21 in the Departments of Orthopedic Surgery and
22 Bioengineering at the Mayo Clinic in Rochester,
23 Minnesota. My clinical practice includes spine
24 surgery and total joints, and my research is
25 focused on tissue engineering.

1 DR. LI: Steve Li. I am president of a
2 newly-formed company called Medical Device Testing
3 and Innovations located in Sarasota, Florida.

4 DR. SKINNER: My name is Harry Skinner. I
5 am Professor and Chair of Orthopedics at UC-Irvine
6 and Professor of Mechanical and Aerospace
7 Engineering. I do mostly joint reconstruction, and
8 my research interest is in material science.

9 DR. PEIMER: I am Clayton Peimer. I am
10 currently with the University at Buffalo Department
11 of Orthopedic Surgery, the Division of Hand and
12 Upper Extremity Surgery. I am about to move to
13 Northwestern University at the end of this month.
14 My clinical practice is in hand and upper limb
15 musculoskeletal reconstruction, and some of my
16 research interests have included orthopedic
17 implants and devices.

18 DR. ABOULAFIA: My name is Albert
19 Aboulafia. I am currently affiliated with the
20 University of Maryland and the Cancer Institute at
21 Sinai Hospital of Baltimore. My areas of interest
22 are musculoskeletal oncology.

23 DR. WITTEN: Celia Witten from FDA. I am
24 the Division Director of the division that reviews
25 orthopedic devices, among others.

1 MS. MAHER: Sally Maher. I am with Smith
2 & Nephew Endoscopy, and I am the Industry
3 Representative.

4 MR. DACEY: Robert Dacey, Boulder,
5 Colorado. I am the Consumer Representative.

6 DR. LARNTZ: Kinley Larntz, Professor
7 Emeritus, University of Minnesota. I am a
8 statistician. I was at the Department of Applied
9 Statistics at the University, and I am interested
10 in clinical research design and data analysis.

11 DR. CHENG: My name is Edward Cheng. I am
12 on the faculty at the University of Minnesota. My
13 interests are in orthopedic oncology,
14 osteonecrosis, and adult reconstructive surgery.

15 DR. WRIGHT: Douglas Wright. I am
16 academically affiliated with the University of
17 Maryland. I am an orthopedic surgeon, and I do
18 fracture work and lower extremity trauma
19 reconstruction.

20 DR. LYONS: John Lyons. I am an
21 orthopedic surgeon and biomedical engineer, Erie,
22 Pennsylvania. My area of interest is total joints
23 and spine. My area of research is biomechanics
24 mechanisms of injury.

25 DR. FINNEGAN: Maureen Finnegan. I am an

1 orthopedic surgeon at UT Southwestern in Dallas. I
2 do trauma in sports, and my research is in trauma.

3 MR. DEMIAN: Thank you.

4 At this time, I would like to turn the
5 meeting over to our chairman, Dr. Yaszemski.

6 DR. YASZEMSKI: Good morning, everybody.
7 My name is Dr. Michael Yaszemski. I will be the
8 chairman for this meeting.

9 I would like to note for the record that
10 the voting members present constitute a quorum as
11 required by 21 CFR Part 14.

12 First, we'll have Dr. Diane Mitchell,
13 Acting Deputy Division Director of DGRND, provide
14 her update to the panel since the last panel
15 meeting.

16 Dr. Mitchell?

17 DR. MITCHELL: Greetings.

18 I'd like to let you know that there have
19 been two products approved since the last panel
20 meeting. The first is the BAK cervical inner body
21 fusion system. The approval date was April 20,
22 2001. The device is indicated for use in
23 skeletally mature patients with degenerative disk
24 disease of the cervical spine with accompanying
25 radicular symptoms at one disk level. DDD is

1 defined as discogenic pain with degeneration of the
2 disk confirmed by history and radiographic studies.
3 BAKC implants are used to facilitate fusion in the
4 cervical spine and are placed via an anterior
5 approach at the C3 to C7 disk levels using
6 autographed bone.

7 The second approval was a Humanitarian
8 Device Exemption for Prostilac, a hip temporary
9 prosthesis. This device is indicated for use as a
10 short-term total hip replacement in patients who
11 need a two-stage procedure to treat a confirmed
12 infection of their THR and where vancomycin and
13 topromycin are the most appropriate antibiotics for
14 treatment of the infection based on the
15 susceptibility pattern of the infecting
16 microorganisms.

17 I am also pleased to announce that we have
18 a new orthopedist with us in the Orthopedic Devices
19 Branch. Her name is Barbara Buch, and I am sure
20 she will be joining us later so we can introduce
21 her.

22 Thank you.

23 DR. YASZEMSKI: Thank you, Dr. Mitchell.

24 We would like to ask Dr. Witten to provide
25 a special presentation.

1 DR. WITTEN: Actually, I have four special
2 presentations. We at FDA rely on our panel members
3 to provide us with their scientific expertise and
4 guidance and advice during the course of our work
5 at FDA, and we are always a bit sorry when panel
6 members rotate off the panel when they have served
7 us as well as the panel members have in this group
8 today.

9 So today it is my pleasure to give four
10 plaques of thanks to four of the panel members who
11 are rotating off our Advisory Panel as permanent
12 members after this meeting. Those panel members
13 will continue to serve as consultants, which means
14 we may bring them back for panel meetings, and you
15 may see them again--and of course, we can also call
16 on them for their advice on other matters.

17 I am going to read one of the letters that
18 accompanying the plaques and then give them out.

19 This is for Dr. Aboulafia, signed by Dr.
20 Haney.

21 "I would like to express my deepest
22 appreciation for your efforts and guidance during
23 your term as a member of the Orthopaedics and
24 Rehabilitation Devices Panel of the Medical Devices
25 Advisory Committee. The success of this

1 committee's work reinforces our conviction that
2 responsible regulation of consumer products depends
3 greatly on the participation and advice of the
4 nongovernmental health community."

5 "In recognition of your distinguished
6 service to the Food and Drug Administration, I am
7 pleased to present you with the enclosed
8 certificate."

9 [Applause.]

10 DR. WITTEN: It looks from the letter like
11 we planned ahead. The other plaques and letters I
12 have are for Dr. Edward Cheng, Dr. Michael
13 Yaszemski, and Dr. Harry Skinner.

14 [Applause.]

15 DR. YASZEMSKI: Thank you, Dr. Witten.

16 We will now proceed with the open public
17 hearing Session of this meeting.

18 I would ask at this time that all persons
19 addressing the panel come forward and speak clearly
20 into the microphone, as the transcriptionist is
21 dependent on this means of providing an accurate
22 record of this meeting.

23 We are requesting that all persons making
24 statements during the open public hearing session
25 of the meeting disclose whether they have any

1 financial interest in any medical device company.

2 Before making your presentation to the
3 panel, in addition to stating your name and
4 affiliation, please state the nature of your
5 financial interest, if any.

6 At this time, is there anyone wishing to
7 address the panel?

8 [No response.]

9 DR. YASZEMSKI: Since there are no other
10 requests to address the panel and seeing no hands
11 to address the panel during this open session, we
12 will now proceed to the open committee discussion.

13 We will now begin the discussion of the
14 reclassification petition for metal-on-metal total
15 hip arthroplasty devices.

16 We will begin with the Petitioner's
17 presentation followed by the FDA presentation.
18 This will be followed by two lead panel member
19 reviews. Next, we will have a general panel
20 discussion about this topic, followed by panel
21 discussion aimed at answering FDA's questions while
22 going through the reclassification worksheet and
23 supplemental worksheet. We will finish by voting
24 upon our recommendation.

25 I would like to remind public observers at

1 this meeting that while this portion of the meeting
2 is open to public observation, public attendees may
3 not participate except at the specific request of
4 the panel.

5 The order will be first, the Petitioner
6 presentation by OSMA.

7 Mr. Tom Craig. Hi, Mr. Craig.

8 **Petitioner Presentation**

9 MR. CRAIG: Good morning. I am Tom Craig,
10 representing the Orthopaedic Surgical Manufacturers
11 Association. Our member companies are all medical
12 device companies and biological companies.

13 We are here to present the
14 reclassification petition for metal-on-metal
15 semi-constrained hip prostheses.

16 OSMA is an organization that is made up of
17 orthopedic device companies. We represent all of
18 the major orthopedic device companies, many smaller
19 orthopedic device companies, and are interested
20 primarily in standards development, labeling
21 guidelines, cooperation with health care
22 professionals, both domestic and international
23 regulatory issues, and patient education.

24 [Slide.]

25 Metal-on-metal hip prostheses predated the

1 Medical Device Amendments of 1976, and they were
2 classified by FDA as Class III Pre-Amendment
3 Devices on September 4, 1987. Class III devices
4 are not subject to premarket approval.

5 FDA allowed manufacturers to market
6 metal-on-metal hips under the 501(k) provisions of
7 the Act provided they were able to determine to be
8 substantially equivalent to the predicate device.
9 FDA required data from clinical trial of the device
10 or a similar device to support substantial
11 equivalence.

12 On April 19, 1994, FDA issued a memorandum
13 that scheduled FDA to call for PMAs for
14 metal-on-metal hips that same year. However, no
15 action has been taken to this point by FDA.

16 OSMA formed seven committees to develop
17 reclassification petitions for devices that were
18 subject to call for PMAs or PDPs, and this is the
19 latest of those types of reclassification
20 petitions. We believe that sufficient information
21 now exists to support the conclusion that the risks
22 from metal-on-metal hips are no greater than those
23 for metal-polyethylene hip prostheses. This
24 conclusion is supported by reports in the medical
25 and scientific literature, the results of clinical

1 use of these devices, the low frequency of reported
2 adverse events, and the availability of recognized
3 standards for ensuring the use of optimal implant
4 materials.

5 OSMA believes that the information
6 contained within this reclassification petition
7 clearly shows that the risks imposed by these
8 devices can be adequately controlled through FDA's
9 established authority over Class II devices.

10 [Slide.]

11 These are the classifications as they are
12 written in, and I want to make a point--this is
13 basically what we are asking the reclassification
14 to be changed to. If you look down in the lower
15 right-hand corner in the next-to-last and last
16 lines, we have added "with or without bone cement"
17 to the thermal component. The data in this
18 petition supports unsubmitted acetabular components
19 and cemented and cementless thermal components.

20 The presenters today will be Dr. Thomas
21 Schmalzried, Associate Director, Joint Replacement
22 Institute, Orthopaedic Hospital, Los Angeles,
23 California; Dr. Joshua Jacobs, Crown Family
24 Professor of Orthopaedic Surgery, Rush Medical
25 College, Chicago, Illinois; and Dr. John Medley,

1 Associate Professor of Mechanical Engineering,
2 University of Waterloo, Waterloo, Ontario, Canada.

3 In addition to the presenters I just
4 mentioned, we have several other people here to
5 help support the petition, including clinicians who
6 participated in the two main clinical studies,
7 research engineers, biostatisticians, and the
8 personnel to help support the studies within the
9 company.

10 Thank you.

11 Dr. Schmalzried?

12 DR. SCHMALZRIED: Good morning.

13 I am Tom Schmalzried, from the Joint
14 Replacement Institute in Los Angeles. I am an
15 orthopedic surgeon. My research area of interest
16 is surgical and autopsy retrieval analysis to
17 identify mechanisms of failure of prosthetic
18 joints.

19 [Slide.]

20 I am going to provide an overview this
21 morning of the unpublished studies on
22 metal-on-metal bearings. There are three
23 unpublished studies which we have simply named A,
24 B, and C. Studies A and C are U.S. Investigational
25 Device Exemption studies approved under 21 CFR Part

1 812. Study B is a European study conducted in
2 accordance with the Medical Device Directive
3 Essential Requirements, and there was an open
4 control in that study. The study duration ranged
5 from December of 1995 to February of 2000.

6 The U.S. devices have subsequently been
7 cleared under 510(k) approval and CE-marked in
8 Europe.

9 [Slide.]

10 This is the device configuration for
11 Studies A and B. It is a modular titanium
12 acetabular component with a
13 cobalt-chrome-molybdenum bearing insert. On the
14 femoral side, both cemented and cementless stems
15 were utilized with modular cobalt-chromium alloy
16 femoral heads.

17 [Slide.]

18 For Study C, these are titanium alloy
19 plasma sprayed femoral components with modular
20 cobalt-chromium heads and again, a modular
21 acetabular component that has a titanium or
22 titanium alloy substrate and a modular
23 cobalt-chromium acetabular bearing insert.

24 [Slide.]

25 For the control limb in Study A, the

1 acetabular component is again a modular design with
2 a titanium or titanium alloy substrate and a
3 modular ultra-high molecular weight polyethylene
4 insert shown unassembled on the left, assembled on
5 the right.

6 Metal poly cups in Study C, again, a
7 titanium or titanium alloy substrate, modular
8 insert, shown unassembled and assembled.

9 Studies A and C were prospective and
10 randomized with metal-on-polyethylene controls. As
11 previously mentioned, Study B, conducted in Europe,
12 was prospective, nonrandomized, open-ended,
13 control.

14 [Slide.]

15 The assessment methods included patient
16 histories, a Harris hip evaluation pre-op, 6 weeks
17 post-operative except in Study C, 6 months, and
18 then annually thereafter; radiographic assessments
19 at the same time periods. Documentation was made
20 of operative site and systemic complications.

21 [Slide.]

22 Radiographic review included those of
23 femoral and acetabular radiolucencies and
24 assessment of cup migration.

25 [Slide.]

1 This slide reviews the patient
2 demographics. In total, 706 cases with
3 noninflammatory degenerative joint disease were
4 implanted. There were no statistically significant
5 differences in the distribution of cases between
6 the limbs of the study with regard to gender or
7 etiology.

8 [Slide.]

9 The study data was pooled. In Study A at
10 24 months, there were 87 hips available; Study B,
11 43; and Study C, 81. It is worth noting that
12 there is a statistically significant lower mean age
13 in Study C than from those A and B. It is worth
14 noting that that would apply as well to the control
15 group, so that in Study C, we are looking at
16 younger patients for metal-on-metal as well as
17 younger patients for metal-on-polyethylene, but a
18 difference between the mean age of the other two
19 studies.

20 [Slide.]

21 Looking at gender bias, there is no
22 statistically significant difference across the
23 study groups for the investigational versus
24 control.

25 [Slide.]

1 With regard to clinical outcomes, this
2 slide shows the mean Harris hip function score over
3 time. There is no difference either statistically
4 or practically between the investigational or the
5 control group at any of the time points studied.

6 [Slide.]

7 With regard to the pain component of the
8 Harris hip score, there was no difference between
9 the investigational or the control groups at any
10 time point studied.

11 [Slide.]

12 With regard to the total Harris score,
13 obviously following from the functional and the
14 pain score, there was no difference in the
15 investigational or the control groups at any time
16 point studied.

17 [Slide.]

18 With regard to the radiographic
19 observations, cup radiolucencies--in Study A, 5.1
20 percent had an interface radiolucency in at least
21 one zone of the investigational limb; for the
22 controls, 6.3 percent had a radiolucency in at
23 least one zone. In Study B, 11.1 percent had a
24 radiolucency in at least one zone. Because of an
25 open control, corresponding data is not available

1 for the metal-on-polyethylene group. In Study C,
2 there was a radiolucency in at least one zone in 22
3 percent of the investigational devices and 8.8
4 percent of the metal-on-polyethylene. Pooling that
5 data, 12.6 percent of the components had a
6 radiolucency in at least one zone of the
7 investigational devices compared to 7.3 percent in
8 the control limb. No cup had a radiolucency in all
9 three zones.

10 [Slide.]

11 With regard to the femoral components, in
12 Study A, no radiolucencies were observed in the AP
13 projection in the investigational limb; 8.3 percent
14 radiolucencies observed on the AP projection of the
15 thermal component in the controls. For Study B,
16 8.6 percent had a radiolucency, and again, because
17 of the open nature of the control, corresponding
18 data is not available for the European study. With
19 Group C, 11.1 percent of the femoral components had
20 a radiolucency on the AP projection in the
21 investigational device, and 18.2 percent on the
22 femoral side.

23 With regard to radiolucencies on the
24 femoral component in the lateral view, in Study A,
25 2.6 percent of the investigational, 2.1 percent of

1 the control. Again, this is not available in
2 Europe. The lateral x-rays were not available for
3 either the investigational or the control. And in
4 Study C, 5.7 percent of the femoral components had
5 a radiolucency on the lateral view compared to 3.2
6 percent in the control group. I am sorry if I
7 didn't say that correctly--5.7 for the
8 investigational and 3.2 for the control.

9 In total, femoral radiolucencies on the AP
10 view, 6.4 percent for the investigational and 12.3
11 percent for the control; on the lateral view, 4.1
12 percent for the investigational and 2.5 percent for
13 the control.

14 [Slide.]

15 With regard to cup migration in the
16 superior/inferior plane, in Study A, 23 components
17 had evidence of migration of less than 5
18 millimeters, and 16 had evidence of migration of
19 greater than 5 millimeters in the investigational.
20 In the metal-on-polyethylene control, 32 components
21 had evidence of less than 5 millimeters migration,
22 and 15 had evidence of greater than 5 millimeters.

23 With regard to Study B, 22 components had
24 less than 5 millimeters and 4 greater than 5
25 millimeters. Corresponding data was not available

1 for the controls.

2 In Study C, 36 components had less than 5
3 millimeters of migration, and none had more than 5
4 millimeters of migration.

5 With regard to the controls, 34 had less
6 than 5 millimeters of migration, and none had more.

7 Pooling that data, where were 81
8 components that had less than 5 millimeters of
9 migration and 20 components that had more than 5 in
10 the investigational group; 66 had less than 5, and
11 15 had more than 5 millimeters of migration in the
12 controls.

13 With regard to medial/lateral migration,
14 Study A, 29 had less than 5 millimeters of
15 migration, and 10 had more. In the controls, 40
16 had 5 millimeters or less of migration, and 7 had
17 more.

18 For Study B, 20 components had less than 5
19 millimeters of migration, and 6 had more.
20 Corresponding data was not available on the
21 controls.

22 For Study C, 36 had less than 5
23 millimeters of migration, none had more than 5
24 millimeters of migration. For the
25 metal-on-polyethylene controls, 34 had less than 5

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1 millimeters migration, and none had more.

2 In total, 85 components had less than 5
3 millimeters of migration, 16 had more. For the
4 controls, 74 had 5 millimeters of migration, and 7
5 had more.

6 [Slide.]

7 This slide details the complications.
8 Basically, there were few complications across both
9 groups that numbered in the onesies, twosies, with
10 the exception of the generic category of
11 musculoskeletal, where there were 15 in each group,
12 and this ranges anywhere from back pain to neck
13 pain to muscle twitching and cramping.

14 Serious complications such as pulmonary
15 embolism were low in both cases, and no
16 statistically significant differences.

17 [Slide.]

18 There were intraoperative complications
19 reported. Difficult femoral insertion was
20 identified in one investigational case; none was
21 identified in the metal-on-polyethylene controls.

22 Intraoperative dislocation was identified
23 in three metal-on-metal cases and none of the
24 metal-on-polyethylene cases.

25 A femoral perforation--the femoral stem

1 going through the femur--occurred in three of the
2 metal-on-metal cases and in none of the
3 metal-on-polyethylene cases. And a fracture of the
4 trochanter occurred in one metal-on-metal case but
5 none of the metal-on-polyethylene cases.

6 [Slide.]

7 Postoperative complications at the local
8 site are detailed on this slide. There were two
9 cases of deep infection in the metal-on-metal; none
10 in the metal-on-polyethylene. One of those cases
11 was salvaged, one of them was revised.

12 Dislocation/subluxation, six cases in the
13 metal-on-metal, 1.5 percent; three cases in the
14 metal-on-polyethylene, 1.0 percent.

15 We can go down the list--fracture of the
16 femur, hematoma, heterotopic ossification, nerve
17 palsy, pain--six cases reported pain at the
18 operative site in metal-on-metal, and only one case
19 in the metal-on-polyethylene. There were no
20 statistically significant differences between the
21 two groups.

22 [Slide.]

23 The next slides detail a summary of
24 first-generation metal-on-metal designs. The
25 selected studies are presented because they

1 represent an average follow-up of less than 5
2 years. So we are trying to get some
3 apples-to-apples comparison with relatively
4 short-term follow-up comparing the unpublished data
5 that was just presented to previous published data
6 on first-generation designs.

7 There are fairly good numbers here. You
8 are looking at a total of 1,624 devices in which
9 there were 37 dislocations, giving a dislocation
10 rate of 2.28 percent.

11 Loosening in the short term, 147 cases
12 presented for a loosening rate of 9.05 percent.
13 Although not specifically stated in the previous
14 data, there were no aseptic loosening in either
15 the metal-on-metal or metal-on-polyethylene cases
16 from the unpublished dataset.

17 [Slide.]

18 This slide looks at comparisons to
19 second-generation designs. These are basically
20 metal-on-metal devices introduced subsequent to
21 1985, initially in Europe and subsequently in the
22 United States. The numbers of cases are
23 comparatively small when we look at this slide
24 compared to the first-generation designs, but if we
25 look across dislocation rate, in Study 15, 54

1 devices, 2 dislocations, for a 3.7 percent rate of
2 dislocation, none loose. If we look at Study 23,
3 74 devices, 3 dislocations, a dislocation rate of 5
4 percent, none looses. Study 75 reports 100
5 devices, but neither the dislocation nor the
6 loosening rate were actually reported in that
7 publication.

8 Below is the comparison of the unpublished
9 studies. Study A, one dislocation, for 0.45
10 percent; Study B, 3 dislocations, at 3.45 percent;
11 and Study C, 2 dislocations, at 3.17 percent, for
12 an overall dislocation rate of 1.49 percent.

13 I stand corrected--actually, that is not
14 correct. The loosening shown here was septic
15 loosening, one of the infected cases, that was
16 revised, so the loosening is a septic loosening,
17 and there were no aseptic loosening in the pooled
18 dataset.

19 [Slide.]

20 In conclusion, total hip replacement is a
21 technically demanding procedure. In the
22 unpublished studies, there was no design-related
23 device removal. The sole device that was taken out
24 was for septic loosening. There was a
25 significantly lower loosening rate compared to

1 first-generation metal-on-metal devices, and I want
2 to use that term generically, because we are
3 looking at more than just the cup or the
4 articulation; we are looking at the entire
5 reconstruction, which includes the prosthetic
6 components as well as the surgical component.

7 The unpublished studies are at least
8 equivalent to the second-generation reports in the
9 literature to date.

10 [Slide.]

11 A review of the published literature has
12 been conducted from 1966 to 1998. Articles were
13 written in English only and searched from Medline,
14 Embase, and Biosis databases. Key words and key
15 phrases included "metal-on-metal hips", "hip
16 prostheses", "acetabular", "McKee-Farrar", "Ring",
17 "Sivash" and "Metasul"--the last terms being the
18 trade names of previous-generation or even
19 current-generation metal-on-metal devices.

20 Tabulations of the clinical results and
21 compilations from 47 articles were presented as
22 display tables in the reclassification petition.
23 Most of the articles summarized were reporting on
24 first-generation metal-on-metal hips.

25 [Slide.]

1 There is a lot of heterogeneity in that
2 data. Patients were treated for a variety of
3 indications and in varying proportions, all of
4 which were standard indications for total hip
5 replacement. Metal-on-metal prosthesis designs
6 include the Ring, McKee-Farrar, Urist, Metasul,
7 Howse, McMinn, Postel, Low-Friction Band, McBride,
8 Sivash, Gaenslin, and Stanmore.

9 Follow-up ranged from 6 months to 24-1/2
10 years, with the majority reporting between one and
11 5 years of follow-up.

12 The mean patient ages ranged from 36 to 72
13 years, but the mean ages in most fell between 60
14 and 69 years.

15 A number of clinical outcome measures were
16 utilized including Charnley score, Harris,
17 d'Aubigne, Iowa, Mayo, and UCLA.

18 The majority of articles reported on a
19 large patient series of at least 100 cases, ranging
20 from 6 to 1,808 cases.

21 [Slide.]

22 Clinical results are summarized and
23 presented in Display Table 8, pages 49 to 63 of the
24 reclassification petition. Overall clinical
25 ratings reported 21 articles and, not surprisingly,

1 were highly variable.

2 Good to Excellent ratings ranged between
3 38 percent and 99 percent of the cases. Fourteen
4 of the 21 articles rated 80 percent or more of the
5 cases as Good to Excellent, and 7 of 21 had less
6 than 80 percent rated as Good to Excellent.

7 [Slide.]

8 This is an overview of the published
9 articles. You can see tremendous variable in the
10 number of devices, the percent Good to Excellent,
11 the percent Fair to Poor.

12 [Slide.]

13 It may be worth noting that perhaps the
14 biggest problem in looking at historical data is
15 that there has been a tremendous evolution in the
16 manner in which clinical evaluations and
17 radiographic evaluations are conducted. So we have
18 to resort to some relatively gross overview
19 statistics because the details of the studies are
20 sufficiently different.

21 Complications and adverse events from the
22 published studies were compiled, tabulated, and
23 presented in Display Table 9, pages 64 to 77 of the
24 reclassification petition. The complications
25 reported were generally the same types as those

1 reported in the unpublished studies as well as
2 those known to occur with metal-on-polyethylene
3 hips. Evidence of radiographic loosening in device
4 removals occurred with greater frequencies for
5 metal-on-polyethylene hip prostheses.

6 Radiographic loosening ranged from 8 to
7 82.5 percent, with the majority of articles
8 reporting loosening rates between 1 and 10 percent,
9 that being 11 of the included articles.

10 Higher frequencies of metal-on-metal cups
11 were reported as having evidence of radiographic
12 loosening than the femoral prostheses.

13 [Slide.]

14 Device removal ranged from 1.3 to 100
15 percent, with the majority of articles reporting
16 removal rates between 1 and 10 percent--that would
17 be 16 articles; and 11 and 20 percent, or 14
18 articles.

19 The reasons cited for device removal are
20 not unique to metal-on-metal devices and occur with
21 metal-on-plastic devices and include acetabular
22 migration, stiffness, aseptic loosening, loose
23 screws, component dislocation, femoral fracture,
24 femoral necrosis, fracture of the prosthesis,
25 infection, inflammatory loosening, limited

1 ossification or heterotopic ossification, pain,
2 patient trauma, femoral perforation, rheumatoid
3 arthritis, septic loosening, technical error--but
4 note that within this, there are no reasons for
5 removal listed that are specifically related to the
6 bearing surfaces themselves or excessive wear.

7 [Slide.]

8 The reports from the published clinical
9 studies on the metal-on-metal hip prostheses have
10 identified the risks to patients with these
11 devices. The risk can be minimized through the use
12 of recognized standards, special controls, and
13 device labeling.

14 Mandatory manufacturing and design control
15 requirements, guidance documents, and testing of
16 metal-on-metal hip prosthesis designs will further
17 ensure the manufacture and safe use of these
18 devices.

19 Risks have been categorized in the
20 reclassification petition and the means to control
21 or minimize them is specified.

22 Thank you very much. I meant to do this
23 at the beginning--I need to make a disclosure. I
24 have been a paid consultant to DePuy for about the
25 past 5 years and have been working with them in the

1 development of their metal-on-metal bearing system.

2 Thank you.

3 DR. YASZEMSKI: Thanks, Dr. Schmalzried.

4 MR. CRAIG: Thank you.

5 Next will be Dr. Jacobs.

6 DR. JACOBS: Good morning, and thank you.

7 My name is Josh Jacobs. I am currently a
8 professor of orthopedic surgery at Rush Medical
9 College. My clinical practice consists of adult
10 reconstructive surgery, and my research interests
11 are in biomaterials and biocompatibility.

12 I receive research funding support from
13 Wright Medical, from Merck, and from Zimmer; I am
14 also a paid consultant from Zimmer.

15 [Slide.]

16 My charge here is to summarize some three
17 decades of investigation that have looked at
18 various aspects of the biocompatibility of
19 metal-on-metal bearings.

20 Specifically, I am going to discuss what
21 has been reported on the tissue responses as well
22 as any potential biological effects that have been
23 associated with these bearings.

24 There has actually been considerable
25 literature on this issue since we have had, as I

1 mentioned, over three decades of experience with
2 metal-on-metal bearings, and I draw your attention
3 to one publication in particular, and this is a
4 supplement to Clinical Orthopaedics that was
5 actually a symposium that was presented in 1994 and
6 1995 in Santa Monica that was really a prelude to
7 the new era of metal-on-metal bearings and really
8 summarized the extant literature at that time.
9 Many of the studies that we have discussed already
10 and will continue to discuss today are published in
11 this volume.

12 Particles and inflammatory
13 response--studies have shown that both polyethylene
14 and metal wear particles can generate a cellular
15 response. Whole polyethylene elicits predominantly
16 mononuclear histiocytes, and for larger particles,
17 multinucleate foreign body giant cells, metal
18 particles tend to elicit predominantly a
19 mononuclear histiocyte with very rare giant cells,
20 and when they occur, they tend to be associated
21 with methacolate voids and barium sulfate
22 particles.

23 [Slide.]

24 There have been retrieval analyses on
25 patients with failed metal-on-metal devices--and I

1 remind you that these are failed devices retrieved
2 for cause. There is not a large series available in
3 the literature that have looked at successfully
4 performing devices, that is, at autopsy. In a
5 retrieval analysis performed on 9 such implants, it
6 was found that metal wear debris did not evoke
7 multinucleate giant cells as mentioned. In
8 general, there was a lower amount of histiocytic
9 reaction as compared to polyethylene wear debris,
10 and there was evidence of transport of metal debris
11 to lymph and/or deeper soft tissues.

12 The volume of debris generated was
13 generally low, with some authors suggesting that
14 there is probably an equilibrium that is maintained
15 between the generated wear debris and histiocytic
16 activity and then clearance mechanisms that tend to
17 clear the particles through lymphatic or vascular
18 channels.

19 Fewer generated metal particles and
20 macrophages were noted in the metal-on-metal
21 retrievals compared to comparable polyethylene
22 retrievals.

23 Hans Willert, who has a great deal of
24 experience with this--he is a European orthopedic
25 surgeon who works in Germany--looked at 19

ah

1 retrieved metal-on-metal devices. He analyzed them
2 for the presence of metal ions using atomic
3 absorption spectrophotometry and coupled plasma
4 mass spectrometry. He found that the chromium
5 levels were highest, followed by cobalt, nickel,
6 and molybdenum in the tissues.

7 Very little particulate wear was found in
8 all tissues analyzed, and the particles that were
9 examined ranged from 0.5 to 5.0 microns. But there
10 is one caveat here in that this analysis was
11 restricted to light microscopy, and in fact, some
12 of the newer literature would suggest that if you
13 look at electron microscopy, some of the particles,
14 and perhaps the majority of the particles, may
15 actually be in the tens of nanometer size range.

16 Again, these authors have confirmed
17 previous reports of wear particles are transported
18 systemically via perivascular lymphatics, and in
19 fact, Willert was the first to propose this with
20 regard to metal-on-polyethylene debris back in the
21 1970s.

22 Systemic debris has also been documented.
23 A published report that has been presented in the
24 petition includes one from Langkamer from the UK.
25 He looked at systemic wear debris in two total hip

1 cases--these were not patients with metal-on-metal
2 bearings, but patients with other implants,
3 metal-on-polyethylene, and I think in one case,
4 internal fixation devices. They found that
5 chromium ion levels were elevated in the synovium,
6 in the bursa and lymph nodes, and they could be up
7 to 10 times normal. There is widespread particle
8 dissemination in the spleen, liver and lymph nodes,
9 and confirmation was made that the particles moved
10 via lymphatic system. Whereas they have identified
11 primarily metal particles because of their ease of
12 identification, polyethylene particles can also be
13 identified, as other authors have, using more
14 exacting techniques.

15 [Slide.]

16 In terms of toxicity, the hexavalent form
17 of chromium is known to be quite toxic, and because
18 it is able to cross the cell membrane, can be
19 associated with the cell and exert intracellular
20 toxicities.

21 Fortunately, studies have shown that with
22 regard to solid metal implants, the form that is
23 generally produced is the trivalent form, which
24 tends to have less toxicity. So there has been no
25 documentation that solid metal implants can release

1 the toxic hexavalent form of chromium.

2 In terms of cobalt ions, Kathy Merritt and
3 others have reported that in certain animal models,
4 although they can be initially toxic to cells,
5 cobalt ions in general can be rapidly cleared by
6 the organism, and the toxicity tends to diminish
7 with time.

8 [Slide.]

9 Another issue that emerged back in the
10 McKee-Farrar era and is currently of concern is the
11 issue of metal hypersensitivity. Evans really
12 brought this issue to the fore in a publication
13 back in the mid-seventies when he was looking at
14 patients with failed metal-on-metal devices, and he
15 suggested a causal relationship between loosening
16 and sensitivity in 39 cases that he examined. Nine
17 of the 14 cases with loose components tested
18 positive for metal sensitivity, and no case having
19 well-fixed components exhibited sensitivity.

20 Now, there are a few caveats that need to
21 be issued with regard to this study. Sensitivity
22 was determined in this study by cutaneous patch
23 testing, and there is a question about whether
24 cutaneous patch testing is relevant to the
25 hypersensitivity phenomenon that may occur in the

1 deep tissues.

2 For example, the antigen-presenting cells
3 in the dermis, the Langerhans cells in the dermis,
4 are unique to that location and may elicit unique
5 reactions that are not necessarily seen in deep
6 tissues. So the correlation between cutaneous
7 hypersensitivity and deep hypersensitivity has
8 really not been well-established.

9 Another caveat is that other studies that
10 have looked at this issue have not established a
11 relationship between metal sensitivity and implant
12 loosening.

13 Also, there is an issue of a
14 chicken-or-egg argument here, and that is is the
15 metal sensitivity a cause for loosening, or is it
16 simply an epi-phenomenon that reflects the fact
17 that when an implant becomes loose, it generates
18 more debris, and thus there is more likely to be a
19 hypersensitivity response which in fact did not
20 mediate the initial loosening process.

21 So it is a very complicated issue and very
22 difficult to establish causality.

23 [Slide.]

24 The final issue that needs to be discussed
25 is the issue of carcinogenicity. The reason this

1 has emerged and has been a topic of discussion
2 concerning metal-on-metal bearings is that it is
3 known that certain metals in certain chemical forms
4 can be carcinogenic. For example, in metal
5 refining industries where workers may deal with
6 metal vapors or ores, there have been reports of
7 increased cancer incidence. So the question has
8 always been before us as to whether implanted
9 metallic devices can cause either local or remote
10 carcinogenesis.

11 Visuri from Helsinki, Finland had a large
12 series of 433 patients with McKee-Farrar
13 metal-on-metal implants whom he had clinical data
14 on and whom he could then cross-reference with a
15 cancer registry in Finland to determine relative
16 risk of cancer. In this study, he showed that
17 while there was no increase in overall incidence of
18 cancer, the incidence of certain site-specific
19 cancers did vary. In particular, there was lower
20 incidence of breast cancer and higher incidence of
21 leukemia and lymphoma. He concluded in his initial
22 report in 1991 that longer-term studies were needed
23 with longer follow-up.

24 [Slide.]

25 In his follow-up report, which is

1 published in the volume that I mentioned, Clinical
2 Orthopaedic Supplement, he again compared cancer
3 rates in patients with metal-on-metal and
4 metal-on-polyethylene implants to the general
5 population in Finland, and again he had access to
6 the Finnish Cancer Registry. In these cohorts,
7 there were lower rates for lung cancer, and there
8 was no variation in other cancers for the pooled
9 metal-on-metal and metal-on-polyethylene hip
10 implant patient groups. No local sarcomas were
11 noted in either total hip patient group, and while
12 there were slightly higher incidences for lymphoma
13 and leukemia for the metal-on-metal hip patients,
14 this observation was not statistically significant.
15 Furthermore, he has commented that the higher
16 incidences of lymphoma and leukemia did not appear
17 when reexamined in a later report with longer
18 follow-up.

19 [Slide.]

20 Bill Gillespie et al. have also studied
21 this. In a study similar to the design of
22 Visuri's, he looked at 358 total hip patients, and
23 he compared this to the New Zealand Cancer
24 Registry. Now, it is not precisely known how many
25 of these patients had metal-on-metal bearings, but

1 I have heard Dr. Gillespie state that he felt that
2 maybe as many as half of these patients may have
3 had metal-on-metal bearings.

4 Overall, the total hi patients had a
5 significantly lower overall incidence of cancer, up
6 to 10 years, and had a significantly higher
7 incidence after 10 years following hip replacement.
8 Breast, colon, and rectal cancers occurred less
9 frequently up to 10 years, whereas lymphatic and
10 hemopoietic cancers were significantly higher for
11 patients with total hip replacements.

12 He acknowledged the fact that other
13 underlying factors and/or mathematical probability
14 may have brought about these results. The way he
15 described or tried to bring together these two
16 observations was that he supposed that there was
17 overall a chronic immune stimulation of the
18 organism that resulted in increased immune
19 surveillance for certain malignancies but over time
20 could actually cause malignancies in the cells
21 involved in the immunological blockade.

22 [Slide.]

23 There have been other, larger studies that
24 have been conducted. For example, Mathiesen looked
25 at a much higher number of patients; he looked

1 10,785 total hip patients and compared this to the
2 Swedish Cancer Registry. The incidence of tumors
3 was lower than expected, as had been shown by the
4 previous studies. The overall cancer incidence was
5 slightly higher for patients with 10 or more years
6 of follow-up, and the risk of leukemia and lymphoma
7 was lower for total hip patients after 10 years.

8 So these findings would appear to be
9 exactly opposite to those reported by Gillespie.
10 But it should be pointed out that metal-on-metal
11 bearings were not particularly common in Sweden,
12 and it is unlikely that there is a high proportion
13 of these 10,000 patients who had metal-on-metal
14 bearings.

15 [Slide.]

16 A recent review has been published in
17 Journal of Bone and Joint Surgery, looking at six
18 of the best published studies which have examined
19 the relative risks of cancer following
20 metal-on-metal and metal-on-polyethylene total hip
21 replacement. Six studies that have been published
22 were pooled to calculate relative risks, and the
23 relative risk ratio was calculated by dividing the
24 total number of observed cancer cases following
25 total hip replacements by the number of expected

1 cancer cases within the general population.
2 Relative risk ratios were calculated for all types
3 of cancers in general and for hematopoietic cancers
4 and sarcoma.

5 [Slide.]

6 If we look at the combined relative risk
7 for all these studies, we can see that the combined
8 relative risk is 0.97 with confidence intervals
9 that are actually less than unity, indicating that
10 that is a statistically significant finding.

11 Does this suggest that we should be
12 putting in joint replacements to protect our
13 patients from cancer? No, I do not think that is
14 what this is saying. But it does suggest that
15 there may be some population effects that are
16 dictating these results other than the presence of
17 the total hip replacement patients. For example,
18 patients who receive total hips may in general come
19 from a healthier patient population.

20 So this combined incidence certainly does
21 not indicate any causal relationship between
22 malignancy and hip replacement, and it also shows
23 the broad widths of the confidence intervals of the
24 previous studies.

25 [Slide.]

1 If we look specifically at hematopoietic
2 malignancies, the combined relative risk is near
3 unity, so there is no statistically significant
4 increase in the risks of these hematopoietic
5 malignancies, and there is no causal association.

6 The studies that have suggested this
7 association, Gillespie's and Visuri's, have very
8 wide confidence intervals, and this is largely
9 because of their small patient samples. But again,
10 these studies do have a higher proportion of
11 patients who have metal-on-metal bearings.

12 [Slide.]

13 In terms of sarcoma, the combined relative
14 risk is 1.0. There are broad confidence intervals
15 in the studies, and they do not support a causal
16 relationship, and in fact, in a study by Visuri,
17 there were no sarcomas reported, which is why the
18 confidence intervals are so broad.

19 [Slide.]

20 Now, if we look at metal-on-metal versus
21 metal-on-polyethylene, for all cancers, after
22 metal-on-metal, 0.95; metal-on-polyethylene, 0.93.
23 Hematopoietic malignancies after metal-on-metal,
24 1.59; metal-on-polyethylene, 0.93--but because of
25 the large confidence intervals, this is not

1 statistically significant. In terms of sarcoma
2 after metal-on-metal, 0.00; after
3 metal-on-polyethylene, 0.76--but again because of
4 the large confidence bands, there are no
5 statistically significant differences.

6 [Slide.]

7 Where does this leave us? It leaves us
8 with the knowledge that the available data do not
9 support a causal link between total hip
10 replacements and the development of cancer.

11 While there is an apparent increased risk
12 of cancer after metal-on-metal total hip, and while
13 this was not seen, the numbers of metal-on-metal
14 THR patients used for comparison were too small for
15 reliable assessment to be made. So to really
16 resolve this issue, it is generally recognized that
17 future studies must include larger, more diverse
18 patient populations with longer follow-up.

19 [Slide.]

20 In a consensus statement that was produced
21 during the meeting in Santa Monica, a number of
22 leading investigators in the field came up with
23 this consensus statement with regard to the issue
24 of carcinogenicity, and that is specifically, that
25 "Current studies of carcinogenicity rates in total

1 hip patients are inadequate. More studies with
2 longer follow-up are needed. A 20-year latency
3 period for tumor induction may be a concern for
4 younger and total hip patients. Current evidence
5 is compatible with a small increase in risk for
6 cancer. However, the potential benefits of
7 improved wear properties, less periprosthetic bone
8 resorption, and lower revision rates must be
9 weighed against a slight increase in the risk for
10 cancer."

11 That is an important point that I want to
12 leave you with, that although slight risk may
13 exist, it has to be balanced against the other
14 risks and the benefits that we may see with lower
15 revision rates from the use of this technology.

16 [Slide.]

17 So in summary of some of the biological
18 issues, both metallic and polyethylene wear
19 particles elicit inflammatory responses, but differ
20 with respect to the degree and type of cellular
21 response.

22 Cobalt ions are initially toxic to cells
23 but may normalize after clearance, which can occur
24 rapidly for cobalt.

25 Chromium ions, which are toxic in the

1 hexavalent state, have not been documented to have
2 been released by solid metal implants.

3 Wear particles from metal-on-metal
4 implants are typically extremely small and may
5 extend in the tens of nanometer range.

6 Metallic wear particles are usually
7 highest in the immediate surrounding tissues and
8 taper off at more distant organs supplied by the
9 lymphatic and blood systems.

10 Cancer studies show no or very slight
11 correlation with the presence of cobalt-chrome wear
12 particles.

13 Current studies to assess the risk for
14 cancer associated with total hip replacement are
15 inadequate.

16 The 20-year latency period for tumor
17 generation may be a concern for the younger hip
18 replacement patient; however, any slight increase
19 in the risk for cancer with metal-on-metal hip
20 prostheses must be assessed against the probable
21 benefits associated with these devices.

22 Thank you very much for your attention.

23 MR. CRAIG: Dr. Medley?

24 DR. MEDLEY: My name is John Medley. I am
25 associate professor of mechanical engineering, and

1 my research interests are in simulator testing,
2 orthopedic tribology, large thrust bearings--but
3 that is not relevant here.

4 I have no financial disclosures to
5 make--at least, I don't think I do.

6 [Slide.]

7 In the early 1960s, metal-on-metal was
8 competitive with metal-on-polyethylene implants,
9 but some of the McKee-Farrar implants had early
10 failures, many for reasons unrelated to the bearing
11 surfaces.

12 The cause of the ones that were related to
13 the bearing surfaces appeared to be high friction
14 and wear associated with equatorial contact--in
15 other words, they had lower negative clearances.

16 There was strong support for this from the
17 classic study of Walker and Gold in 1971 and a more
18 recent study by McKellop. The early failures with
19 this led to a decline in the use of metal-on-metal
20 implants.

21 However, as most of you already know, the
22 osteolysis associated with polyethylene wear
23 particles led to a revival of interest in
24 metal-on-metal implants because they can have very
25 low volumetric wear.

1 [Slide.]

2 This is a McKee-Farrar implant after being
3 in the patient for 25 years, and it almost looks
4 like it has come out of the package.

5 [Slide.]

6 It was also found very early on that high
7 clearance and low clearance can cause increased
8 wear. Semlitsch et al. were the ones who looked at
9 that.

10 The idea then, with the modern
11 metal-on-metal implants, was to have an optimal
12 clearance, low wear, reduced osteolysis, and
13 improved clinical performance.

14 [Slide.]

15 The fact that higher clearance correlates
16 with higher clinical wear can be shown in a
17 retrieval study, again by McKellop. And if you
18 plot it on the graph, you can see it fairly
19 clearly, that the high-clearance end tended to have
20 higher wear--this was measured from retrievals--and
21 the low-clearance had lower wear.

22 There is one value that I did not include.
23 The atypical value for some reason was very low
24 wear with this perhaps not very active patient.

25 The "R" on the bottom is what I call

1 "effective radius." It is a way in which you can
2 compare a number of different implants with
3 different head sizes and clearances. So it is not
4 just clearance that is the only issue here.

5 If you put one more data point on that had
6 a very high clearance, you can get a more dramatic
7 curve that kind of hides some of the details, but
8 it does show very clear that as the clearances
9 increase, you do get increased wear.

10 [Slide.]

11 This brings us to the end of the
12 introduction. This is what we knew by the
13 mid-1990s, and the question that I am addressing
14 now is simulator testing and possible regulatory
15 control with it.

16 Why do you do simulator testing? In
17 tribological applications, often of much less
18 complexity than the hip implants, simulation
19 provides the only reliable approach to make some
20 prediction of wear. This is fairly
21 well-established for other applications in
22 tribology, not just the bio-tribology that we are
23 dealing with here.

24 [Slide.]

25 The reason you do simulator testing is to

1 understand and predict clinical wear performance,
2 improve implant design, and avoid poor designs.

3 [Slide.]

4 If you are going to do this with a
5 simulator, you have to be sure that your simulator
6 represents clinical wear rates.

7 [Slide.]

8 The clinical wear rate has not been widely
9 published, but based on these studies that are in
10 our original petition, I plotted some of the
11 results, and those are what you will see on the
12 next slide.

13 [Slide.]

14 These were all from retrievals, and there
15 are two classes shown there. There is the Modern
16 Sulzer components that go up to about 5-1/2 years;
17 and there is a selection of the McKee-Farrars from
18 the McKellop study that I showed earlier; they were
19 the ones that had the low clearance, and I am
20 including them mainly because they had that data
21 point up there, and the other one down here, which
22 were both at 24 years. This is the only 24-year
23 data that I could find, and it gives you some idea
24 that the Modern Sulzer components if you
25 extrapolate them are more or less doing the right

1 thing. It is very hard to get a really precise
2 idea because the clinical data is fairly scattered,
3 but you certainly do see a trend. You see a trend
4 to increasing wear and tending to level off a bit.

5 These wear rates are incredibly low when
6 you compare them to polyethylene. Polyethylene,
7 looking at 30 or 40 or maybe 50 cubic millimeters a
8 year, by 25 years would be way, way off this graph.
9 I haven't shown them, and I can't show them on this
10 graph, but polyethylene has much, much higher wear
11 volumes than metal-on-metal.

12 [Slide.]

13 You can hardly see it here, but that
14 little circle--I am going to compare the simulator
15 data in this region. The simulator data we have
16 only goes out to 3 million cycles, which is
17 approximately 3 years. In a very proximate way,
18 you can say about a million cycles equals one year
19 in the body; there is some scatter on that
20 designation. But that is the region where I am
21 going to do the comparisons.

22 [Slide.]

23 I am going to compare with existing
24 simulator wear rates from a number of different
25 investigators, simulators and protocols, all of

1 which are referenced in the petition, but this
2 graph has not been published before.

3 DR. WITTEN: Excuse me. From the
4 information that you are providing, if it is new
5 and it is not in the petition, we will need it.

6 MR. MEDLEY: It is not new. It is based
7 on--

8 DR. WITTEN: It is based on what is in the
9 petition.

10 DR. MEDLEY: Yes.

11 DR. WITTEN: It will help us if it gets
12 submitted to the petition later, after this
13 meeting.

14 DR. MEDLEY: Yes. I was careful to take
15 studies that were referenced in the petition, to
16 pull this data.

17 What you see here are the clinical rates
18 from before--there is the McKellop one, and there
19 is the Sulzer one--and then, a variety of different
20 simulator wear rates from different studies.

21 In general--you'll notice the trend--they
22 fall within the scatter of the clinical results.
23 This one in particular was a bit high because we
24 had fairly rough surfaces, and I'll talk about that
25 later. In some of the other ones, there was a

1 definite leveling off of the wear. This set in
2 here--this is our data--had very smooth implants
3 with low clearance. So these were ideal implants
4 and did very well in our simulator testing.

5 [Slide.]

6 The other thing to look at in a simulator
7 test is the surfaces. We have looked at the
8 surfaces from the simulator-tested components and
9 clinically retrieved surfaces, and there are
10 distinct similarities between them. They both show
11 an abrasive scratching that tends to polish out
12 over time. They show micro-pitting. Some of the
13 micro-pits have fractured carbides in the pits.
14 But the micro-pitting did not correlate with
15 higher wear and did not seem to be too important a
16 phenomenon as far as we could tell.

17 [Slide.]

18 We have looked at wear particles as well.
19 This is fairly current work. This reference is in
20 the petition, and in it, there is a distinct
21 similarity between size and shape of particles from
22 the simulator and from periprosthetic tissues
23 around metal-on-metal implants.

24 [Slide.]

25 This means, then, that we have established

1 to some extent that simulators do represent
2 clinical wear. Now the question is what can we
3 learn about the wear phenomenon from the
4 simulators.

5 One of the first things we looked at was
6 the diametrical clearance, and we found that with
7 increasing diametrical clearance, you could
8 certainly get increasing wear in the simulator. A
9 number of studies have found this.

10 We also found--and not so many studies
11 looked at this, but we did this work--that wear
12 increased with increasing surface roughness.

13 Now, very quickly, I will say why we think
14 this happens. We believe this happens because
15 there is to some extent fluid film lubrication
16 occurring in the articulation. A number of people
17 have postulated this; no one can be absolutely
18 certain, although there are some measurements from
19 Dowson et al. where they did electrical resistance
20 measurements across the film that gave fairly
21 convincing evidence that there was some sort of
22 film action.

23 [Slide.]

24 How this works is that you have surfaces
25 with converging/diverging geometry; wealth of

ah

1 surface motion; and just enough lubricant maybe in
2 train to separate most of the asperities.

3 This schematic shows a very thick fluid
4 film--fluid films are in the order of tens of
5 nanometers thick by our predictions--and the
6 surfaces are smooth enough that that is still
7 effective enough to separate some or maybe all
8 asperities under certain activities.

9 [Slide.]

10 The next issue to deal with is can
11 simulators identify high-wear metal-on-metal
12 implants--in other words, can they identify a bad
13 implant.

14 We do not have much evidence on this,
15 mainly because nobody has been paying us a lot of
16 money to study bad implants, but there is some data
17 that has shown that if you have negative clearance
18 implants in the simulator, they got two of them to
19 seize at 20,000 cycles. This was a bad implant.

20 [Slide.]

21 We had one bad result that had a very high
22 diametrical clearance and gave us incredibly high
23 wear. We only had one, and we didn't pursue why,
24 and we don't fully understand it, but it certainly
25 picked out a high-clearance implant and showed it

1 to be clearly very bad.

2 [Slide.]

3 If you are going to use simulators for
4 regulatory control, the idea would be to take
5 selected implants, do simulator testing, and
6 compare the results with controls. In our
7 petition, the controls we advocate now are cleared
8 metal-on-metal implants.

9 [Slide.]

10 Cleared metal-on-metal implants have these
11 geometric features--the clearance is in this range;
12 the roughness is less than about 30 nanometers;
13 sphericity is fairly good. These are the features
14 of the cleared implants.

15 [Slide.]

16 We would expect that new metal-on-metal
17 implants would probably have similar geometries,
18 but it is simulator testing that can determine
19 substantial equivalence.

20 [Slide.]

21 In conclusion, then, we can explain the
22 earlier failures of the McKee-Farrar implants. We
23 can link simulator wear to clinical wear in the
24 amount, surfaces, particles, clearance influence,
25 and poor design identification. And we can propose

1 regulatory controls.

2 Thank you.

3 MR. CRAIG: Thank you.

4 That concludes the OSMA presentation.

5 DR. YASZEMSKI: Thank you, Mr. Craig, and
6 thank you to all the presenters.

7 We are going to proceed now with the FDA
8 presentation by Mr. Steigman, after which we'll
9 take a 10-minute break before proceeding with the
10 lead panel member presentations.

11 MS. WITTEN: I would just like to clarify
12 for the petition sponsor that a lot of this
13 discussion about how the articles relate to the
14 testing, how the testing can be linked up to the
15 devices, which wasn't provided in the petition,
16 although the articles were referenced, will be
17 discussion that will need to be provided to us
18 after the panel meeting for review.

19 DR. YASZEMSKI: Thank you, Dr. Witten.

20 **FDA Presentation**

21 MR. STEIGMAN: Good morning, ladies and
22 gentlemen, Chairman, distinguished panel, and
23 members of the audience.

24 I am Glenn Steigman, a biomedical engineer
25 with the Orthopaedic Devices Branch.

1 The device type under consideration for
2 reclassification is metal-on-metal semi-constrained
3 hip prosthesis.

4 The FDA review team consisted of myself as
5 lead reviewer, Dr. Martin Ithiro as clinical
6 reviewer, and Melvin Sideman as the statistician.

7 [Slide.]

8 Today I will discuss the device history.
9 I will then present to you the current and proposed
10 CFR classification, the proposed indications for
11 use and device description. I will then discuss
12 the evolution of metal-on-metal hips. Then, the
13 supporting information will be shown along with a
14 summary of the supporting information, several of
15 our concerns dealing with metal-on-metal hips.
16 Risks to health and special controls to minimize
17 these risks will then be discussed. I will then
18 conclude with the panel questions on which the FDA
19 is seeking panel input.

20 [Slide.]

21 The use of metal-on-metal hip joints
22 predates the Medical Device Amendments of 1976. A
23 final rule was published in 1987 classifying
24 metal-on-metal hips into Class III. Although these
25 devices were pre-amendments Class III, no date was

1 established was established for a call for PMAs.
2 Therefore, manufacturers can market these devices
3 via Pre-Market Notification until there is a call
4 for PMAs.

5 Last year, OSMA submitted a
6 reclassification petition for these devices to be
7 reclassified from Class III to Class II.

8 [Slide.]

9 The current classification has been
10 covered by the sponsor. The classification is
11 split into two parts--888.3320, which is
12 metal/metal hip joints with a cemented acetabular
13 component, and 888.3330, which is metal/metal hip
14 joints with uncemented acetabular components.

15 [Slide.]

16 This slide shows the current
17 classification for the metal-on-metal,
18 semi-constrained, cemented acetabular components,
19 which is currently Class III and is proposed to be
20 Class II.

21 [Slide.]

22 This slide shows the CFR classification
23 for hip joints with uncemented acetabular
24 prosthesis. It is also being proposed to be
25 reclassified from Class III to Class II.

1 [Slide.]

2 The Petitioner originally proposed three
3 classification definitions, one of which was for
4 threaded acetabular cups. The current proposal has
5 two classifications, and threaded cups are included
6 in this one.

7 [Slide.]

8 The Petitioner has stated the proposed
9 indications for use. These indications for use are
10 the same as the indications cleared for
11 metal-on-metal hips.

12 [Slide.]

13 The Petitioner has also provided a device
14 description of the types of metal-on-metal hips
15 that are being reclassified in the petition. This
16 device description features early hips and
17 contemporary hips.

18 [Slide.]

19 Early metal-on-metal devices were present
20 in the 1960s and 1970s, but soon fell out of favor
21 due to high revision rates and the use of
22 metal-on-polyethylene hips. Some of the
23 metal-on-metal hips that were being implanted
24 during this period are listed here.

25 In the late 1990s, metal-on-metal hips

1 made a resurgence into the European market, and
2 recently, contemporary metal-on-metal hips have
3 been cleared for market in the U.S. The clearance
4 of these devices was based on the use of wear
5 testing and limited short-term clinical
6 information. The wear testing compared the
7 metal-on-metal devices to metal-on-polyethylene
8 devices.

9 [Slide.]

10 The literature has demonstrated that early
11 hip devices experienced both early and late
12 failures. Some of these failures were a result of
13 loosening from runaway wear and thread design,
14 dislocation, and fracture. Most of these early
15 devices had oversize heads and equatorial contact.
16 Also, fixation of these devices were different; for
17 instance, some of the devices had threat acetabular
18 cups, which may have contributed to high rates of
19 loosening in these early devices.

20 The contemporary metal-on-metal hips have
21 head sizes that are common in metal-on-polyethylene
22 hips. They have polar contact of the
23 metal-on-metal couple, and they have different
24 materials than the early devices. Because of the
25 high revision rates of the early device design, the

1 Petitioner has proposed mechanical testing and wear
2 testing to control the risk of the early devices.

3 [Slide.]

4 In order to identify the risk associated
5 with metal-on-metal hips, the sponsor has provided
6 three types of supporting information--published
7 literature of early devices; published literature
8 of contemporary devices; and four unpublished
9 clinical trials. The primary focus was to identify
10 all the risks associated with the early and
11 contemporary hip devices.

12 [Slide.]

13 The sponsor provided two types of
14 literature articles for supporting information--a
15 series of articles on early devices such as the
16 McKee-Farrar, Ring, Muller, among others. The
17 sponsor provided 46 out of 79 of these articles
18 because of the acceptance/rejection criteria set
19 forth by the Petitioner. Five articles on
20 contemporary metal-on-metal hips were also
21 provided.

22 The following risks were identified in
23 these early and contemporary articles. Runaway
24 wear was prevalent in older devices. No runaway
25 wear has been observed in contemporary devices, but

1 these hips do not have long-term data. The
2 literature articles also show loosening was a risk
3 for both early and contemporary devices. The
4 presence of threaded acetabular cups is thought to
5 be the cause of loosening in some of these early
6 devices.

7 Fracture of the femoral component was
8 observed in the early devices, and fracture of the
9 femur was seen in some of the contemporary device
10 articles.

11 Migration of the implant was noted in the
12 older literature articles but not in the
13 contemporary literature articles. Migration was
14 seen, though, in the unpublished clinical studies
15 provided by the Petitioner.

16 Dislocation, metallosis, and infection
17 were seen both in early device designs and in
18 contemporary devices.

19 [Slide.]

20 The sponsor also provided four unpublished
21 clinical studies--Studies A, B, C, and D. Study D
22 had limited value because only six patients were at
23 the 24-month time point, and only the Harris hip
24 score and complications were provided.

25 Studies A and B were performed with

1 DePuy's Ultima metal-on-metal hip system, while
2 Study C was performed with Biomet's metal-on-metal
3 articulation system.

4 [Slide.]

5 Study A was a prospective randomized study
6 that contained 219 patients in the investigative
7 group and 206 in the control group. The Harris hip
8 score at 24-plus months for the investigative group
9 was 95.1, and 91.5 for the control group.

10 There were no removals in the
11 metal-on-metal group and only one in the
12 metal-on-polyethylene group.

13 Acetabular cup migration was seen in 42.1
14 percent of the investigative patients and 31.3
15 percent in the control group.

16 Acetabular cup radiolucencies were seen in
17 approximately 5 percent in the metal-on-metal group
18 and 6 percent in the control group. It has been
19 noted that the petition did not differ between the
20 nature of the radiolucency, whether it was progress
21 or not, and the petition did not define cup
22 migration.

23 These results are based on a follow-up
24 rate of 37 percent and 46 percent for
25 metal-on-metal and metal-on-polyethylene groups,

1 respectively.

2 [Slide.]

3 Study B was a prospective, historical
4 control, open, European study on the use of DePuy's
5 Ultima metal-on-metal hip. There were 87 patients
6 in the study. The Harris hip score was 98.4 at
7 24-plus months, and there was one revision.

8 The sponsor reported 12.9 percent of the
9 acetabular cups migrated, and the metal-on-metal
10 group saw 10.8 percent acetabular radiolucencies.
11 This data was reported with a follow-up of 43
12 percent.

13 [Slide.]

14 Study C was a prospective, randomized
15 clinical study of Biomet's metal-on-metal
16 articulation system. Both the investigative and
17 control groups had 97 patients. The Harris hip
18 score at 24-plus months was 97.4 for the
19 investigative and 94.1 for the control. There were
20 no revisions or cup migrations. Acetabular
21 radiolucencies were seen in 22 percent of the
22 investigative group and 8.8 percent of the control
23 group. These results were based on a follow-up of
24 47.2 percent and 56.1 percent for the investigative
25 and control groups, respectively.

1 [Slide.]

2 This slide summarizes the supporting
3 information the sponsor provided, separated by the
4 two different hip designs, early and contemporary.
5 Included in the table is what was presented in the
6 petition and our concerns associated with these
7 different categories.

8 The clinical data from the published
9 literature dealing with the early design was able
10 to show long-term data and data on several
11 different devices. The articles also showed
12 varying results, some articles showing poor results
13 with high revision rates, and some articles showing
14 acceptable results.

15 Some of the concerns with these published
16 articles included use of different protocols,
17 different patient populations, different
18 follow-ups; also, no clinical definitions were
19 identified, such as success/failure criteria and
20 clinical endpoints.

21 Short- and long-term risks were
22 identified, but one cannot specifically know what
23 caused these risks.

24 Finally, in vitro wear testing on these
25 early devices was absent from the petition. These

1 early devices could be used as a positive control
2 to compare to the contemporary devices.

3 [Slide.]

4 This table summarizes the clinical
5 information for the contemporary devices. From the
6 clinical results of the unpublished clinical
7 studies and the published clinical articles, the
8 data shows acceptable Harris hip scores and few
9 revisions. However, from these articles, there
10 were no definitions for cup migration and
11 radiolucencies.

12 Also, the articles contained only the
13 results of one type of hip, and the unpublished
14 clinical studies provide data on two other hips.

15 The risks identified from these studies
16 were short- to mid-term risks because there was no
17 long-term data out past 7 years for these
18 contemporary devices.

19 The Petitioner provided a wear proposal
20 that will be outlined later in this presentation.
21 The Petitioner does not, however, propose the use
22 of a positive control or provide any validation of
23 the wear proposal. The issues outlined here will
24 be the focus of panel questions that I will
25 summarize at the end.

1 [Slide.]

2 Risks associated with metal-on-metal hips
3 identified by a previous panel and the Petitioner
4 are listed here. These risks are: loss or
5 reduction of joint function, which includes
6 loosening, revision, implant failure, fracture,
7 wear, and dislocation. The other two risks are
8 adverse tissue reaction such as osteolysis and
9 sensitivity to metal implants, and infection.

10 [Slide.]

11 The special controls identified by the
12 petition to minimize the risk of loss or reduction
13 of joint function include voluntary standards,
14 guidance documents, wear proposal, mechanical
15 testing, and labeling.

16 [Slide.]

17 This slide contains a list of voluntary
18 material standards and voluntary testing standards
19 proposed by the Petitioner.

20 [Slide.]

21 In addition, several guidance documents
22 were identified as special controls that describe
23 materials, testing, and sterility for generic as
24 well as different components of the total hip
25 prosthesis. These include testing orthopedic

1 implants in modified surfaces, guidance for femoral
2 stem prostheses, and guidance document for testing
3 acetabular cups.

4 The other guidances are for orthopedic and
5 generic implants. Currently, there is no guidance
6 for wear testing of metal-on-metal hips.

7 [Slide.]

8 The Petitioner has proposed a wear test
9 based on ASTM 1714 to measure the wear debris.
10 Please note that this ASTM standard was developed
11 for metal-on-polyethylene hips and is not a hip
12 simulator test method.

13 The control hip would be a 28-millimeter,
14 legally marketed metal-on-metal hip that is within
15 a range of design parameters suggested by the
16 Petitioner. The design parameters include
17 diametrical clearance, sphericity, surface
18 roughness and materials.

19 The ranges are currently legally marketed,
20 metal-on-metal, 28 millimeter hips. FDA is
21 requesting panel input regarding the use of this
22 wear test method and how to interpret the results
23 of this test method.

24 [Slide.]

25 In addition to the wear testing proposal,

1 the Petitioner proposes kinematic testing, push-out
2 and lever-out testing, cyclic wear, degradation,
3 and corrosion testing, along with hip simulator
4 tests.

5 [Slide.]

6 Labeling is the final special control for
7 this particular risk. Petitioner proposes the same
8 labeling that has already been used for cleared
9 metal-on-metal and metal-on-polyethylene hips.

10 [Slide.]

11 Another risk identified by the Petitioner
12 was adverse tissue reaction. The controls for
13 adverse tissue reaction are voluntary material
14 standard, voluntary biocompatibility standard, and
15 labeling.

16 [Slide.]

17 Voluntary material standards are proposed
18 special controls to minimize the risk of adverse
19 tissue reactions. Listed here are material
20 standards for cobalt-chromium and titanium alloys.

21 [Slide.]

22 Other voluntary standards can also provide
23 ways to minimize tissue reactions, such as this ISO
24 biocompatibility standard.

25 [Slide.]

1 Lastly, a specific set of indications,
2 contraindications, warnings, and precautions are
3 able to warn against possible adverse tissue
4 reactions.

5 [Slide.]

6 The Petitioner proposes a Sterility Review
7 Guidance as a special control to minimize the risk
8 of infection.

9 [Slide.]

10 Here are the panel questions. Again, here
11 are the risks to health identified by the
12 Petitioner, which leads us to Question 1.

13 "Has the Petitioner identified all the
14 risks associated with this device type? If not,
15 please identify any additional risks from
16 metal-on-metal hips."

17 Question 2: "Based on the risks of
18 migration and loosening of metal-on-metal hip
19 implants, has the Petitioner adequately identified
20 special controls to minimize these risks? If not,
21 please identify additional special controls that
22 can be used to minimize these risks."

23 Question 3: "Does the wear testing
24 proposal, including the use of a negative
25 control--that is, a 28 millimeter legally marketed

1 metal-on-metal hip having design parameters within
2 a specified range--adequately minimize the
3 identified risks? Is a positive control--such as
4 early devices--needed for comparison as well? If
5 not, will the proposed wear testing minimize the
6 risks associated with wear?"

7 Thank you.

8 DR. YASZEMSKI: Thank you, Mr. Steigman.

9 We are going to take a 10-minute break
10 now. It is just about 11 o'clock, so let's please
11 try to be back by 11:10, at which time we'll start
12 with the lead panel member reviews.

13 [Break.]

14 DR. YASZEMSKI: May I ask everybody to
15 please take your seats. We're going to get started
16 again.

17 We will proceed now with the lead panel
18 member reviews, and first up is going to be Dr. Li,
19 who is going to give the preclinical review.

20 Dr. Li, please.

21 **Lead Panel Member Reviews**

22 DR. LI: Thank you.

23 I'd like to provide my comments on
24 metal-on-metal total hip replacements and the
25 reclassification. Before I get too far, let me

1 congratulate the applicants for an extremely
2 well-put-together and thorough presentation and
3 certainly the gathering of experts in Dr.
4 Schmalzried, Jacobs, and Medley, whom I personally
5 have great respect for.

6 [Slide.]

7 The question that I am going to focus on
8 as the materials and design person is, is there
9 enough information, data, et cetera, to allow
10 meaningful preclinical evaluation of metal-on-metal
11 total hip replacements, and then some comments on
12 what I believe are key issues and concerns
13 regarding metal-on-metal total hips.

14 [Slide.]

15 In the reclassification area, the areas
16 that I am going to touch upon are materials issues,
17 wear debris issues, actual preclinical testing, and
18 then a summary of general comments.

19 [Slide.]

20 First, on the materials issue, the
21 proposal is that basically all forms of
22 cobalt-chrome-molybdenum, cast or wrought in
23 nature, would be allowed, although I saw no data to
24 differentiate the two, and the question I have is
25 do they really both give you the same clinical and

1 laboratory results.

2 They also propose that the
3 titanium-vanadium-aluminum alloy be used as an
4 alternate material; however, there is even less
5 data regarding that particular metal combination.

6 [Slide.]

7 They provide what they call design
8 parameters for these devices, specifying a range of
9 diametrical clearance, sphericity, surface
10 roughness, and description of materials that
11 encompasses the two forms of cobalt-chrome and
12 titanium mentioned previously.

13 However, it appears that these design
14 parameters as they feature it really were not
15 chosen on any kind of scientific or laboratory data
16 but were chosen basically to encompass the
17 properties or description of all previous devices.
18 And it is also unclear, because there is just a
19 collection of parameters designed to cover a range
20 of materials, that there is actually a connection
21 from complying to these design parameters and
22 guaranteed low performance results. In particular,
23 if you took the outside range of these, 200 microns
24 of clearance, 7 microns of sphericity, and 30
25 nanometers of surface roughness, would you in fact

1 get low wear for all forms of metal that you want,
2 and I believe that question is unanswered.

3 So the question for the design parameters
4 is how were these actually arrived at, although it
5 appears they just picked a range describing
6 previous results. Does compliance mean low wear;
7 are the parameters the same for all materials and
8 designs; and other issues such as sizes:

9 [Slide.]

10 The other thing is that these parameters
11 assume testing--which I'll get to in a bit--of what
12 I will call ideal cases of hip simulation where it
13 is a controlled test that doesn't have all the
14 clinical factors and does not carry what I'll call
15 non-ideal cases, for instance, what if the
16 component is malaligned or cups put in at high
17 abduction angles.

18 [Slide.]

19 On the issue of diametric clearance, their
20 recommendation is basically inherently based on the
21 fact that all cups are in fact spherical. However,
22 the question is is this a limitation, because there
23 are designs of acetabular liners which are not
24 entirely spherical. Is this diametrical clearance
25 actually also true if the cup is placed in high

1 abduction angles, and then also, in photographs of
2 some of the devices used in Studies A, B, C, and D,
3 it appears that the metal liner is actually held in
4 place with a polyethylene interlayer, and if the
5 polyethylene deforms or creeps over time, giving
6 you a different kind of alignment, if you will, do
7 the diametrical clearance criteria still hold.

8 [Slide.]

9 Other design parameters actually are not
10 design parameters in the sense of describing the
11 metals, but design as far as the total system goes.
12 For instance, cup modularity, alignment of the
13 liner--this, what I call "canting," was something
14 that came up on the ceramic-on-ceramic total
15 devices where, again, in some of the photographs of
16 the devices in Studies A, B, C, and D, the liner
17 was essentially a large Morris taper that fits into
18 the metal shell, and it is quite possible to
19 actually put these taper in off-angle and either
20 not know it or have it be very difficult to remove.

21 Some also have raised rims that basically
22 increase the possibility of impingement; and again,
23 this issue of the presence of polyethylene layers.

24 Also mentioned briefly by one of your
25 speakers but not really mentioned very much in the

1 application is that it appears that their design
2 parameters would include surface replacements, so
3 the question is do the applicants intend to include
4 all surface replacements in the
5 down-classification; if so, there appears to be
6 even less specific data on metal-on-metal surface
7 replacements.

8 [Slide.]

9 Other design parameters--although the
10 manufacturer application said that the devices
11 should not mix manufacturers, they actually do not
12 preclude the mixing of metals--for instance, if you
13 can use a cast cobalt-chrome ball and wrought stem;
14 or even, oddly enough, if someone should decide to
15 use a cobalt-chrome liner and a titanium head.
16 Although these things a priori are perhaps unusual
17 and less likely, the application does not preclude
18 their combination.

19 The effective of corrosion or wear--Dr.
20 Jacobs and his coworkers have reported on
21 corrosion, which I'll get back to later, which
22 changes the chemistry--but is there increased
23 incidence of corrosion? Are there other
24 impingement factors such as proximal femoral
25 sleeves, again used in one of the studies--I

1 believe it was Study A and B--or extended femoral
2 necks that basically put the metal-on-metal devices
3 in a separate category from the
4 metal-on-polyethylene.

5 [Slide.]

6 To go to preclinical wear testing, their
7 proposal is they use the same protocol as
8 metal-on-polyethylene testing, and in fact they
9 would propose that the metal-on-polyethylene would
10 serve as the control for any metal-on-metal
11 devices.

12 In the applications, the numbers could be
13 slightly longer, but basically, all the joint
14 simulations show somewhere between 15 an 100 times
15 lower weight loss than metal-on-polyethylene in hip
16 simulation.

17 However, there are two additional factors
18 besides just plain weight loss--size of debris and
19 is this test clearly meaningful.

20 The metal debris, Dr. Jacobs mentioned it
21 is difficult to detect debris less than 0.2
22 microns, because it requires electron microscopy,
23 and it is a very difficult experimental procedure.
24 However, Gordon Blun's [phonetic] group did take
25 the trouble to isolate particles and studied them

1 with electron microscopy and found that the
2 predominant size of the particles they found in
3 periprosthetic tissue in metal-on-metal was
4 actually .02 microns, less than one-tenth the size
5 of metal-on-polyethylene.

6 [Slide.]

7 There are literature references to effects
8 of cobalt-chrome debris. There is less on
9 titanium-vanadium-aluminum debris. But again, as
10 Dr. Jacobs and Jeremy Guilford [phonetic] have
11 pointed out, in corrosion products of
12 cobalt-chrome, there are actually orthophosphates
13 found in the retrievals of the
14 metal-on-polyethylene devices, and the question is
15 on metal-on-metal devices, are there higher
16 concentrations of orthophosphates, and if so, do we
17 know the long-term biological consequences of
18 orthophosphate compounds.

19 [Slide.]

20 If the biological activity is surface
21 area-related rather than surface number of
22 particles related, then a 20-time reduction in wear
23 by weight is only about a 25 percent reduction in
24 wear surface volume.

25 So although you may get a 95 or more

1 percent improvement in weight loss because of the
2 vast disparity in size of the metal particles, the
3 surface area reduction is much smaller than one
4 would like. And also, as Dr. Jacobs pointed out,
5 size-for-size, metal debris appears to be more
6 reactive than polyethylene debris.

7 [Slide.]

8 So the clinical relevance is will
9 metal-on-metal devices go into younger and more
10 active patients. Again, one of the problems with
11 comparing the metal-on-polyethylene is that a lot
12 of the new bearing couples such as
13 ceramic-on-ceramic or the crosslinked polys are
14 targeted for younger, more active patients. If so,
15 then, standard hip simulator wear, for instance,
16 may not reflect actual clinical results.

17 [Slide.]

18 I have projected four histories just to
19 demonstrate that although hip simulation is
20 important and a necessary test to pass, it does not
21 guarantee clinical success.

22 Four quick examples are polyacetals used
23 in the early eighties that have absolutely
24 excellent 5-year clinical data and incredibly bad
25 7- to 8-year clinical data. Somewhat after the

1 fact, hip simulation followed the clinical designs
2 and demonstrated that actually, the polyacetal did
3 have a slightly higher wear rate on the hip
4 simulator, but there was a huge difference in
5 design between the acetal test on the hip simulator
6 and that found in the actual device. The actual
7 device actually had to bearing surfaces, not only
8 the femoral ball and the liner, but also a trunion
9 [phonetic] that the femoral ball and the femoral
10 neck spun on.

11 The second, more recent example is
12 hyalomere, which always showed equal or better wear
13 in hip simulations; but the clinical reports on
14 hyalomere are at best mixed. Dr. Schmalzried in
15 the commentary on JBS pointed out a very strong
16 patient age relationship with the hyalomere
17 components, again demonstrating that hip
18 simulations may not accurately reflect all the
19 possible clinical combinations the device will
20 face.

21 [Slide.]

22 Two other areas are ceramic-on-ceramic
23 devices, which always have very low simulator wear.
24 However, there have been several series where there
25 are actually ceramic-on-ceramic devices with high

1 forms of osteolysis and also the hip simulators
2 don't cover things like fracture and loosening that
3 are also prevalent in ceramic-on-ceramic clinical
4 devices.

5 Lastly, an area that is very up-to-date is
6 the issue of crosslinked polyethylene that shows 80
7 to 100 percent hip simulator wear reduction.
8 However, we have three clinical series, although
9 using very different technologies, that demonstrate
10 that the clinical series always has higher wear
11 than the virtually zero wear hip simulators
12 propose. Oonishi's group back in the late
13 seventies, early eighties, used 100 Mrad radio to
14 high-density polyethylene that had virtually zero
15 laboratory wear, yet his 8- and 9-year follow-up
16 had a wear rate equal to metal-on-polyethylene
17 Charnley.

18 Wroblewski had silane crosslinked
19 polyethylene, again a very different technology
20 that showed wear rates in the first year up to 0.4
21 millimeters per year although after about three
22 years, that seemed to have quieted down; but again,
23 no long-term results are available.

24 Lastly, Weber's group in South Africa had
25 a 15-Mrad polyethylene that was irradiated in the

1 presence of acetylene. Although they implanted
2 thousands of these, less than 100 were available
3 for follow-up. They found that this group had two
4 groups. Sixty percent of them showed virtually
5 zero wear as with the hip simulators, but 40
6 percent of those cups that were found actually had,
7 again, wear rates similar to metal-on-polyethylene,
8 again unpredicted by the hip simulation.

9 [Slide.]

10 So I believe, based on this, that there
11 needs to be a negative control for metal-on-metal
12 hip simulations, and it must replicate high wear in
13 what I'll call nonoptimal conditions, which might
14 include earlier designs, different design
15 parameters, load and abduction angles, as
16 previously discussed.

17 [Slide.]

18 So metal-on-metal hip simulation, I
19 believe, is a necessary but minimum requirement to
20 test against metal-on-polyethylene, and perhaps
21 more aggressive tests are needed to reflect actual
22 patient population and activity, and it must
23 demonstrate that it can identify unequivocally a
24 bad device or material.

25 [Slide.]

1 Materials need to validate all forms of
2 metal specified in the design parameters and need
3 to have some validation of the design parameters
4 other than encompassing all previous commercial
5 devices.

6 [Slide.]

7 My general comments are that clinical
8 trials A through D as discussed by the FDA reviewer
9 were relatively short and somewhat inconclusive,
10 although there were signs of radiolucency. I think
11 I found it kind of sobering that we are asked to
12 down-classify a device when I don't believe there
13 are any long-term prospective successful clinical
14 trials.

15 [Slide.]

16 As Dr. Jacobs pointed out, there are
17 controversial errors on metal ion sensitivity and
18 carcinogenicity. Although there are no conclusive
19 results, there are some mixed results, and again,
20 no prospective study of long-term follow-up with
21 patients with metal-on-metal devices.

22 [Slide.]

23 So, will metal-on-metal devices fail in
24 ways other than intended articular wear--because
25 this would mean the hip simulator is not going to

1 weed out all the bad things that could happen.
2 Possible failure modes would be loosening, wear of
3 unintended wear surfaces like impingement, or
4 long-term biological concerns.

5 [Slide.]

6 Just as a reminder, it is not necessarily
7 true that you can straightaway compare
8 metal-on-metal wear with metal-on-polyethylene.
9 There are several differences, including chemistry
10 and size of the debris; biological differences in
11 the debris are not well-established; difference in
12 device designs; no long-term prospective successful
13 clinical series for metal-on-metal; no in vitro
14 testing that predicted failures of earlier devices;
15 and really were based on the fact that the hope
16 that the modern designs have solved the problems of
17 the past.

18 [Slide.]

19 In summary, there is no differentiation of
20 materials and designs provided by the applicant.
21 Design parameters provided are not well-supported.
22 Preclinical testing does not appear to be able to
23 tell the difference between good and bad implants.
24 The particle sizes are small while biological
25 activity may be higher size-for-size. Other

1 long-term biological responses are uncertain. And
2 again, there are no long-term prospective clinical
3 trials.

4 [Slide.]

5 So I am hopefully, actually, that his is a
6 potential solution to metal-on-polyethylene wear
7 issues, at least in the non-crosslinked case for
8 young, active patients. The history has been long
9 but with mixed results and poor follow-up;
10 relatively small amount of literature on
11 preclinical and in vitro testing compared to
12 metal-on-polyethylene. I believe, based on this,
13 that it is perhaps a little too early for
14 down-classifying.

15 Thank you.

16 DR. YASZEMSKI: Thanks very much, Dr. Li.

17 Next, we'll ask Dr. Larntz to give the
18 statistical perspective.

19 DR. LARNTZ: Thank you.

20 We didn't see a lot of statistics this
21 morning, and a lot of people were probably pleased.
22 Let me just say that there is actually room for a
23 lot of statistics in this material.

24 I am going to just say what I think I
25 heard but I'm not sure I heard. Reports have

1 changed over time, and there is lots of variation,
2 so we can just use gross statistics, whatever that
3 means. But let me say that that is exactly when we
4 need to study it carefully.

5 I think the literature--there was lots of
6 literature, and I think it is very important that
7 we understand that there wasn't a great deal of
8 statistical analysis in that literature.

9 A meta-analysis, done either from a
10 classical, random effects approach or a Bayesian
11 [phonetic] approach, seems to be really crying out.
12 There is lots of data here. You could do a lot.
13 You could understand what happens by looking at the
14 variation in studies, comparing first and second
15 generation, looking at time trends. Surely things
16 have improved over time--they have in most other
17 areas of medicine, or at least the reports have
18 improved over time. How about controlling for the
19 amount of follow-up? All of those things could be
20 done.

21 As far as I could tell, nothing much was
22 done, although with respect to the epi-analysis of
23 cancer, there were at least some attempts to
24 combine the data, and I actually like that, as you
25 might imagine. Those are actually reasonable first

1 starting points, and I think they gave us some
2 valuable information, at least with respect to
3 carcinogenicity.

4 So historical data--not much was done;
5 lots of papers; not much--hardly anything--in the
6 way of statistical analysis summarizing that
7 information so we could understand that
8 information.

9 I think that saying rates are between zero
10 and 100 percent is not helpful, okay? Zero to 100
11 percent is a big range--in fact, I could do that
12 without looking at the papers. So it could be
13 done. That is the number one point, a
14 meta-analysis in some level would be quite useful.

15 With respect to the clinical studies, we
16 saw some nice plots over time of Harris hip scores,
17 and we saw them start out low and go up high. As
18 far as I could tell, that is just based on reports
19 of the means at those data points--that's a
20 question I would have for the sponsor. Were those
21 graphs that we saw anything other than just the
22 means of the time point values?

23 There are different numbers of patients at
24 each time point. There are actually very few
25 patients at 24 months and beyond--very few. These

1 studies have gone on for a few years, but the
2 number of patients going out further than, say, 2
3 years is actually quite small.

4 I didn't see any what I would call true
5 longitudinal analysis that accounted for the
6 relationships of scores across time--nothing like
7 that. The only analysis I saw was just the
8 snapshot at 24 months, based on actually a small
9 subset of patients.

10 There was--well, if you didn't do a
11 longitudinal analysis, you weren't going to think
12 of doing any kind of missing data sensitivity to
13 see what would have happened if in fact there were
14 some differential problems with the patients who
15 had data missing.

16 Okay. So what do I think? What I think
17 is we didn't see anything bad statistically. We
18 didn't see anything bad. We might have seen some
19 statistics that weren't so good--how is that--but
20 we didn't see anything coming out that was really
21 bad statistically.

22 Is there anything hidden away here? I
23 don't know. I don't know. I think it would take a
24 fair bit of statistical analysis, meta-analysis of
25 historical data, longitudinal analysis, perhaps

1 with some missing data sensitivity, of the clinical
2 data to allow us to draw a firm statistical
3 conclusion. But at least, as I say, we didn't see
4 anything bad.

5 I don't think the data provide us a great
6 deal of information with respect to supporting the
7 petition.

8 DR. YASZEMSKI: Thanks very much, Dr.
9 Larntz.

10 We'll move now to Dr. Skinner to provide a
11 clinical evaluation.

12 Dr. Skinner?

13 DR. SKINNER: Thanks.

14 First, I would like to take a little issue
15 with my colleague across the way. I am not sure a
16 meta-analysis would do a lot in this situation
17 because things have changed so much since much of
18 this data was produced. Much of the data came from
19 20 years ago when the surgeons were different, had
20 different skills, the prostheses were different,
21 the follow-up was different, the patients were
22 different. I am not sure that using that data
23 would be terribly helpful.

24 That means that I think we have to rely a
25 lot on the recent data, and as Dr. Larntz alluded

1 to, that data is short-term, but there is a
2 significant number of patients--I hate to use
3 "significant" because that means statistical--but
4 there are a number of patients who go out past two
5 years, and that is the typical criterion used by
6 the FDA for approval of prostheses, and there are
7 two prostheses now on the market, apparently, based
8 on those studies.

9 The typical study has been 100 patients in
10 the study group, 100 patients in the control group,
11 followed for two years, and we have a number of
12 patients who have gone out two years with good
13 results, low revision rates, good Harris hip
14 scores. The only concern I have about some of that
15 data is the radiologic data, and Dr. Li alluded to
16 that, and the FDA reviewer alluded to that--whether
17 the radiolucent lines that were observed are
18 progressive or whether they are stable.

19 Doing total hips, you get radiolucent
20 lines, but they should be stable, and when you are
21 talking about particle disease, you have to be
22 worried about progressive radiolucent lines.

23 When it comes to the rest of the clinical
24 data, I think the toxicology information is
25 interesting. First of all, the cancer risk is

1 there. These are ions that have been shown in
2 industry to cause cancer or problems at high
3 concentrations, and we are talking about relatively
4 low concentrations, but we are talking about very
5 long-term exposure, so there is a concern there.
6 But I think that Dr. Jacobs addressed that, and I
7 don't think that's a very great concern.

8 Regarding the immunologic sensitivity
9 issue, if you have taken care of total hip
10 patients, total knee patients for a while,
11 everybody has run into a patient who has had the
12 complaint that they are sensitive to whatever, and
13 when you delve into these--and I have delved into a
14 bunch of them--you find that there is an occasional
15 patient, but they are extremely rare. And I don't
16 think that sensitivity in these prostheses is a
17 significant concern.

18 There is another concern, though, that
19 does worry me a little bit, and that is comorbid
20 conditions. This brings to mind the situation that
21 happened in Quebec in the early sixties. The
22 bartenders in Quebec developed the bad habit of
23 washing their glasses, and when they washed their
24 glasses, they left some surfactant on the surface,
25 and that meant that the beer foam did not look very

1 good, and it made Le Batt's beer look like a cheap
2 beer. The manufacturer responded to this by
3 putting small amounts of cobalt into the beer.
4 When they did that, it made the foam stay present
5 after it was poured into the glass--but
6 unfortunately, a very small number of patients
7 developed a cardiomyopathy.

8 One of the things that we talk about in
9 doing patients with metal-on-metal hips is doing
10 them in young patients who have--and one of the
11 main concerns is avascular necrosis, and how do you
12 get avascular necrosis--you get it from drinking
13 beer.

14 So I am a little concerned about comorbid
15 conditions in combination with metal-on-metal hips,
16 because Dr. Jacobs has reported increased levels of
17 cobalt in the urine of these patients. Now, this
18 is very low levels of cobalt that we are talking
19 about. The cardiomyopathy patients obviously, even
20 though they were drinking liters of beer per day,
21 were getting small levels of cobalt, and it was
22 small levels in relation to people who have taken
23 cobalt to stimulate hematopoiesis. I believe that
24 is in the range of 20 milligrams a day, but those
25 patients probably weren't alcoholics.

1 health have been identified by the Petitioner and
2 the July 1987 Orthopaedics Rehabilitation Panel.
3 The petition lists the following risks for
4 metal-on-metal semi-constrained hips: loosening,
5 revision, failure, wear, sensitivity, pain,
6 vascular disorders, gastrointestinal and
7 genitourinary complication, migration, dislocation,
8 fracture, osteolysis, infection, nerve
9 impingement/damage, pulmonary embolism.

10 Has the Petitioner identified all the
11 risks associated with this device type? If not,
12 please identify any additional risks for
13 metal-on-metal hips.

14 Question 2. Based on the risks of
15 migration and loosening of metal-on-metal hip
16 implants, has the petition adequately identified
17 special controls to minimize these risks? If not,
18 please identify additional special controls that
19 can be used to minimize these risks.

20 Question 3. Does the wear testing
21 proposal, including the use of a negative control,
22 that is, 28 millimeter legally marketed
23 metal-on-metal hip having design parameters within
24 a specified range, adequately minimize the
25 identified risk? Is a positive control, that is,

1 early deices, needed for comparison as well? If
2 not, will the proposed wear testing minimize the
3 risks associated with wear?

4 DR. YASZEMSKI: Thank you, Mr. Steigman.

5 I'll also say to the panel members for
6 quick reference--the handout that you have from Mr.
7 Steigman's presentation in front of you on pages 11
8 and 12 are these three questions that you can be
9 looking at and referring to, since we can only put
10 one up at a time.

11 Dr. Finnegan, may we ask you for your
12 thoughts and comments at this time?

13 DR. FINNEGAN: Actually, I have several
14 areas of concern, but I would really like to ask
15 the Petitioner a number of questions, because that
16 might help clear this up.

17 My first question has to do with the
18 lucencies on the acetabular cup and in particular
19 whether there is any relationship between these and
20 threaded acetabular cups. I noticed that
21 initially, the petition contained an application
22 for threaded cups. The FDA lead talked about that,
23 but it seems to me that the more recent one does
24 not. Are you actually asking for threaded
25 acetabular cups, or not? And particularly in group