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DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION

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ORTHOPAEDICS AND REHABILITATION DEVICES  
ADVISORY PANEL MEETING

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9:35 a.m.

Friday, January 19, 2001

20B  
9200 Corporate Boulevard  
Rockville, Maryland

MILLER REPORTING COMPANY, INC.  
735 C Street, S.E.  
Washington, D.C. 20003-2802  
(202) 546-6666

P A R T I C I P A N T SPanel Participants

Michael J. Yaszemski, M.D., Panel Chair  
Hany Demian, M.S., Executive Secretary

Voting Members

Albert J. Aboulafia, M.D.  
Edward Y. Cheng, M.D.  
Maureen Finnegan, M.D.  
Stephen Li, Ph.D.  
Harry B. Skinner, M.D., Ph.D.  
Floyd Larson, Ph.D., Industry Representative  
Karen Rue, Consumer Representative

Consultants (Deputized to Vote)

Jens Chapman, M.D., (Via Speakerphone)  
Fernando Diaz, M.D., Ph.D. (Via Speakerphone)  
Richard Simon, Ph.D.  
Timme Topoleski, Ph.D.

FDA Participants

Celia Witten, Ph.D., M.D.  
Mark Melkerson, M.S.  
Barbara Zimmerman, B.S.  
Holly Rhodes, B.S.  
Gene Pennello, Ph.D.  
Martin Yahiro, M.D.

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P R O C E E D I N G S

1  
2 MR. DEMIAN: We're ready to begin this meeting of  
3 the Orthopedic and Rehabilitation Devices Advisory Panel.  
4 My name is Hany Demian. I'm the Executive Secretary of this  
5 panel.

6 I would like to remind everyone that you are  
7 requested to sign in on the attendance sheets which are  
8 available outside the doors. You may also pick up an agenda  
9 and information about today's meeting, including how to find  
10 out about future meeting dates through the Advisory Panel  
11 phone line and how to obtain meeting minutes or transcripts.

12 I will now read three statements that are required  
13 to be read into the record: two deputization of temporary  
14 voting member statements and one conflict of interest  
15 statement.

16 Pursuant to the authority granted under the  
17 Medical Device Advisory Committee Charter, dated October 27,  
18 1990, as amended August 18, 1999, I appoint the following  
19 individuals as voting members of the Orthopedic and  
20 Rehabilitation Devices Panel for this meeting on January 19,  
21 2001: Jens Chapman, Timme Topoleski, Fernando Diaz. For  
22 the record, these individuals are special government  
23 employees and consultants to this panel or other panels  
24 under the Medical Device Advisory Committee. They have  
25 undergone the customary conflict of interest review and have

1 reviewed the materials to be considered at this meeting.  
2 And this is signed by Dr. David Feigal, Director of Center  
3 for Devices and Radiological Health.

4           This is the second appointment to temporary voting  
5 status: Pursuant to the authority granted under the Medical  
6 Device Advisory Committee Charter of the Center for Devices  
7 and Radiological Health, dated October 27, 1990, as amended  
8 August 18, 1999, I appoint Richard Simon as a voting member  
9 of the Orthopedic and Rehabilitation Device Panel for the  
10 meeting on January 19, 2001. For the record, Dr. Simon is a  
11 voting member of the Oncologic Drugs Advisory Committee of  
12 the Center for Drugs Evaluation and Research. He is a  
13 special government employees who has undergone the customary  
14 conflict of interest review and has reviewed the material to  
15 be considered at this meeting. And this is signed Linda  
16 Suydam, Senior Associate Commissioner.

17           Conflict of interest statement. The following  
18 announcement addresses conflict of interest issues  
19 associated with this meeting and is made part of the record  
20 to preclude even the appearance of any impropriety. To  
21 determine if any conflict existed, the agency reviewed the  
22 submitted agenda for this meeting and all financial  
23 interests reported by committee participants.

24           The conflict of interest statutes prohibit special  
25 government employees from participating in matters that

1 could affect their or their employer's financial interest.  
2 However, the agency has determined that the participation of  
3 certain members and consultants the need for whose services  
4 outweighs the potential conflict of interest involved is in  
5 the best interest of the government. Therefore, waivers  
6 have been granted for Drs. Edward Cheng, Stephen Li, Harry  
7 Skinner, and Jens Chapman for their interests in firms that  
8 could potentially be affected by the panel's recommendation.  
9 Copies of these waivers may be obtained from the agency's  
10 Freedom of Information Office, Room 12A-15 of the Parklawn  
11 Building.

12           We would like to note for the record that the  
13 agency also took into consideration other matters regarding  
14 Drs. Li, Chapman, and Michael Yaszemski. Each of these  
15 panelists reported current or recent interests in firms at  
16 issue, but in matters that are not related to today's  
17 agenda. The agency has determined, therefore, that they may  
18 participate fully in all discussions.

19           In the event that the discussion involves any  
20 other products or firms not already on the agenda for which  
21 an FDA participant has a financial interest, the participant  
22 should excuse him- or herself from such involvement, and the  
23 exclusion will be noted for the record.

24           With respect to all other participants, we ask in  
25 fairness that all persons making statements or presentations

1 disclose any or previous financial involvement with firms  
2 whose products they may wish to comment upon.

3           Before turning this meeting over to Dr. Yaszemski,  
4 I would like to introduce our distinguished panel members  
5 who have generously given their time to help FDA in matters  
6 being discussed today and other FDA staff seated at this  
7 table. So we are just going to go around the room; give  
8 your affiliation, your areas of interest.

9           Dr. Yaszemski?

10           CHAIRMAN YASZEMSKI: Michael Yaszemski. I'm an  
11 orthopedic surgeon. I primarily do spine surgery and adult  
12 reconstructive surgery. I work at the Mayo Clinic in  
13 Rochester, Minnesota.

14           [Note: Microphone out, some words inaudible.]

15           DR. SKINNER: My name is Harry Skinner. I am an  
16 orthopedic surgeon, and I am located at the University of  
17 California-Irvine, Department of Orthopedic Surgery and  
18 Mechanical and Aerospace Engineering. My interests are  
19 [inaudible] analysis, stress analysis, and implant  
20 interactions [inaudible].

21           DR. FINNEGAN: Maureen Finnegan. I'm an  
22 orthopedic surgeon at U.T. Southwestern Medical Center in  
23 Dallas, and my interests are trauma and implant research.

24           DR. ABOULAFIA: My name is Albert Aboulafia. I'm  
25 an orthopedic surgeon as well, and I'm at the University of

1 Maryland and Sinai Hospital in Baltimore. And my area of  
2 interest is orthopedic [inaudible].

3 DR. WITTEN: Dr. Celia Witten. I'm the FDA  
4 representative [inaudible].

5 MS. RUE: My name is Karen Rue. I'm an RN  
6 [inaudible].

7 DR. LARSON: Floyd Larson, PaxMed International,  
8 with an interest in [inaudible].

9 DR. SIMON: I'm Richard Simon. I'm chief of the  
10 [inaudible] research branch at the National Cancer  
11 Institute.

12 DR. TOPOLESKI: I'm Timme Topoleski from the  
13 University of Maryland, Baltimore County. My main interests  
14 are in [inaudible] mechanical response of both natural and  
15 [inaudible] biomaterial.

16 CHAIRMAN YASZEMSKI: Dr. Chapman, are you with us?

17 DR. CHAPMAN: Yes, I am.

18 CHAIRMAN YASZEMSKI: Can I ask you to introduce  
19 yourself?

20 DR. CHAPMAN: My name is Jens Chapman. I'm an  
21 associate professor at the University of Washington in  
22 Seattle, and I'm the chief of [inaudible] for the Department  
23 of Orthopedic Surgery [inaudible].

24 CHAIRMAN YASZEMSKI: Thank you.

25 Dr. Diaz, are you with us?

1 DR. DIAZ: Yes, I am.

2 CHAIRMAN YASZEMSKI: Can I ask you to introduce  
3 yourself, please?

4 DR. DIAZ: My name is Fernando Diaz. I am the  
5 Chairman of Neurosurgery at Wayne State University, and my  
6 main [inaudible] surgery, especially reconstruction of spine  
7 in the cervical area.

8 CHAIRMAN YASZEMSKI: Thank you.

9 MR. DEMIAN: At this time I would like to turn the  
10 meeting over to our Chairman, Dr. Michael Yaszemski.

11 CHAIRMAN YASZEMSKI: Good morning. I'm Michael  
12 Yaszemski. I'm the Chairman of this panel. Today the panel  
13 will be making recommendations to the Food and Drug  
14 Administration regarding the premarket approval application.  
15 The committee will discuss and make recommendations for an  
16 interbody fusion system intended to stabilize and promote  
17 fusion in the cervical spine.

18 I would like to note for the record that the  
19 voting members present constitute a quorum, as required by  
20 21 C.F.R, Part 14.

21 We will now proceed with the open public hearing  
22 session of this meeting. I would ask at this time that all  
23 persons addressing the panel come forward and speak clearly  
24 into the microphone. The transcriptionist is depending upon  
25 this as a means of providing an accurate record of the

1 meeting. Please, I will ask your pardon at the present time  
2 if you start speaking without your name and I interrupt you,  
3 because it's real common for people to forget when they step  
4 up the mike.

5 We are requesting that all persons making  
6 statements during the open public hearing at the meeting  
7 disclose whether they have a financial interest in the  
8 medical device company or any medical device company.

9 Before making your presentation to the panel,  
10 please state your name, affiliation, and the nature of your  
11 financial interest, if any.

12 At this point is there anyone who wishes to  
13 address the panel?

14 MR. MELKERSON: [inaudible] public session, but I  
15 would like to make some introductions, please?

16 CHAIRMAN YASZEMSKI: Okay, Mr. Melkerson.

17 MR. MELKERSON: My name is Mark Melkerson, Deputy  
18 Director for the Division of General, Restorative, and  
19 Neurological Devices, and the introduction I'd like to make  
20 is sitting at the table and working the phones for us is one  
21 of our new reviewers, Glen Stagman. Behind me [inaudible]  
22 branch chief, Barbara Zimmerman. And sitting in the second  
23 row is Michele Matera. We also have a third new reviewer in  
24 our group, and his name is Sam Kim. In the orthopedic area,  
25 those are the new faces to go along with the names you've

1 been hearing.

2 Thank you.

3 CHAIRMAN YASZEMSKI: You're welcome. Is there  
4 anyone else who would wish to address the panel at this  
5 time?

6 [No response.]

7 CHAIRMAN YASZEMSKI: Seeing no one, we will now  
8 proceed to the open session for the PMA of the day. We will  
9 now consider the premarket approval application for Sulzer  
10 Spine-Tech's BAK/C Interbody Fusion System. I would like to  
11 remind public observers at this meeting that while this  
12 portion of the meeting is open to public observation, public  
13 attendees may not participate except at the specific request  
14 of the panel.

15 We are now ready to begin with the sponsor's  
16 presentation, which will then follow with the FDA  
17 presentation. I would like to ask again that each speaker  
18 state his or her name and affiliation to the firm before  
19 beginning the presentation.

20 Is the representative from the sponsor ready at  
21 this time?

22 MR. MANS: I am Dan Mans, and I am an employee of  
23 the study sponsor.

24 Dr. Yaszemski, other distinguished members of the  
25 panel, Dr. Witten, other members or staff of the FDA, thank

1 you for this opportunity today to present to you the result  
2 of over six years of product development, preclinical  
3 testing, clinical and regulatory activity on BAK/C interbody  
4 fusion system.

5 I would like to introduce physician repre-  
6 sentatives and clinicians participating in the clinical  
7 study with the study sponsor today: Dr. Joe Cauthen is the  
8 practicing neurosurgeon in the North Florida Regional  
9 Medical Center in Gainesville, Florida; Dr. Gregg Dyste,  
10 also a practicing spine surgeon, neurosurgeon at Abbott-  
11 Northwestern Hospital in Minneapolis; Dr. Robert Hacker, a  
12 neurosurgeon from Sacred Heart Medical Center in Eugene,  
13 Oregon; and Dr. John Sherman, a practicing orthopedic  
14 surgeon and medical director of Sulzer Spine-Tech.

15 Also joining us are Dr. Kinley Larntz, professor  
16 emeritus at the University of Minnesota at Twin Cities, and  
17 Sulzer Spine-Tech staff, Janell Colley, Susanna Kennedy,  
18 Rose Griffith, and Tim Miller from our clinical  
19 organization, and Dr. Steve Griffith, in charge of our  
20 research department.

21 First I'd like to set the stage and answer a  
22 question that is often asked of us as a medical device  
23 manufacturer as we present the concept of the cervical cage  
24 through our medical advisers and through potential clinical  
25 investigators. We're asked, Why cervical fusion cage?

1 Because, after all, there are currently a number of  
2 acceptable alternatives to cage fusion that have excellent  
3 clinical results for treatment of this disorder.

4 Let me say that the reason that the BAK/C  
5 interbody fusion system has been developed is not to improve  
6 on the clinical outcomes of current therapies. It's to  
7 equal those outcomes and address a number of deficiencies  
8 that exist with current treatment, such as complications  
9 associated with graft collapse or such as morbidity  
10 associated with the harvest of bone from the patient's iliac  
11 crest.

12 I'd like to review for a moment some history to  
13 indicate that the first implant in the clinical study was  
14 performed in December of 1994, and following patient  
15 enrollment and patient follow-up in December of 1998, Sulzer  
16 Spine-Tech submitted the first submission of the PMA. At  
17 that time the FDA granted expedited review processing  
18 [inaudible] due to the potential for a clinically meaningful  
19 benefit associated with the elimination of autograft  
20 harvest.

21 I'd like to say that the intention of our  
22 presentation today is to demonstrate that the BAK/C  
23 interbody fusion system is safe and effective for the  
24 intended treatment population and that it provides  
25 clinically meaningful benefit over existing technologies and

1 treatments by minimizing the need of autograft harvest.

2 Next slide?

3 The way you'll see this is, first, Dr. Steve  
4 Griffith will present the design rationale for this device,  
5 and he'll review preclinical testing. This preclinical  
6 testing will demonstrate that the BAK/C interbody fusion  
7 system is strong. It will demonstrate that it provides  
8 immediate rigidity upon insertion into the cervical spine.  
9 It will demonstrate that there were no untoward effects  
10 identified in the preclinical animal testing associated with  
11 the product. And it will show histologically that bone  
12 grows in and around the implant in an animal model.

13 We will then hear from Dr. Robert Hacker, who will  
14 present an overview of the study design and give a  
15 clinician's perspective on the data that was generated  
16 during the clinical study. Following that, Dr. Larntz will  
17 present a statistical analysis that is the basis for  
18 determination of safety and effectiveness for the study  
19 criteria that were identified in [inaudible]. I will then  
20 close with some summarizing statements.

21 I'd like now to introduce Dr. Steve Griffith.

22 DR. GRIFFITH: Good morning. My name is Steve  
23 Griffith, and I am employed by the study sponsor. I'd like  
24 to review for you the design characteristics of the BAK/C  
25 interbody fusion system. It was designed to be mechanically

1 strong enough to maintain the disc space and withstand the  
2 anticipated load within the disc space that the cervical  
3 spine sees. It was designed also to provide positive  
4 [inaudible] mechanical fixation with reduced range of motion  
5 and increased stiffness of [inaudible]. We designed it as a  
6 load-sharing--in a load-sharing environment as a result of  
7 its implantation and specific instrumentation that will  
8 provide for graft-to vertebral body contact while the  
9 implant rests on the cortical inplates.

10           The ability of this device to maximize fusion  
11 potential [inaudible] design and the porosity of the device  
12 without compromising the strength or the integrity of the  
13 device. Furthermore, the [inaudible] integration of the  
14 cervical device with the HA-coated device [inaudible] is  
15 also [inaudible] fusion.

16           The ability of the implant to be congruent with  
17 normal anatomy is particularly with respect to its ability  
18 to be countersunk beyond the anterior lip of the vertebral  
19 body, but also various sizes of the implant to accommodate  
20 various anatomical variations in the normal population.  
21 Ultimately, we tried--we're trying to obviate the need for  
22 autograft harvest in that second procedure from the iliac  
23 crest bone.

24           The BAK/C interbody fusion system is, in fact, a  
25 threaded, hollow, porous titanium alloy cylinder. It may be

1 used as a single device. There are four sizes. In this  
2 clinical trial, there is a 6-millimeter diameter device, an  
3 8-, a 10-, and a 12-millimeter device. The smaller ones  
4 could be used in pairs. All devices are 12 millimeters in  
5 length.

6 The BAK/C, we refer to it as an uncoated device if  
7 it does not have HA coating on it. We also refer to it as  
8 an HA-coated device during this presentation, coated to a  
9 thickness of about 35 to 65 microns, according to ASDM  
10 specifications, with hydroxyapatite.

11 The ability of this device to gather bone as it's  
12 being inserted is given by the fact that certain [inaudible]  
13 holes in this device are slightly angulated to the central  
14 axis of the device. So as you screw this in, it shaves  
15 local bone against the implant during insertion.

16 In terms of the preclinical [inaudible] testing,  
17 we performed in the laboratory strength and stability(?)  
18 testing according to the proposed ASDM standard that's being  
19 worked on in [inaudible] committee. The goal of these  
20 experiments was to provide a design load criteria of at  
21 least 80 pounds. This is based on the average weight of the  
22 head as well as the loads and pressures that are anticipated  
23 within the disc space. This also includes a safety factor,  
24 an engineering safety factor of three. So we actually  
25 anticipate the actual loads of the cervical spine

1 [inaudible] pounds.

2           The results of these tests indicate to us, as you  
3 can see on the left, a 6-millimeter gauge, which by  
4 [inaudible] analysis is the worst-case scenario in terms of  
5 strength, yielded an ultimate compressive load of over 1,000  
6 pounds, well above--actually, 13 times above the design  
7 criteria of 80 pounds. On the right you can also see a 10-  
8 millimeter cage which was tested. This was tested because  
9 it was the most common device that we anticipated being used  
10 in the clinical trial.

11           The fatigue runout load in these experiments to 5  
12 million cycles was at least 120 pounds, which represents 50  
13 percent over the design criteria of 80 pounds.

14           The ability of this system to provide  
15 biomechanical stability was tested in two separate  
16 laboratories, independent contract laboratories, one being  
17 McGill University in Montreal. Classic biomechanical  
18 testing with cadaveric specimens looking at flexibility and  
19 stability were performed. The goal of these experiments was  
20 to reduce the range of motion below intact non-operative  
21 spines. In general, the results showed us and taught us  
22 that the unilateral and paired implants both provided about  
23 a 20 to 50 percent reduction in the range of motion,  
24 depending on which motion you look at--flexion, extension,  
25 lateral bending, or rotation. Also, there was no

1 statistical difference--

2 CHAIRMAN YASZEMSKI: May I interrupt you for just  
3 a second? We are having technical problems picking up sound  
4 from the microphones. Mr. Demian is going to bring the  
5 working microphone of his to you [inaudible].

6 [Pause.]

7 CHAIRMAN YASZEMSKI: Is it picking up now? Okay.  
8 Thank you, Dr. Griffith.

9 DR. GRIFFITH: In conclusion of the biomechanical  
10 testing, we learned that there was no statistical difference  
11 between paired implants or single implants in the disc  
12 space.

13 In terms of the preclinical animal studies, we  
14 attempted to look at histological evidence of bone growth in  
15 and around the cage, and we used two separate models. We  
16 used a goat model and a sheep model. In the goat model, it  
17 was a three-level cervical fusion; in the sheep model, a 2-  
18 level cervical fusion. Both of these experiments had a  
19 three-month follow-up time point.

20 On the right you can see an example of a cervical  
21 spine in a goat that had been implanted for three months,  
22 and you can see trabecular inside the cage as well as nice  
23 implant-to-bone contact on the outside of the cage. During  
24 these experiments there were no HA-related adverse events.  
25 There also were no device-related fractures, extrusions, or

1 collapse of the device.

2           So, in summary, the preclinical data taught us  
3 that the device--we are confident the device has a high  
4 mechanical strength, a high fatigue integrity. It does  
5 provide a positive, rigid, biomechanical fixation with  
6 reduced range of motion in the motion segment, as well as  
7 increased stiffness. We were able to demonstrate bone  
8 growth in and around the fusion mass. We also were able to  
9 demonstrate safety with this device with no unanticipated  
10 adverse events occurring in the animal trials.

11           All of this is good information, but the more  
12 important information is going to be given from the human  
13 clinical study by Dr. Hacker.

14           CHAIRMAN YASZEMSKI: Again, Dr. Hacker, before you  
15 start, may I ask you--we're going to do a microphone check.  
16 Mr. Demian?

17           MR. DEMIAN: We're just going to go around the  
18 table and make sure that everybody's mike is being heard by  
19 the transcriptionist. So we'll just do a mike check with  
20 each person, and make sure Dr. Chapman's is checked as well.

21           [Microphone check.]

22           CHAIRMAN YASZEMSKI: Thank you. We'll move to Dr.  
23 Hacker now.

24           DR. HACKER: Thank you. Mr. Chairman,  
25 distinguished panel members, I'm Bob Hacker. I'm a

1 neurosurgeon in private practice in Eugene, Oregon. I was  
2 also a participant in this clinical investigation, and I'm  
3 here at the request of Sulzer Spine-Tech company. They have  
4 paid for my travel here, and they're compensating me to  
5 appear here today.

6 I'd like to present the clinical data, and I'd  
7 like to summarize where we've been and some of the data and  
8 where we think this is taking us to.

9 Anterior cervical discectomy and fusion is not a  
10 new approach in the treatment of degenerative cervical disc  
11 disease and radiculopathy. Forty years ago, Ralph Cloward  
12 introduced this technique, and its durability is evidenced  
13 by the fact that we still continue to recognize this as the  
14 standard of care.

15 Nuances have developed over the years. The simple  
16 discectomy approach or so-called graftless fusion is  
17 preferred by many surgeons. Cloward and Smith-Robinson  
18 dowel and bone block techniques, respectively, are also part  
19 of the standard of care.

20 The graft material has varied, some surgeons  
21 preferring autograft, hip harvest, others using allograft  
22 and even bone graft substitutes such as coralline. Plate  
23 fixation has also found a role for some in the treatment of  
24 cervical degenerative disc disease with 1- and 2-level  
25 fusion, and, of course, now a variation, a modification, if

1 you will, of our traditional technique in which an interbody  
2 fusion cage is utilized.

3           The purpose of this clinical study was to  
4 determine whether or not this device could be safely applied  
5 to the human model or patients and if it was effective in  
6 the treatment of radiculopathy due to degenerative cervical  
7 disc disease.

8           Now, the design of the study was such that we  
9 randomized patients. It's a prospective randomized study  
10 with a control group, and the randomization was such that  
11 the two-cage types were randomized equally with a control  
12 group. So there's one-to-one-to-one randomization.

13           There were 578 patients, 28 sites, and around 50  
14 surgeons participating. Long-term follow-up is defined as  
15 follow-up equal or greater than two years following the  
16 surgical approach.

17           The hope was to demonstrate equivalence between  
18 the treatment or control group or superiority for the  
19 treatment group, and data cutoff was June 2000.

20           To be considered as a patient, the surgeon had to  
21 identify radiculopathy signs or symptoms resulting from  
22 degenerative cervical disc disease. The patients could be  
23 treated for simultaneously symptomatic 1- or 2-level disease  
24 between C3 and C7. The patients could not have myelopathy,  
25 moderate or severe in severity, acute cervical trauma, or a

1 previous fusion at the site of treatment.

2           Now, before I run through all the results and a  
3 lot of slides, I'd like to make my summary points first.

4           From the data I'm going to show you, I believe it  
5 is very reasonable to conclude that the device is safe. I  
6 think you'll see this by the low rate of complications and  
7 advantages in the investigational group.

8           Second, when you look at our results--and we've  
9 used several tools to measure results--I think that you will  
10 see that we compare or better the results obtained in the  
11 control group.

12           And, finally, as a clinician, I can speak directly  
13 from experience and from the study results that there is  
14 clinical utility, clinical benefit associated with the use  
15 of this device.

16           So here we go with all the numbers: 578 patients  
17 randomized to three categories. You'll notice when you look  
18 at these slides, you'd wonder if we randomized correctly  
19 since there seems to be more patients in both the  
20 investigational groups and fewer in the ACDF group. I can  
21 tell you from my experience as an investigator I had some  
22 patients who, upon finding out they had been randomized to  
23 the control group, declined to participate in the study. We  
24 further stratified between 1- and 2-level disease between  
25 all three of the categories of treatment.

1           Now, you'll notice from the information that you  
2 have before you and information from our published study  
3 that the results between the hydroxyapatite-coated cage and  
4 the uncoated cage were identical in almost every category.  
5 No significant difference in outcomes, surgical technique,  
6 surgical parameters could be identified, and to make this a  
7 more easily followed presentation, I'm going to combine the  
8 two treatment groups and call them the cage group from this  
9 point forward. So we'll compare the results of cages to our  
10 control group.

11           Now, here we go with some of the treatment  
12 parameters or the patient demographics, I should say.  
13 You'll notice that between the cage group and our control  
14 group that there's really not much difference in the 1-level  
15 patients, no statistically significant difference between  
16 the age of the patients, smoking status, gender, and  
17 workmen's compensation-related issues. This holds true in  
18 the 2-level group as well, the same, more or less, breakdown  
19 in age, gender, and smoking. You will notice--and I think  
20 this is important--that there is a slightly greater trend  
21 toward smoking in our 2-level cage group. This did not  
22 reach statistical significance, but 45 versus 32 percent.

23           Next?

24           Now, the surgical technique, all of us who perform  
25 anterior cervical discectomy recognize that this is in many

1 regards a two-part operation. You commence with your  
2 exposure of the neck, the patient under general anesthetic.  
3 The tissues are dissected, the disc space exposed; usually  
4 with the microscope for most of us or vision assistance with  
5 loops, the disc material is removed, the neural element  
6 decompression, the goal of the surgery is accomplished, and  
7 at that point is really where the difference between the two  
8 groups, the investigational and control, can then be  
9 identified. And here are the differences.

10 In the control group, the surgeon had the option  
11 to utilize the technique that he was most comfortable with  
12 or felt most appropriate for the patient he was treating.  
13 He or she. That means a Smith-Robinson or Cloward dowel  
14 could be used; further, a choice of autograft versus cadaver  
15 bone, allograft, was available.

16 Now, in the treatment group, our cage group, this  
17 group, following performance of the successful discectomy  
18 and decompression, the surgeon then used instruments  
19 provided by the manufacturer, specific distraction,  
20 measurement, drilling, graft harvesting, tapping, and device  
21 placement. Often this was assisted with fluoroscopic  
22 control.

23 Now, I need to explain the autograft harvest. The  
24 drill, which is used to prepare the inplates, is a specially  
25 designed drill with flutes that cut and, if you will,

1 collect the bony inplate reamings. This cortical bone,  
2 devoid of cartilaginous inplate, can then be removed quite  
3 easily from the drill and put directly into the cage.  
4 That's our source of bone graft. The cage flutes are  
5 designed in such a fashion that, as the cage is advanced, it  
6 actually scoops and further autofills the cage as you're  
7 twisting it into place. And this can be observed by the  
8 surgeon if he directly visualizes it, usually through the  
9 microscope, as it's being inserted.

10 Next slide, please?

11 Let's look at the operative characteristics, the  
12 majority of cases in our 1-level treatment group performs at  
13 C5-6 and C6-7. The source in the control group--that's the  
14 column on the right--you'll notice the majority of surgeons  
15 in practice, nearly two-thirds of cases were treated with  
16 autograft--that's iliac crest harvest bone placed into the  
17 neck--and about a third relied on cadaver bone.

18 Now, in the control group, you'll notice the  
19 majority of surgeons used autograft, and occasionally--the  
20 lower number down there, 2.3 percent--supplemented their  
21 autograft with a cage by harvesting bone from the iliac  
22 crest. In those cases, the surgeon felt he needed  
23 additional bone.

24 In the allograft category, you'll notice that 43  
25 percent of surgeons utilized allograft. Allograft in this

1 column is meant more to represent the fact that surgeons  
2 would oftentimes, myself included, use substances such as  
3 Graft-On, demineralized bone matrix, to fashion a coagulum,  
4 if you will, a congealing of the bone fragments within the  
5 cage. This seemed to allow placement of the fragments into  
6 the case a little more easily than trying to take the fine  
7 shavings and get them to stay in the cage.

8           These same breakdowns are seen for the 2-level  
9 characteristics, the autograft to allograft, the levels, and  
10 the supplementation with the Graft-On or allograft for the  
11 investigational group.

12           Complications as a clinician are to me one of the  
13 most important parts of this study. Since there were no  
14 mortalities, no serious morbidities, no devastating  
15 neurologic outcomes of any sort in this study, the next most  
16 serious level of complication as a surgeon to me are those  
17 which require repeat surgery. These are the percentages for  
18 1-level patients, those patients who required additional  
19 surgery, and I'd like to take some time with this in the  
20 next slide.

21           You'll notice that we identified as complication  
22 the development of transition segment disease, and that's  
23 identified as the degeneration at another disc or at the  
24 adjacent disc. These are generally recognized outcomes  
25 which may occur with any fusion approach, be it lumbar or

1 cervical or thoracic, and you'll see that there was no  
2 significant difference between the control and the  
3 investigational group.

4           The same is true of pseudoarthrosis. Although the  
5 investigational group far trumped percentage-wise the  
6 control group, there was not a significant difference on  
7 analysis.

8           Where there is a statistically significant  
9 difference is when we look at the actual implant itself. If  
10 we consider implant complication in regards to collapse and  
11 the need to repeat an operation, there was a statistically  
12 significant difference here, such that the control group  
13 required repeat operation 3.7 percent of the time for graft  
14 collapse, and this was not seen in any of the patients in  
15 the 1-level group. In fact, it wasn't seen in any patient  
16 in the 2-level group; whereas, 10 percent of the patients--  
17 well, a little more than that--required repeat operation in  
18 the control group for graft material collapse.

19           Could we go back, please?

20           On this slide I want to draw your attention to  
21 something I found interesting, so please follow with me.  
22 Under complication, you'll notice the term "fractured  
23 vertebra." When I had not had direct clinical experience  
24 with this, in reviewing the clinical study I had a chance to  
25 review X-rays and study this complication. My perception of

1 fractured vertebra was that--well, super-maximal or untoward  
2 force had been applied to a vertebral body and actually  
3 broken it somehow in the insertion of the instruments or  
4 guide tube. That is not the case.

5 Fractured vertebra here is actually, in my  
6 opinion, a technical issue where the surgeon, either by his  
7 trajectory of implant placement or his drilling, actually  
8 over-violated the cortical inplate of the vertebral body,  
9 and this is not actually a fracture, but it's actually  
10 significant subsidence of a vertebral body once the cortical  
11 inplate has been disrupted.

12 So fractured vertebra, I want to make sure that  
13 this is clear. This is not a forceful, traumatic sort of  
14 event but, rather, a disruption of the vertebral body with  
15 subsidence.

16 Next slide?

17 Judging effectiveness, we looked at fusion rates,  
18 and these were measured by an independent radiologist using  
19 an overlay flexion-extension approach. Neck pain was  
20 evaluated with a VAS scale. Radicular pain was also  
21 assessed with a VAS scale, but also with a neurologic  
22 examination. And function relied on the SF36 with both  
23 components.

24 Here's the fusion rate, and really not a  
25 statistically significant difference. You'll notice that

1 we're at the 100 percent category, pretty much all the way  
2 across in our investigational group using the criteria  
3 applied equally to both categories, both the control and the  
4 investigational. In the 2-level group, as we all know,  
5 fusion rates go down, and they went down in commensurate  
6 fashion for both the control and the investigational group.

7           Let's look now at what the patients tell us. If  
8 we look at patients before surgery in neck pain and arm and  
9 shoulder pain--and they're on the left and right,  
10 respectively--you'll see that our average pain score for the  
11 neck decreased from around 6 down to about 3 for both groups  
12 following treatment. That's from the pre-op to post-op  
13 initial data point of six months.

14           The same, but even a greater degree of decline,  
15 which, for those of us who treat radiculopathy, is not  
16 surprising, is seen in the arm and shoulder pain group.  
17 Importantly, it is maintained throughout the length of the  
18 study, even at long-term follow-up.

19           Again, checking the pain scores for the 2-level  
20 patients, we see this same commensurate drop in values.

21           The SF36 gives us on the left our mental component  
22 and on the right our physical component. This slide,  
23 recognize, please, that the normal score is in the lighter  
24 shaded area that's above 40 percent or above a score of 40  
25 on both sides. You'll note that pre-operatively the

1 patients are recorded, and by six months in both categories  
2 or in both scales, please, the range has increased and is  
3 maintained in the normal value range. This is also true,  
4 again, for the 2-level patients.

5           Let's look at clinical utility because this is  
6 where we discuss how difficult is the surgery. Is it a  
7 surgery associated with lots of blood loss? What are our  
8 variables? And what we'll see here, first of all, looking  
9 at those surgical variables, considering timing, no  
10 significant difference for the 1-level patients. Blood  
11 loss, there's a greater loss in the control group, probably  
12 related to bone graft harvest, and hospitalization at 1.4  
13 days is equal between the two groups.

14           The same findings really are evidenced here in the  
15 2-level patients. Again, the hospital stays, the blood  
16 loss, all without a significant difference.

17           Here is, in my opinion, one of the most telling  
18 slides of our presentation or my presentation. We recognize  
19 from authors like Solwin and Traynelis, Rob Heary, that  
20 donor site pain is a common and not unexpected outcome in  
21 patients who have hip graft harvest. At our last national  
22 meeting, figures were reported whereas surgeons may hear  
23 levels of 5 to 10 percent, independent follow-up may  
24 document levels as high as 25 to 30 percent of patients who  
25 report chronic pain of some degree in their iliac crest

1 following harvest.

2 In this slide, you'll notice the control group is  
3 in blue, and there are the times from left to right, 6, 12,  
4 and long-term follow-up intervals of data collection.  
5 You'll note at long-term follow-up about 8 to 9 percent of  
6 patients still report pain in their iliac crest from graft  
7 harvest.

8 I would like you also to consider the way that  
9 number was generated. That's our control group. Please  
10 remember that a third of those patients didn't have an iliac  
11 crest graft harvested. They had allograft. So we have to  
12 decrease that denominator by a third, which actually bumps  
13 that number up close to 15 percent of patients with chronic  
14 iliac crest graft site pain that they didn't have before  
15 surgery. There is one patient in the treatment group that  
16 did report pain long term from harvest.

17 Employment status, again, these both show, as  
18 expected, patients get better. They get back to work in the  
19 1-level and also in the 2-level.

20 Next slide, please?

21 This is when we asked the patient how they're  
22 doing. Let's look at the poor results. They're identical  
23 for both the cage and the control group. Less than 10  
24 percent of patients--I believe it's around 4.8 percent, I'd  
25 have to look. Both report poor outcomes. The majority of

1 patients report good or excellent results when they judge  
2 their outcome. And this is true for the long-term patients-  
3 -excuse me, for the 2-level patients as well.

4 Next slide?

5 I'd like to wrap up my part of this thing and  
6 state conclusions based on this study and my own experience  
7 with the device as an investigator.

8 I believe the device is safe and effective. I  
9 believe it can be used successfully in treating degenerative  
10 disc disease, related radiculopathy in patients from C3 to  
11 C7. This study shows fusion and clinical outcomes that are  
12 comparable or superior to those of the traditional anterior  
13 cervical discectomy and fusion approach.

14 I believe there are distinct benefits, and in my  
15 own practice, every one of the techniques that I showed  
16 before, I have used for at least two or three years in my 20  
17 years of practice. I believe the BAK/C allows not so much  
18 greater results, but it avoids some of the drawbacks and  
19 pitfalls associated with the other techniques.

20 For instance, we provide a non-collapsing columnar  
21 support with the cage. There is no instance of this cage  
22 collapsing in any of the study patients treated so far in  
23 this country or elsewhere. Collapse resulting in repeat  
24 surgery is a significant complication in the control group  
25 in this study. Also, Howard Ahn and Yang and others have

1 demonstrated greater pullout strength for a threaded device.  
2 Autograft biology I believe is superior to allograft  
3 technology, whether there is additional supplemental  
4 fixation with the allograft or not.

5           Finally, the elimination of a painful donor site,  
6 in my opinion, makes this device very attractive to our  
7 patient population.

8           Thank you. Next will be Dr. Larntz. He's a  
9 statistician, and he's going to speak to the bioanalysis.

10           DR. LARNTZ: Good morning. I'm Kinley Larntz.  
11 I'm professor emeritus, University of Minnesota. I work as  
12 an independent statistical consultant, and I've worked with  
13 this sponsor for quite a number of years.

14           I've got an outline of what I want to tell you  
15 about, statistical analysis, and in particular the  
16 statistical techniques we've used for the basic conclusions  
17 was we wrote a protocol that included using Bayesian  
18 techniques for decisionmaking, and so we're going to talk  
19 about that. Data you saw already are collected over time,  
20 that is, the visits are taking place at 6 months, 12 months,  
21 24 months and beyond, long term. So we actually used the  
22 data from 12-month and beyond in our analysis, although our  
23 primary goal was to understand what happened long term.

24           This is an equivalence--the protocol, that is, in  
25 the protocol we defined what we meant by equivalence, and I

1 want to talk about that protocol definition and tell you  
2 whether or not the clinical results met that definition in  
3 the results. And I'll talk about--it says there sensitivity  
4 analysis. I feel very--statisticians talking about  
5 sensitivity seems kind of funny to me, but we have a soft  
6 side, too. So we'll talk about that. I'll actually try to  
7 explain what that means as best I can.

8           So Bayes techniques have been around for a long  
9 time. Typically, they incorporate prior information to  
10 understand study results. That's not actually how we're  
11 using them here. We're incorporating a model for  
12 decisionmaking by using Bayes techniques, and Thomas Bayes,  
13 Reverend Thomas Bayes--that tells you how important Bayes  
14 techniques are in statistics; they were started by the  
15 clergy--provided a theorem on conditional probability that  
16 serves as the basis for--actually, it serves as the base for  
17 lots of headaches in teaching elementary statistics, but  
18 beyond that it also serves as the basis for Bayes inference,  
19 and especially the idea of conditional probability. And for  
20 a long time, these techniques have been hard to use because  
21 we didn't actually have the ability to carry out the  
22 computations. That's been solved by some wonderful advances  
23 in--well, we all know about computing-power advances, but  
24 also there have been some very, you know, super work done in  
25 computing methods to allow us to actually compute the Bayes

1 posterior distributions.

2           In general, the key feature for what we're doing  
3 here--the key feature, the key feature--is we allow--we  
4 actually get a probability statement about model parameters,  
5 a probability statement based on the data. We can actually  
6 make probability statements about the model parameters, and  
7 in particular, our hypothesis here, our hypothesis we want  
8 to study, the event we want to study, is equivalence. So we  
9 can actually calculate a probability that equivalence holds,  
10 actually calculate a probability that equivalence holds.  
11 That's an advantage that we can't do with classical  
12 techniques. But, in fact, it's a very powerful--well, I  
13 think it's a very powerful technique.

14           So let's go ahead. Technically--oh, wow, a linear  
15 model for the log odds of success. Well, everyone  
16 understands what that means, don't they? So what we do is  
17 we construct--we're looking at binary outcomes. Binary  
18 outcomes, we'll see that. And in statistical terms, we  
19 typically analyze log odds. I think that's the right thing  
20 to do. And then we have an underlying linear model.

21           This model--excuse me, I'm sorry, Rose. This  
22 model includes something that I think is important and  
23 actually allows--it could be done in a classical framework,  
24 but it's done very effectively in the Bayes framework. This  
25 is a multi-center study. A multi-center study. Lots of

1 multi-center studies are done, right? What do we typically  
2 do when we come up with multi-center data? Well, the  
3 typical thing that comes up is people say, Can you pool the  
4 data? Can you pool the data? I don't know how many  
5 statisticians are here, but we get asked all the time, Can  
6 you pool the data and do a pooling analysis?

7           This model says directly that centers may have  
8 different probabilities of success. That's built into the  
9 model. So if the data are--we don't assume that we have  
10 identical probabilities of success by center. We allow that  
11 to vary. And we estimate the degree at which it varies from  
12 the data itself. So if the centers are quite different with  
13 respect to success probability, the model will find that.  
14 The Bayes analysis will adaptively discover that. If the  
15 models are basically the same, it will automatically pool  
16 them. That's true for the overall probability of success.

17           We also incorporate into the model very important-  
18 -this is really the key for poolability. Do we have the  
19 same treatment effect by centers? Are some centers doing  
20 better or worse than others with respect to the treatment?  
21 And, again, we allow for centers--we allow for centers to  
22 have different treatment effects, and the Bayes analysis  
23 automatically pools or doesn't pool the data in a sense.

24           What this amounts to, when you put these random  
25 effects into the model, is when we look at the spread of the

1 estimated treatment effects, the spread of the estimated  
2 treatment effects will be larger than if we just assumed  
3 everything were automatically just poolable.

4           Okay. Well, I'm not sure this came through very  
5 well on the presentation. This is supposed to be a grid, a  
6 two-by-three grid. You can see the grid lines there. Does  
7 everyone in the room see those? Okay. I don't have that  
8 good of vision, actually, come to think of it. But, in  
9 fact, this is a study involving 1- and 2-level patients, and  
10 as we saw earlier, there are two devices, one an uncoated  
11 device, one a coated device, and a control. So there are  
12 six possible treatment cells.

13           And what we're going to do in our presentation is  
14 primarily look at what are called simple comparisons. The  
15 model allows us to make these comparisons. The protocol  
16 actually was written to have a more summary comparison, that  
17 is, combining things across 1- and 2-level, combining across  
18 the coated and uncoated devices. But for clarification and  
19 for presentation purposes, we've been focusing on 1-level  
20 comparisons.

21           So this comparison right here is the 1-level,  
22 looking at 1-level patients, comparing the BAK/C uncoated  
23 device--you see there's no HA there, so that's uncoated--to  
24 the control patients. So we'll look at that comparison, and  
25 then--we'll actually look at four comparisons.

1           The next comparison will be--the simple comparison  
2 that we would look at would be among 1-level patients  
3 looking at the BAK/C coated device versus control patients,  
4 and we have the same comparisons for 2-level patients,  
5 uncoated versus control and coated versus control.

6           Comparisons that we made in the written materials,  
7 I'm not going to talk a lot about them today. We can also  
8 compare the results for 2-level patients as a whole to 1-  
9 level patients as a whole. We can do that, and there are  
10 some differences. You saw some--Dr. Hacker showed you  
11 clearly that fusion rates are, for instance, lower for 2-  
12 level patients, and that was--well, that's what was found,  
13 and I think--I'm just a statistician, but I think that was  
14 what was expected.

15           We could also make and do make some comparisons  
16 between the uncoated device, that is, the BAK/C, versus the  
17 coated device, the BAK/C-HA. And we can do that at 1-level,  
18 and we could do the same comparison at 2-level. And I will  
19 show you a slide with those comparisons on it.

20           Okay. So multivariate--oh, wow, I've got to get  
21 my words straight. Multivariate longitudinal modification  
22 of a model. What are the advantages of this model? And  
23 this is the model, the basic model we used for drawing our  
24 conclusions.

25           Well, we include both 12-month and long-term data

1 in the same model, and we obviously have much--much of the  
2 data has data on the same patient both at 12 months and long  
3 term, and that's good. But some patients, a number of  
4 patients, have data at 12 months, but we for various reasons  
5 didn't attain long-term data for them. One reason might be  
6 that they weren't due for long-term follow-up, so we only  
7 had 12-month data. Another reason may be that we had 12-  
8 month data, but the patient for whatever reason decided not  
9 to come back, or they came back and perhaps some of the  
10 information wasn't collected.

11           So if we were looking just at the long-term data,  
12 we could do that. We would be basically throwing away the  
13 information that we gather at 12 months. So the model that  
14 we have incorporates the information from 12 months and long  
15 term together using an odds ratio multiplier. Does everyone  
16 understand what that means? Well, it's a technical term to  
17 allow us to understand how closely the data at 12 months and  
18 long term are.

19           For instance, at fusion--for instance, at fusion,  
20 I think almost every patient that was fused at 12 months was  
21 also fused long term. So if a patient were a fusion success  
22 at 12 months, they tended to be a fusion success long term.  
23 So that gave us information about the long-term data. And  
24 it's true of the other success measures as well. If a  
25 patient was a failure at 12 months and we didn't have the

1 long-term data, that would inform us that the odds that they  
2 would be a failure long term are actually higher than if  
3 they had been a success. That's what's incorporated in the  
4 model. And this allows us to give more precise estimates of  
5 the long-term effects. Actually, we're using all the data,  
6 which is, I guess, a principle of statistics, we should use  
7 all the data whenever we can, and it accounts for missing  
8 long-term data.

9           Okay. Now, protocol definition of equivalence.  
10 The protocol definition of equivalence, typically what we do  
11 in an equivalence study, we look for a delta, that is, we  
12 try to say this success rate is no worse than delta worse  
13 than the control, if I want to say it that way, no worse  
14 than delta worse than, okay?

15           Now, what we did, because we're doing things in  
16 the log odds scale, we have to translate that into a number  
17 that will apply across the entire range of log odds, and the  
18 delta that we specify then is done in terms of the log odds.  
19 And the one we derive corresponds to comparing a 10 percent  
20 delta for a 90 percent success rate. So we wind up with a  
21 boundary. We'll see in the pictures--we're going to show  
22 pictures. Maybe--I'm a statistician. I should show tables  
23 and tables of numbers. Wouldn't that be fun? But what I'll  
24 do is I'll show pictures, and this boundary, lower boundary,  
25 this boundary of negative 0.8109 corresponds to the

1 protocol-defined boundary for equivalence.

2           Now, what do we get out when we do our Bayes  
3 analysis? What do we get out? We get out picture. Isn't  
4 that nice? If we decide to draw them. Here's the result,  
5 what we call the posterior distribution of the effect of  
6 BAK/C versus control, that is, comparing the uncoated device  
7 at 1-level versus control. And it's hard--I'm quite sure  
8 it's difficult to read, but there's a zero down here and  
9 this line in the middle corresponds to zero, which would be  
10 a line that says zero corresponds to--there's no difference  
11 in the log odds scale between BAK/C and control.

12           We have another line here--do you see the line on  
13 the left? The line on the left, that's our boundary for  
14 equivalence, the minus 0.81 we just talked about. And in  
15 thinking about that and looking at that, the protocol  
16 definition of equivalence said when you look at the  
17 posterior distribution--this is an estimate of the effect--  
18 actually, this looks positive, right? Isn't it shifted to  
19 the right of zero? That looks like for this--this is the  
20 overall success measure, whatever that is, and we'll define  
21 it in a second. It looks like the BAK/C uncoated device is  
22 better, that is, the further to the right, the higher the  
23 estimate of effect in favor of the BAK/C device. It looks  
24 like it's better than the control. That is, here's the zero  
25 line, which would say they're equal, and this is shifted to

1 the right.

2           In fact, at the bottom--and we're going to  
3 summarize, although I'd love to give you all these pictures,  
4 I think someone said I have a time limit. Do I? Well,  
5 anyway, I'll assume I do. And what I did is summarize in  
6 what are called credible intervals, and these credible  
7 intervals are--there's a bar at the bottom. You see there's  
8 a line there and a line there. Actually, there's a line in  
9 the middle, too. This doesn't show up very well.

10           This credible interval is generated such that 5  
11 percent of the distribution is below this bar, the lower  
12 bar. Five percent of the distribution is above the bar. So  
13 this is a centered 90 percent credible interval.

14           The protocol definition of success would say the  
15 bottom part, this lower part here, in order to satisfy the  
16 protocol definition of success, which was that 95 percent of  
17 this distribution be shifted to the right of the equivalence  
18 line, then this lower bar should be to the right of that  
19 line, negative 0.81. Okay. So we're going to see these  
20 credible interval bars.

21           What are the study objectives? The study  
22 objectives are to demonstrate equivalence between--  
23 equivalence, that's our protocol; it was written for  
24 equivalence--equivalence between the treatment arm and the  
25 control arm. We have five outcome measures. They're binary

1 measures: fusion, neck pain defined as an improvement of, I  
2 think, on the scale of two points; radicular effectiveness,  
3 also defined in the same way; and function defined as  
4 improvement in the SF36; and overall measure of success,  
5 which I don't think has been defined yet, and I'll define  
6 that in a second. We also have safety outcomes involving  
7 device complications, and I'll talk about analysis of both  
8 the effectiveness and the safety in the Bayes context.

9           Okay. First I'll define overall success for you.  
10 To be an overall success, what do you have to do? Well, you  
11 have to be a fusion success. You have to be a neck pain  
12 success. You have to be a radicular success. You have to  
13 be function success. And, in addition, assuming if you've  
14 got these and measured them and they're all successful, you  
15 have to be not a technical failure, which--well, I'm a  
16 statistician, but my understanding is if you had to  
17 reoperate on the site and do something to improve the  
18 device, then you're a technical failure. So that's my  
19 understanding of what that is.

20           Okay. So we have this overall success measure  
21 which is a composite of all them, that is, you have to have  
22 all of them, plus not be a technical failure.

23           Okay. Now, we studied this and carried out this  
24 study--the company carried out the study. I have to be  
25 careful. I'm only a statistician. I didn't go out and

1 collect any data, by the way. I analyzed the data. And we  
2 use for the effectiveness outcome what I will call a  
3 restricted cohort, and these are the patients that were due  
4 for 24-month follow-up at November 15, 1999. And the reason  
5 we're doing that is--well, I guess it's no secret. We saw  
6 that the original PMA was filed when? December 1998, is  
7 that right? Okay. When the data were analyzed and when the  
8 agency looked at the data, they said, really, you know, your  
9 compliance rate long term isn't very high, relatively.

10 So what was done was it was said, well, let's go  
11 back and find these patients, let's go back and see if we  
12 can find them and look at them and make an intensive effort.

13 Now, depending on how you look at it, you could  
14 say let's make an intensive effort to find everybody, and,  
15 of course, I'm sure that's what everyone wants to do. But,  
16 in fact, for the patients that were due for 24 months at  
17 November 15, 1999, a very intensive effort was made to find  
18 these patients long term. These patients long term, it was  
19 a very intense effort. So we're looking at the restricted  
20 cohort of those patients for long-term effectiveness.

21 It turns out we have analyzed and presented the  
22 so-called unrestricted analysis, and no results changed.  
23 Actually, they look a little better from the unrestricted  
24 analysis. Okay? So in some sense, it's a conservative  
25 analysis.

1           The compliance rate turned out to be 80--we're  
2 aiming at 80. We made it, right? 81.3. Everyone happy?  
3 Okay. So with respect to that.

4           Now, that does mean, however--does it not?--that  
5 there is some missing data long term. And so we'll see--and  
6 this is where sensitivity comes in. We'll see, if we make  
7 some assumptions about that missing long-term data, where  
8 that--what might have happened. So let's go to the next  
9 slide.

10           This is our basic conclusion slide, so let's just  
11 spend a little time. This is for fusion, and some of the  
12 lines aren't showing up very well. At the bottom here, this  
13 is comparing 1-level BAK/C versus control, and that's our 90  
14 percent credible interval. Do you see that? And you see  
15 the lower line there. Actually, it's to the right of zero,  
16 let alone the bar, the negative 0.81. So that actually  
17 indicates--well, that indicates with respect to fusion the  
18 uncoated 1-level is better than control.

19           I have put on these charts--I have put on these  
20 charts numerical values which give, remember I promised, the  
21 probability of equivalence. So the numerical values are the  
22 probability of equivalence, and it put 99.9 percent there.  
23 I refuse to round it to 100 percent. I'm a statistician.  
24 I'm not going to let anyone say there's 100 percent chance,  
25 okay? So 99.9 is as big as they get.

1           And we can see that--you can see that for 1-level  
2 BAK/C versus control we get 99.9. For the coated we get  
3 also a 99.9. In fact, it's also to the right of the zero  
4 line. For the 2-level BAK/C versus control, it's hard to  
5 read, but, in fact, the lower bar is actually to the left of  
6 the equivalence line. The probability turns out to be 86.1  
7 percent. That's the number there. And the 2-level coated  
8 versus control, the probability of equivalence is 90  
9 percent. Okay. So that's we did for fusion.

10           We did this for each of the results. For neck  
11 pain, let's see, the protocol said we had to have at least  
12 95 percent probability of equivalence. Well, that number  
13 is--you see the line that's very close to the equivalence  
14 line? We got 95.1. Okay? So it meets the protocol  
15 definition of equivalence. If someone wants to say, well,  
16 that's pretty close, I'd say, well, it could get closer, but  
17 not by much. Okay? 95.1.

18           That's true--for the coated device, it actually is  
19 95.2. If anyone knows me, they'll know tongue-in-cheek I'd  
20 say that's a lot bigger than 95.1, and they'll know I'm  
21 being facetious, right? They're actually very--but they  
22 both meet the definition. The 2-level ones are 88.1 and  
23 89.6, but they don't meet the protocol definition or  
24 requirement in and of themselves for 2-level.

25           Look at radicular results. Again, for the 1-

1 level, uncoated and coated, the probabilities actually are  
2 high, 99.5 and 99.3. For 2-level, neither one meets the  
3 protocol definition of success, although 80-point--well,  
4 someone could say you have 82 percent probability of  
5 equivalence. Isn't that pretty high? Well, it is, but our  
6 requirement was 95. The one for 2-level uncoated was 41,  
7 and I guess I'd say that isn't very high. Okay?

8           Looking at function success, again, for 1-level we  
9 have probabilities of 99.4 percent, meeting the requirement  
10 of equivalence, and 99.9. We have 85.9 for the coated  
11 versus control at 2-level--excuse me, uncoated versus  
12 control at 2-level. And for the coated device versus  
13 control at 2-level, we actually get 96.2. So at the 2-  
14 level, although, remember, there aren't--there are a limited  
15 number of 2-level patients. That's the reason these lines  
16 are wider for 2-level than they are for 1-level. But for  
17 the 2-level patients, even with the small number of  
18 patients, there's evidence that the protocol definition of  
19 success is met with respect to function.

20           And the final one I think is for overall success,  
21 and we wind up with 99.9. Actually, this is the picture we  
22 saw originally. Remember the picture with the histogram of  
23 results. This is the bottom one right here. You can see I  
24 put 99.9 percent probability of equivalence. It's actually  
25 just to the right of the line of zero. We might even say

1 the results were superior for the BAK/C uncoated device for  
2 the overall measure; 79.5, almost 80 percent for 2-level;  
3 99.9, again--this one actually is to the left slightly of  
4 the zero line--and 96.4 percent for the 2-level. Oh, that  
5 one's bigger than 95, again, right? So that meets the  
6 protocol definition of equivalence. Okay?

7           So I promised you that we'd do uncoated versus  
8 coated to see if there are differences, and there's no--to  
9 see if there are differences, and there's no definition of  
10 equivalence for these two. But what we can see--and, again,  
11 the lines are here--all the lines cross the zero line. All  
12 the lines cross the zero line. Do you see that? The 1-  
13 level comparisons for the five, 1-level measures are at the  
14 bottom, and although they didn't show up very well--I think  
15 they're on your slides, on your copy of the slides--they all  
16 cross and there's really no hint that there is any  
17 difference in one direction or another. So 2-level, I guess  
18 I would say there's a slight hint, but, again, I guess I  
19 would say there's no--in statistical terms, we don't have  
20 strong evidence since we didn't have it on either side of  
21 the zero line. But there might be a hint that maybe the  
22 uncoated device does better for these measures, although not  
23 for neck pain or fusion.

24           Okay. So, to summarize, for 1-level patients,  
25 here are the equivalence probabilities. We required 95

1 percent. They're all 95 percent or higher. And, in fact,  
2 most of them are 99 except for neck pain. Okay?

3 So our summary conclusions for 1-level patients is  
4 equivalence is satisfied for all outcomes, and, in fact, we  
5 actually have the uncoated and coated devices superior to  
6 control in the Bayes scale for fusion and the BAK/C superior  
7 to control in overall success, the BAK/C uncoated, but the  
8 coated was actually close but it didn't meet the bump over  
9 the line. Okay?

10 For 2-level patients, the equivalence  
11 probabilities are given here. Remember, two of them are  
12 greater than 95 percent, the function and overall for  
13 coated. Actually, all the others are, you know, at least  
14 relatively high in some sense depending on your decision-  
15 making criteria. Remember, 80 percent probability would  
16 correspond to 4:1 odds for equivalence. We usually require  
17 19:1 odds in statistics to call it "significant."  
18 Radicular, the 41 is obviously low. Okay?

19 So our conclusion for 2-level patients,  
20 equivalence is satisfied both for--equivalence is satisfied  
21 for the coated device for function and overall, and we have--  
22 -I'm sorry, 80 percent. I had a 79.5. I apologize. I'm a  
23 statistician. I round it, okay? Eighty percent or better  
24 with a rounded value for equivalence except for the BAK/C  
25 radicular outcome.

1           Sensitivity. I promised you sensitivity. So what  
2 does that mean? Okay. There are patients that are missing  
3 long-term data. Now, what if--what if--now, we don't know  
4 about their long-term results, right? We don't know. If we  
5 have their 12-month results, we can estimate their long-term  
6 results, and that's fine and that's what we do, actually.  
7 If we have their 12-month data, we actually use the 12-month  
8 data to estimate their long-term results, and we do that in  
9 the model.

10           What we did was said, well, when could these  
11 missing data results cause us a bias? When could they cause  
12 us a bias? Well, they could cause us a bias if what? If  
13 the missing control patients, the data we don't have on  
14 control patients, if they're better, they have higher  
15 success rates than the missing BAK/C patients, right? So  
16 if, in fact, the missing control patients do better, then we  
17 would have a bias.

18           Do we know that? No. This is a hypothetical,  
19 okay? We don't know the results, but hypothetically, if  
20 they were missing and if the control patients did better,  
21 then we've somehow overestimated the effect for the vaccine.

22           So what I did for--in increments of--well, what if  
23 they are in terms of odds 10 percent better, 25, 50, 100,  
24 250, 500 percent, 1,000 percent better? What if they were  
25 better by any of those numbers? I decided not to make a

1 search of what the actual number is, and I would check to  
2 see do our conclusions change, okay?

3           So looking at the next slide, with respect to  
4 fusion, actually the superiority results that we found in  
5 the Bayes analysis are maintained even if the missing data--  
6 now, remember, we aren't missing everybody, okay? We aren't  
7 missing everybody. We're missing a small fraction. And, in  
8 fact, people that are fused at 12 months, you know, tend to  
9 be fused long term. So it's really the failures at 12  
10 months that this has a big effect on. But if we assume that  
11 there's a 1,000 percent advantage in terms of log odds,  
12 superiority is actually maintained.

13           With neck pain, now, remember neck pain? Do you  
14 remember how close we were, 95.1 and 95.2 percent? And  
15 these are all, by the way, results from 1-level. With  
16 respect to neck pain, with respect to the uncoated device,  
17 we actually lose the equivalence, the 95.1 that goes across,  
18 that bar goes across the equivalence line if there is--and  
19 it's a hypothetical--if there is a 10 percent advantage in  
20 terms of log odds for the control, and with respect to the  
21 uncoated device, it's maintained at 10 percent but lost at--  
22 actually, it's lost at 25. Okay.

23           With respect to radicular, function, and overall,  
24 these measures, equivalence actually is main--equivalence is  
25 maintained. Those lines are far enough to the right of the

1 equivalence line that even if you had a 1,000 percent  
2 advantage--even if you had a 1,000 percent advantage in  
3 terms of log odds, it would still--the conclusions would  
4 still say the same. Okay.

5           Let's go to safety. Remember I talked about using  
6 a restricted cohort for effectiveness. For the safety  
7 analysis, we used everyone, all the time, unrestricted. So  
8 it's an unrestricted cohort, I think is the way I would term  
9 it. And why did I do that? Well, in fact, most  
10 complications occur relatively early on. Most complications  
11 occur relatively early on. And so, in fact, what we--when I  
12 looked at this and said, well, you know, if we look at the  
13 restricted cohort, we're throwing away a lot of patients we  
14 have information and complications on. So I felt very  
15 strongly that we had to include all the patients, and, well,  
16 the company decided to do that--okay?--with respect to  
17 complications. Most complications occur relatively early  
18 on.

19           I could do a Bayes analysis using the same delta  
20 that we've used for effectiveness, and that's what I did.  
21 We also did, in addition, Kaplan-Meier analyses, which are  
22 time-to-event analyses, and those are important to do  
23 because many of--the complication rate is certainly not  
24 constant across time. Most complications occur early.  
25 Complication rates go down through time. They're relatively

1 low later in time.

2           So what are the results? The results are with  
3 respect to overall complications, we actually could see  
4 this, BAK/C devices actually turn out to be superior to the  
5 control. For complications requiring additional surgery--  
6 that's the main analysis, in my estimation, looking at  
7 total complications. But total complications requiring  
8 additional surgery, that is, reoperations, BAK/C devices are  
9 also superior. And we saw--actually, this is the result we  
10 saw reported by Dr. Hacker in the previous part of the  
11 discussion.

12           With respect to--did we miss a slide? I'm sorry.  
13 Okay. I think there is a slide in your packet--and I'm  
14 sorry if it's missing--that reports the results. I think  
15 there is equivalence with respect to--now I've got to  
16 remember.

17           A slide got left out, but, in fact, with respect  
18 to other complications--with respect to complications,  
19 implant-related complications, I remember--this is a test,  
20 right, of a statistician to remember something? Implant-  
21 related complications, the BAK/C device was superior, I  
22 think, at 1-level, if I recall correctly, and with respect  
23 to--remind me of the other--other related complications,  
24 there may be--the BAK/C--other things aren't specified. The  
25 BAK/C device may, in fact, turn out to be--there might be a

1 slight advantage for the control. Okay?

2           So what are our conclusions then? Conclusions  
3 from this analysis is that the BAK/C HA devices are safe and  
4 effective at 1-level. The 2-level performance actually is  
5 similar. In the original protocol, we were going to combine  
6 these. If we combine these, we clearly would have  
7 established equivalence overall for everything. But the  
8 number of 2-level patients is not great. And looking at our  
9 simple comparisons, looking at our simple comparisons, for  
10 two of the five measures we established equivalence, for the  
11 first three we did not. And the sensitivity analysis that  
12 was done says, well, if the missing data are--if there are  
13 missing data and if they're missing with respect to--biased  
14 in favor of the device, that is, the control missing  
15 patients tend to have higher level of success, it's unlikely  
16 to affect study conclusions, although it would move the neck  
17 pain results over the line of equivalence.

18           Thank you.

19           MR. MANS: This is Dan Mans.

20           To summarize--

21           CHAIRMAN YASZEMSKI: This is Dr. Mans?

22           MR. MANS: Sorry?

23           CHAIRMAN YASZEMSKI: Identify yourself.

24           MR. MANS: Yes, Dan Mans with the study sponsor.

25           CHAIRMAN YASZEMSKI: Thank you.

1 MR. MANS: To summarize, you've seen a  
2 presentation of the design rationale and preclinical testing  
3 by Dr. Griffith that demonstrated there was biomechanical  
4 stability, implant strength, bone growth in and around the  
5 cage, and no unsuspected adverse events in the preclinical  
6 data.

7 Dr. Hacker then presented to you a result of his  
8 perspective of participation in this study, a review of the  
9 study data, and concluded that it was safe and effective per  
10 the data and had clinical utility.

11 And then you heard from Dr. Larntz, who presented  
12 the overall statistical analysis, evaluating the protocol-  
13 defined elements of equivalence for safety and effectiveness  
14 as well.

15 As a result, we feel Sulzer Spine-Tech has  
16 demonstrated that the BAK/C interbody fusion system is safe  
17 and effective for the treatment of cervical degenerative  
18 disc disease for patients with accompanying radiculopathy,  
19 and that it provides a clinically meaningful benefit over  
20 the existing technology through the elimination of autograft  
21 harvest.

22 Thank you. We'll look forward to taking your  
23 questions later in the day.

24 CHAIRMAN YASZEMSKI: Thank you very much.

25 We are going to proceed with the FDA presentation.

1 I'll ask FDA to start getting ready.

2 We're going to take just a few-minute break,  
3 though, if I might, and I'd like to ask our FDA colleagues  
4 if we might ask you to move and occupy the seats over to the  
5 left. We have some people standing, and we'll ask them to  
6 take these seats here, please.

7 [Recess.]

8 CHAIRMAN YASZEMSKI: Holly, if you're ready, let's  
9 go ahead. Dr. Yaszemski here. We'll now resume the  
10 meeting. Ms. Rhodes from the FDA is the lead reviewer and  
11 is going to present the FDA lead review now.

12 MS. RHODES: Good morning. Aside from me,  
13 contributors to this presentation included Dr. Martin Yahiro  
14 and--

15 DR. DIAZ: Can you hear me?

16 MS. RHODES: Yes, we can hear you.

17 DR. DIAZ: I can barely hear you. You have a very  
18 soft voice.

19 MS. RHODES: Okay. I'll get a deep voice now.

20 Aside from me, contributors to this presentation  
21 included Dr. Martin Yahiro and Dr. Gene Pennello. First I  
22 will summarize FDA's--

23 DR. DIAZ: Excuse me. I can virtually not hear  
24 you. If we could turn the microphone up, please, that would  
25 be most helpful.

1 MS. RHODES: How is that? Can you hear me now?

2 DR. DIAZ: Barely better.

3 [Pause.]

4 MS. RHODES: How is that?

5 DR. DIAZ: That's better.

6 MS. RHODES: Okay. First I will summarize FDA's  
7 review of the preclinical testing. Then I will present the  
8 team's clinical review.

9 As Sulzer Spine-Tech previously reported, here are  
10 the results of mechanical tests on the BAK/C. The bench  
11 testing indicates the device is strong enough to withstand  
12 anticipated physiologic loading. Sulzer Spine-Tech already  
13 summarized these results. FDA agrees there are no  
14 significant differences in initial range of motion or  
15 stiffness based on the number of BAK/Cs implanted at a  
16 level; however, data were not stratified based on the spinal  
17 level implanted.

18 Animal testing was also summarized. I'd like to  
19 go in just a little more detail. In the goal model, three  
20 adjacent levels were instrumented with either an uncoated  
21 BAK/C filled with autograft or an HA-coated BAK/C filled  
22 with autograft to allow comparison of stability and fusion  
23 rates.

24 Harvested spines were subjected to stability tests  
25 followed by histological analysis. At 12 weeks, there were

1 no statistically significant differences between the two  
2 groups. Fusion was determined from micro-radiographs of  
3 histological samples of each motion segment. Forty-eight  
4 percent of the uncoated devices were fused, and 62 percent  
5 of the HA-coated devices were fused.

6 The last animal study reported by Sulzer Spine-  
7 Tech was a sheep cervical fusion model. The study compared  
8 fusion rates in sheet treated with a BAK/C with autograft,  
9 an anterior plate with autograft, and autograft alone.

10 For fusion which was assessed radiologically at 12  
11 weeks, 33 percent of the BAK/C group, 100 percent of the  
12 anterior plate group, and 67 percent of the autograft-only  
13 group were fused. In all three groups, many deemed  
14 radiologically fused were not fused histologically; however,  
15 the sponsor speculates that additional post-operative  
16 healing time would increase the number of histological  
17 fusions.

18 Here is a summary of FDA's evaluation of the  
19 clinical data contained in this PMA.

20 The investigational protocol defines patient  
21 overall success as the achievement of radiographic fusion,  
22 pain, function, and radicular success, and the absence of  
23 additional surgery.

24 The rates of long-term overall patient success  
25 was--

1 DR. DIAZ: Excuse me. My connection is breaking  
2 up. You come in and out of the mike. I can't hear  
3 everything you're saying.

4 MS. RHODES: Okay. The rates of long-term overall  
5 patient success are reported in this table: approximately  
6 66 percent, 61 percent, and 53 percent for the 1-level  
7 BAK/C, the HA-coated BAK/C, and control groups; and 42  
8 percent, 59 percent, and 47 percent for the 2-level groups.

9 CHAIRMAN YASZEMSKI: Dr. Diaz, can you hear Ms.  
10 Rhodes now?

11 DR. DIAZ: It breaks in and out. I don't know  
12 what's happening. It's halting.

13 CHAIRMAN YASZEMSKI: I think it's--

14 DR. DIAZ: I hear her well, but it comes in and  
15 out.

16 CHAIRMAN YASZEMSKI: I think it depends on you  
17 being pretty close to the mike.

18 MS. RHODES: Okay.

19 CHAIRMAN YASZEMSKI: Dr. Chapman, how about you?

20 DR. CHAPMAN: It's suboptimal, but I think I can  
21 make out the gist of the message.

22 CHAIRMAN YASZEMSKI: Okay. Thank you.

23 MS. RHODES: As previously presented by Sulzer  
24 Spine-Tech, the study results demonstrated that the  
25 radiographic fusion rates for both treatment groups and the

1 control group are good, especially for 1-level fusions. The  
2 radiographic fusion rates ranged from almost 96 percent in  
3 the control group to 100 percent for both treatment groups  
4 in 1-level fusions and 86.7 percent in the control and  
5 BAK/C-HA groups and 90 percent in the uncoated bak group in  
6 2-level fusions.

7           According to the sponsor's Bayesian statistical  
8 analysis, BAK/C and BAK/C-HA group fusion success rates are  
9 superior to that of the control group for 1-level fusions,  
10 but inconclusive for 2-level fusions.

11           For overall success, the results are superior for  
12 the 1-level BAK/C group and equivalent for the BAK/C-HA 1-  
13 and 2-level groups, but inconclusive for the 2-level BAK/C  
14 group.

15           Dr. Pennello will discuss FDA's concerns with the  
16 sponsor's definition of statistical superiority.

17           FDA has identified potential concerns with certain  
18 aspects of the study: The safety and effectiveness analyses  
19 are performed on different data sets: the restricted and  
20 unrestricted cohorts. The next slide will explain the  
21 difference between the two cohorts.

22           The follow-up rates for patients with complete  
23 data sets fall short of the traditionally accepted standard  
24 of 85 percent.

25           These missing data are not missing at random. A

1 patient's likelihood to return for the 24-month evaluation  
2 is related to a successful 12-month outcome.

3           Lastly, a disproportionate number of patients in  
4 the control group withdrew from the study following  
5 randomization compared to both treatment groups.

6           We will be asking you to discuss the impact of  
7 these concerns on the study's conclusions regarding the  
8 safety and effectiveness of the device.

9           In their attempt to raise the rates of follow-up  
10 in this study, Sulzer Spine-Tech created a restricted cohort  
11 by freezing patients in the follow-up interval they were in  
12 as of November 1999 and concentrated their follow-up efforts  
13 on those who had already reached the 24-month time point.

14           In addition, the window on the 24-month time point  
15 was modified by removing the end of the window. Any data  
16 collected at 24 months or later was grouped into this  
17 window, which is called the long-term window. These efforts  
18 resulted in complete follow-up data being available on 81.3  
19 percent of all patients at the long-term follow-up.

20           In contrast, in the unrestricted cohort, where  
21 patients continue to enter subsequent follow-up intervals,  
22 complete follow-up data is available for only 69.8 percent  
23 of the study patients at the long-term time point.

24           The sponsor's justification for performing the  
25 effectiveness analysis on the restricted cohort is that it

1 is more complete. In addition, they compared the long-term  
2 effectiveness success rates and found similar rates of  
3 success in all comparisons for both cohorts.

4 Our second concern is that this study has a low  
5 follow-up rate. For example, the patient follow-up rates at  
6 the long-term evaluation time point ranged from a low of  
7 75.9 percent to 84.2 percent in the 1-level fusions. The  
8 follow-up rates are marginal despite the sponsor's  
9 substantial efforts to optimize the rates by defining the  
10 restricted cohort and widening the 24-month time window.

11 Our third concern is that the patients are not  
12 missing at random. This table demonstrates that patients  
13 with successful outcomes at 12 months are more likely to  
14 return for the long-term evaluations. As an example, 82.5  
15 percent of the 1-level BAK/C patients with successful 12-  
16 month outcomes returned for long-term evaluations, whereas  
17 only 68.3 percent of the same group who were failures at 12  
18 months returned for long-term evaluations.

19 As will be pointed out by Dr. Pennello in the  
20 discussion of the statistical analyses, the sponsor has  
21 accounted for the missing-ness in the Bayesian models. In  
22 addition, as Dr. Larntz described, the sponsor provided a  
23 sensitivity analysis of the data.

24 Our fourth concern with the effectiveness analysis  
25 is that a disproportionate number of patients in the control

1 group withdrew from the study following randomization  
2 compared to both treatment groups. Those show the rates,  
3 and at any rate, aside from reasons that apply to all three  
4 groups, control group patients also withdrew because of the  
5 treatment assignment. This disproportionate withdrawal rate  
6 introduces a possible bias that confounds the efficacy  
7 evaluation for the treatment groups, particularly since this  
8 is an unblinded study with important subjective efficacy  
9 parameters.

10           Now for the safety analysis. The sponsor has  
11 presented the safety data for this device: the adverse  
12 events associated with the use of the device compared to the  
13 control treatment. Adverse events are categorized as  
14 implant-related, surgery-related, additional surgeries, and  
15 other. In the PMA the sponsor provided a time course  
16 distribution of the adverse events, as well as cumulative  
17 totals.

18           Patients are considered to have an adequate safety  
19 evaluation if they had at least radiographic and neck pain  
20 assessments. In other words, the patient was not required  
21 to have a complete effectiveness evaluation in order to  
22 contribute meaningful safety data.

23           The total number of adverse events, implant-  
24 related adverse events, surgery-related adverse events, and  
25 other adverse events, as well as the type of adverse events,

1 are presented here. Sulzer Spine-Tech made a similar  
2 presentation in their presentation.

3 Here are the adverse events for 2-level fusions.

4 According to the sponsor's Bayesian statistical  
5 analysis, the overall complication rates are equivalent  
6 between the 1-level and 2-level BAK/C groups and the control  
7 group. The 1-level BAK/C-HA group had superior overall  
8 complication rates compared to the control group.  
9 Comparisons to the 2-level BAK/C-HA to the control are  
10 equivalent.

11 The implant-related complication rates of the  
12 BAK/C and BAK/C-HA groups are superior to the control group  
13 for 1-level cases. Comparisons between the BAK/C group for  
14 2-level fusions are inconclusive, but showed equivalency for  
15 the BAK/C-HA group compared to the control.

16 FDA has the following concerns regarding the  
17 safety analysis. As you can see, they are very similar to  
18 what was presented in the effectiveness analysis, and that  
19 is: that the safety and effectiveness analyses were  
20 performed on different data sets; the safety accountability,  
21 which is slightly different than the effectiveness  
22 accountability, demonstrates low rates of follow-up at the  
23 6-month, 12-month, and long-term follow-up evaluations; the  
24 disproportionate control group withdrawal may affect the  
25 safety conclusions; and the sponsor did not perform a

1 sensitivity analysis to determine the effects of missing  
2 data on the safety conclusions.

3           This is the same slide presented with our previous  
4 concerns for the effectiveness analysis. If you look at the  
5 bottom of the right column, safety data are available for  
6 70.7 percent of the unrestricted cohort.

7           The sponsor's justification for performing the  
8 safety analysis using the unrestricted cohort is that the  
9 data set has a longer follow-up time and is actually more  
10 comprehensive. Comparisons between the restricted and  
11 unrestricted cohorts shows that the overall complications,  
12 device-related complications, and surgery-related  
13 complications are not significantly different between the  
14 two cohorts.

15           Our second concern relates to the follow-up rate.  
16 These numbers are a little bit different than what was  
17 presented in the effectiveness, but as you can look at that,  
18 about as high as it gets is 81 percent.

19           This slide showing the rates of withdrawal is the  
20 same as the one presented with FDA's concerns regarding the  
21 effectiveness analysis.

22           These points summarize FDA's concern with the  
23 effectiveness and safety analyses in the PMA for the BAK/C  
24 cervical interbody fusion system: analysis of different  
25 data sets for safety and effectiveness; low follow-up rates

1 for both cohorts; disproportionate patient withdrawal; and  
2 no sensitivity analysis of the safety data.

3 I would now like to introduce Dr. Gene Pennello  
4 who performed the statistical review of this PMA.

5 DR. CHAPMAN: Excuse me, ladies and gentlemen.  
6 This is Dr. Chapman speaking via speakerphone.

7 CHAIRMAN YASZEMSKI: Go ahead, Dr. Chapman.

8 DR. CHAPMAN: I will have to excuse myself for  
9 about 15 to 30 minutes due to child care obligations. I  
10 will report back once I have re-entered my telephone.

11 CHAIRMAN YASZEMSKI: Thank you. We look forward  
12 to hearing back from you.

13 DR. CHAPMAN: Thank you.

14 DR. PENNELLO: Panel members, my name is Gene  
15 Pennello, and I'm in the Division of Biostatistics at FDA,  
16 and I did the statistical review of the clinical data, and  
17 I'm going to summarize my review.

18 First, there will be some redundancy here, but I  
19 think it might be worth it. The design of the study, it was  
20 a multi-center trial. There were 28 centers. It was a three-  
21 way randomized trial. There were three treatments:  
22 uncoated BAK/C device, the coated BAK/C device, and the  
23 control. And in the slides I am going to specify those as  
24 B, H, and C. And if write BAK, I mean either B or H, which  
25 is the uncoated or coated BAK/C devices.

1           This is sort of a summary of the analyses. There  
2 was a restricted cohort and an unrestricted cohort on which  
3 the analyses were made, and as has been mentioned, the  
4 restricted cohort was analyzed for effectiveness in order to  
5 boost the follow-up rate. These were patients who entered  
6 the study at or before November 1999, and the follow-up rate  
7 was low at one point. And so the database was frozen at  
8 this time, and then they tried to retrieve the patients who  
9 were missing at longer follow-up times than at 24 months,  
10 which was the original time point. So the time point was  
11 changed to long term, meaning 24 months or greater, in order  
12 to capture more patients.

13           The effectiveness analysis was done both on the  
14 restricted cohort and the unrestricted cohort, although the  
15 sponsor presented just the restricted analysis. The safety  
16 analysis was done on the unrestricted cohort, and there were  
17 clinical utility variables analysis on the unrestricted  
18 cohort. And there were Bayesian analyses as well as non-  
19 Bayesian analyses, and the primary analysis reflecting this  
20 was Bayesian. Safety, there were several analyses, both  
21 Bayesian and non-Bayesian, and the clinical utility analysis  
22 was non-Bayesian.

23           Dr. Larntz already discussed a little bit about  
24 what Bayesian analysis is. Maybe I should also discuss  
25 this. The idea--well, for a non-Bayesian analysis, you make

1 probability statements about the data given the parameters.  
2 So, for example, what's the probability an observed success  
3 rate for fusion that you observe to be, say, 80 percent in  
4 the sample, what's that probability of observing that given  
5 that the true rate is 90 percent?

6 For Bayesian analysis, you think about the  
7 reverse. What's the probability that the fusion success--  
8 the true rate is 90 percent given that the observed rate was  
9 80 percent, for example? And the way you're able to make  
10 these statements is you start with prior probabilities on  
11 the parameter values, like the true rates, and then update  
12 to what's called posterior probabilities, after observing  
13 the data, using Bayes theorem. And then all inferences are  
14 based on the posterior probabilities, called the posterior  
15 distribution.

16 Now, the hypotheses tested when comparing the  
17 BAK/C devices to the control were ones of whether they were  
18 equivalent or superior to the control. And superior meant  
19 that the success rate for the BAK/C device was greater than  
20 the true success rate for the control. Equivalence might be  
21 confusing, but what it really means is non-inferiority here  
22 in that the BAK device, the true rate had to be greater than  
23 the control rate minus some clinical delta value, dependent  
24 on what the control rate was, and as Dr. Larntz was talking  
25 about, it was because the equivalence was defined on the log

1 odds scale. So I've given three examples here. If the true  
2 control rate was 90 percent, then the clinical delta, the  
3 clinically meaningful difference on which equivalence was  
4 defined was 10 percent, so that the true BAK rate had to be  
5 at least 80 percent. If the control rate was 95 percent,  
6 then the BAK rate had to be at least 90 percent in order to  
7 be determined to be equivalent. And if the control rate was  
8 60 percent, then the BAK rate had to be at least 40 percent.  
9 So that clinically meaningful difference was 20 percent  
10 there. And these claims were demonstrated if the posterior  
11 probability of equivalence or superiority was at least 95  
12 percent.

13           As Dr. Larntz has mentioned, equivalence and  
14 superiority are really defined on the log odds scale for the  
15 probability of success, and that's--meaning if you had a  
16 probability of success  $p$ , then the definition of the log  
17 odds is the log of  $p$  over  $1$  minus  $p$ . And superiority  
18 corresponds to the log odds ratio of being greater than  
19 zero. Equivalence corresponds to the log odds ratio being  
20 greater than minus  $0.811$ . And I've given this example,  
21 that, for example, that compares the control rate of 90  
22 percent to BAK rate of 80 percent.

23           This is a picture of the smallest equivalent rate  
24 as a function of the control rate. The control rate is on  
25 the X axis, and the smallest equivalent rate is on the Y

1 axis. And so you could see it's symmetric over the range of  
2 zero to one. But it gives you the picture of, for example,  
3 for 90 percent control rate the smallest equivalent rate  
4 would have to be at least--would be 80 percent.

5           Holly Rhodes discussed or mentioned that there  
6 could be an alternative definition to superiority than the  
7 one given by the company, and we thought we'd provide that  
8 for you for your consideration. You could think of  
9 equivalence defined symmetrically in terms of the log odds  
10 ratio. So if you think of not just non-inferiority, which  
11 would mean the log odds ratio is greater than minus 0.811,  
12 but in terms of true equivalence, the definition would be  
13 that the two rates are equivalent if the log odds ratio was  
14 between minus 0.811 and 0.811. And if you think about that  
15 idea of equivalence, then you would only say that a  
16 reasonable definition for superiority would be that the log  
17 odds ratio had to be greater than 0.811, not just zero. So  
18 there would have to be some larger increase--some amount of  
19 increase beyond a zero difference in order for the BAK rate  
20 to be declared superiority.

21           You can think of the log odds ratio being greater  
22 than zero as--you could call that a weak superiority  
23 definition, I suppose, and the alternative definition to be  
24 a strong superiority claim.

25           So, for example, if the control rate was 90

1 percent, then under the strong superiority definition, the  
2 BAK rate would have to be at least 95 percent.

3 This is a summary of the Bayesian logistic model  
4 that was used both for effectiveness and for safety, and  
5 I've listed here, again, the endpoints for effectiveness.

6 The logistic model was on the success rate for  
7 each endpoint, so, for example, for fusion, you have a model  
8 on the fusion success rate, a logistic model. And it  
9 included a number of effects in the model to predict what  
10 that rate would be in the long term. There were center  
11 effects. There were 28 centers. There were level effects,  
12 1-level versus 2-level patients. There were coating  
13 effects, whether you're talking about the uncoated device or  
14 the coated device, and there's H and B here, respectively.  
15 You also had some interactions in that included in the model  
16 were center-specific treatment effects, so that treatment  
17 could vary--the treatment effect could vary from center to  
18 center, as Dr. Larntz was talking about. And you also had  
19 level-specific coating effects in that the coating effect  
20 would depend on whether you're talking about 1-level  
21 patients or 2-level patients.

22 What the Bayesian model is doing here, the prior  
23 model specified, is that some of these effects are assumed  
24 exchangeable, and what I mean by that is if you assume--and  
25 Dr. Larntz in his presentation, he called these effects

1 random effect. And when you assume exchangeability, what  
2 that means is you're allowing some pooling of the data  
3 across the effects in proportion to how much variation there  
4 is in between those effects.

5           So, for example, the level-specific coating  
6 effects were assumed exchangeable, and what that means is  
7 that if the two coating--if there was a large coating  
8 effect, for example, for 1-level patients and not much of a  
9 coating effect for 2-level patients, then there's a lot of  
10 variation between the two effects, and there wouldn't be  
11 much pooling. But if they were very similar, if the data  
12 indicated that the effects were very similar, then there  
13 would be a lot of pooling.

14           So it automatically determines what degree of  
15 pooling is appropriate, and I didn't mention it, but one of  
16 the main parts then is how much poolability across centers,  
17 and it automatically decides how much pooling is appropriate  
18 across the centers in terms of the treatment effect.

19           Dr. Larntz presented a lot of pictures, and I've  
20 opted to present a lot of tables. Hopefully this won't be  
21 to many numbers. I am aiming the wrong way.

22           All right. This is a summary of the long-term  
23 effectiveness results on the restricted cohort for 1-level  
24 patients, and I'm comparing B versus C, that is, the  
25 uncoated device versus control, and H versus C, the coated

1 device versus control. Here are the inferences you get,  
2 that the BAK devices were either equivalent or superior  
3 under their definition to the control, and I want to use--  
4 let's take line two here for neck pain comparing B versus C.  
5 This is the 90 percent credible interval in the log odds  
6 ratio, and you can see that the lower bound is minus 0.8.  
7 What does this credible interval mean in relation to the  
8 inference?

9           It means that the log odds ratio being less than  
10 minus 0.8 is 5 percent--the probability that the log odds  
11 ratio is less than minus 0.8 is 5 percent. The probability  
12 that it's greater than 0.6 is 5 percent. So, therefore, the  
13 probability of equivalence that the log odds ratio is  
14 greater than minus 0.811 is at least 95 percent. So that's  
15 why we say B is equivalent to C here.

16           What I did on the left columns is translate this  
17 credible interval into actual success rates so you can see  
18 what it means. The mean of the posterior distribution on  
19 the control rate was 0.83 for neck pain, and given that, and  
20 using this log odds ratio credible interval, you get a rate  
21 of 0.82 for the uncoated device, and if you do a 90 percent  
22 credible interval based on that, you get 0.68 as the lower  
23 bound.

24           So you can see that the difference in the success  
25 rates could be as great as 0.83 minus 0.68, or 0.15, 15

1 percent. But because of the definition of equivalence on  
2 neck pain, we still say that B is equivalent to C. But it  
3 depends on where the control rate is, you know, how far the  
4 difference has to be before you can't say that you're  
5 equivalent.

6           There is a panel question on the coating effect,  
7 and so here I've got comparisons of the uncoated device, B,  
8 versus the coated device, H. And we're looking for  
9 differences, and so we're looking for a lower bound of the  
10 log odds ratio credible interval of zero or greater, and  
11 they're all negative here. So the results say that the  
12 probabilities that the coated device is doing better than  
13 the uncoated device are not greater than 95 percent. So we  
14 can't make any conclusions here for effectiveness for 1-  
15 level patients.

16           This is the 2-level patient results, and the  
17 results are mostly inconclusive. The reason that they're  
18 mostly inconclusive, there are really two reasons. There  
19 are many fewer 2-level patients than 1-level patients in the  
20 study, and another reason is that for some of these  
21 endpoints, the treatment effect, the BAK effect was larger  
22 for 1-level patients than 2-level patients.

23           I don't remember exactly which one of those were,  
24 but there were, I think, for some--for at least three of  
25 these endpoints, the BAK effect was larger in 1-level

1 patients than in 2-level patients, with a posterior  
2 probability over 0.95.

3           This is the comparison of the uncoated device  
4 versus the coated device, and results are mostly  
5 inconclusive, although I would point out for radicular  
6 symptoms, the log odds ratio 90 percent credible interval is  
7 minus 2.1 to .1, so it almost--the interval is almost less  
8 than zero, which would mean that the coated device is doing  
9 better than the uncoated device with a posterior probability  
10 of 95 percent. It's not quite 95 percent, but it's close.  
11 So this could indicate that there might be a coating effect.

12           As was already mentioned, the Bayesian analysis,  
13 first, the effectiveness analysis was done on the restricted  
14 cohort to increase rates of follow-up, but for those that  
15 were missing, the Bayesian analysis incorporated a missing  
16 data adjustment. On one of the previous slides, I didn't  
17 discuss this but one of the effects in the model was 12-  
18 month outcome. That was a predictor of the long-term  
19 outcome. And so there were really two rates--two long-term  
20 rates. There was a long-term rate given that you had a 12-  
21 month failure and a long-term rate given that you had a 12-  
22 month success. And Bayesian model averages over these two  
23 rates, there was a weighted--it was a weighted average. And  
24 the weights are the 12-month success and failure  
25 proportions, and these proportions included patients who had

1 12-month outcomes, but were missing in the long term. So in  
2 this sense, this is really a schematic of how it was done,  
3 but just to have you understand. But because you included  
4 the 12-month outcomes of the missing patients, they were  
5 factored into the long-term analysis in this way.

6           The assumption here that's being made is that the  
7 missing patients followed the same model as the non-missing  
8 patients. And we don't know that because we don't know the  
9 values of the missing values. So there is an assumption  
10 here, and that's why there was a sensitivity analysis done.

11           But this approach does account for--assuming that  
12 the missing patients and the non-missing patients followed  
13 the same model, this does account for the association of  
14 missing-ness with 12-month failure that was noticed. It  
15 wouldn't account for an association of missing-ness with the  
16 missing value, which is--that's an untested. We don't know  
17 if that's true or not because we don't know the missing  
18 values.

19           The last thing I'd point out is that the analysis  
20 did not distinguish between missing patients due for the  
21 exam who were eligible and those who were not yet due.

22           This is a slide on the sensitivity analysis. The  
23 Bayesian analysis assumed, like I was saying, that the  
24 missing patients and the non-missing patients followed the  
25 same model. Sensitivity analysis was done on 1-level

1 patients only because that's where all the conclusions were  
2 made. It considers how the conclusions would change if the  
3 missing control patients were more successful than the model  
4 would have predicted and if the missing BAK patients were  
5 less successful than the model would have predicted.

6 For all endpoints except for neck pain, the  
7 conclusion of equivalence was maintained, even if the odds  
8 of success among missing patients relative to non-missing  
9 patients--and that is really odds ratio--was 1,000 times  
10 greater for control than for either of the BAK devices, B or  
11 H.

12 For neck pain, the equivalence was not maintained  
13 for the uncoated device, B, if the odds ratio of success was  
14 10 times greater for C, and it was not maintained for the  
15 uncoated device, H, if the odds ratio was 25 times greater  
16 than C.

17 Now I'll talk about the safety analysis. As was  
18 mentioned, this was done on the unrestricted cohort only to  
19 capture more complications. There were several analyses,  
20 both Bayesian and non-Bayesian. The Bayesian analysis was a  
21 logistic model on the incidence rate of different  
22 complication types. There was no missing data adjustment  
23 for this model. And it does not consider the time over  
24 which the patients were followed, which you would think  
25 would be a factor on whether you get a complication or not.

1 And so that could bias the conclusions from this Bayesian  
2 model.

3 There was a time-to-complication analysis, Kaplan-  
4 Meier curves, for freedom of complication over time, and  
5 there were some analyses on the number of complications per  
6 person-year.

7 This is just a summary. I'm not going to go over  
8 all of the results, but for the Bayesian and Kaplan-Meier  
9 safety analyses, B and H, which were the uncoated and coated  
10 devices, were superior to C in overall and implant-related  
11 complications. They were equivalent to C in surgery-related  
12 complications and additional surgeries. And the results are  
13 inconclusive for other-related complications.

14 I would point out, though, that when you compare  
15 the uncoated device to the coated device, you do get that  
16 the posterior probability that the coated device did better  
17 in terms of implant-related complications than the uncoated  
18 device was over 95 percent in 1-level patients. So H was  
19 superior to B. For 2-level patients, this was also true,  
20 and I've translated this log odds ratio credible interval  
21 into the complication rates, so you can see what the  
22 difference was.

23 This is a table of the number of complications per  
24 person-year of exposure by cohort. And there's the  
25 restricted cohort; there's also the unrestricted cohort,

1 which was a later time point of database closure. And if  
2 you compare those patients in the restricted cohort to  
3 everybody else, which is unrestricted minus restricted,  
4 which I'm calling "other" here, you can see that the number  
5 of complications per 100 person-years increased for every  
6 complication type when going from the restricted cohort to  
7 everybody else. So it seems to me like over time the  
8 complication--the reporting of complications got better.

9           The clinical utility variables, the three main  
10 ones were donor site pain, patient satisfaction, and patient  
11 employment status. The percentage reporting donor site pain  
12 was significantly lower for B and H than C because of the  
13 autograft--the non-local autograft harvests in the control  
14 patients. Patient satisfaction, B, H, and C, the ratings of  
15 patient satisfaction were comparable among the treatments.  
16 There was no statistically significant differences. And for  
17 patient employment status, there were no statistically  
18 significant differences among the treatments.

19           In summary, for 1-level patients, the BAK devices  
20 were equivalent to the control in all safety and  
21 effectiveness endpoints, and there were some cases where you  
22 did have superiority. And let me mention that again because  
23 for fusion, B and H were superior to C, under the definition  
24 of the sponsor, the weak superiority definition. Under the  
25 alternative definition that I explained, they were also

1 superior in fusion because the log odds ratio lower bound  
2 was over 0.811. It was about 1.1 for fusion for both the  
3 uncoated and coated devices. I didn't mention that before.  
4 For 2-level patients, the results were generally  
5 inconclusive.

6 For 1-level, effectiveness results were adjusted  
7 for missing data, and the results were basically insensitive  
8 to the missing data deviating from the model, except for  
9 neck pain.

10 For safety, there was no missing data adjustment,  
11 but missing data may not be an issue here. Surgery-related  
12 complications happened at the time of surgery, so, in my  
13 opinion, I don't think they would be missed. I don't think  
14 additional surgeries should have been missed, too. And  
15 implant-related complications, the differences were so large  
16 between the BAK devices and the control that if you had done  
17 a sensitivity analysis, it would probably show that the  
18 conclusions were insensitive to patterns in the missing  
19 data.

20 Some of the limitations, and these were already  
21 mentioned: Discontinuations were disproportionate toward  
22 controls; after randomization, many of the control patients  
23 decided not to have the surgery done. There were low rates  
24 of follow-up, and that led to analyses of different cohorts.  
25 And the Bayesian safety analysis did not consider the time--

1 how long the patients were followed up, and that could bias  
2 the results.

3 Now Holly Rhodes will come back and summarize the  
4 panel questions.

5 MS. RHODES: I'm just going to mention the topics  
6 for the panel questions now, and basically we want your  
7 input on how the concerns we identified with the study  
8 relate to conclusions regarding the effectiveness and safety  
9 of the device, and we also have questions related to a  
10 potential post-approval study.

11 CHAIRMAN YASZEMSKI: Thank you, FDA.

12 We're now going to have the general panel  
13 discussion, beginning with the panel member presentations by  
14 Dr. Topoleski on the preclinical studies, Dr. Diaz on the  
15 clinical studies, and Dr. Simon on the statistical analysis.

16 We'll start with Dr. Topoleski's preclinical  
17 review. Dr. Topoleski?

18 DR. TOPOLESKI: Thank you. I'm sorry I don't have  
19 any PowerPoint presentation, but I'll briefly go over five  
20 major preclinical mechanical tests that were performed, and  
21 they were: the ultimate strength of the device, the fatigue  
22 strength of the device, stability testing--and there were  
23 actually two different stability tests performed--a surgical  
24 implantation study to evaluate the instrumentation,  
25 basically, and two main animal studies, a goat study and a

1 sheep study. So I'll start with the ultimate strength  
2 study, and that was performed by Sulzer Spine-Tech.

3           The methods that they used to examine the ultimate  
4 strength was at first they used a single 10-millimeter  
5 implant. In one of the presentations, I think you saw, I  
6 believe, the four different sizes available. So they  
7 started with a single 10-millimeter implant, used a tapped,  
8 that is, a fitted fixture that would simulate the type of  
9 surrounding the implant might see when it was in the bone.  
10 They loaded the specimen at a constant loading rate, and  
11 they loaded beyond a point which they defined as a yield  
12 point for the implant and recorded the load versus  
13 displacement.

14           In this first test, they showed that the yield  
15 occurred at greater than 1,600 pounds. And before I go on,  
16 I just wanted to emphasize that the tests that were done,  
17 the results that they reported in terms of, say, pounds are  
18 all specific to the type of implants that were tested. So  
19 one would not expect the 10-millimeter implant to react the  
20 same as, say, the 6-millimeter implants because of size  
21 differences, for example.

22           So their second set of ultimate strength tests,  
23 they used three 6-millimeter implants and, again, another  
24 10-millimeter implant. And the reasoning behind choosing  
25 the 6-millimeter implants and the 10 were based on a finite

1 element analysis that was performed, but I can't give you  
2 any details of that right now because I don't have any. But  
3 they assumed that the 6-millimeter implant would represent a  
4 worst-case geometry.

5           And for the three specimens, they calculated an  
6 average yield strength of around 993 pounds for the 6-  
7 millimeter implant, and the 10-millimeter implant yielded a  
8 2,362 pounds, although I'm not sure how yield was defined in  
9 this case.

10           Then based on the ultimate strength tests, they  
11 went on to perform some fatigues tests, also performed by  
12 Sulzer Spine-Tech. In the methods, they used similar  
13 fixtures to the ultimate strength and defined what's called  
14 an endurance limit, and that's generally defined as, in this  
15 case, the load beyond which the--or below which the device  
16 will not fail under a certain number of cycles, and they  
17 defined the number of cycles as 3 million, and basically  
18 developed what we know as an SN curve or, in this case, a  
19 load versus number of cycles curve to estimate an endurance  
20 limit.

21           And what the results of their test was that  
22 eventually they had four runouts, that is, no failure at 3  
23 million cycles, and they estimated their endurance limit  
24 pretty much by hand to be between 300 and 400 pounds. So  
25 what that represents is that, in theory, if the device were

1 loaded to below the endurance limit, say 300 pounds, it  
2 would never fail, or at least not fail after 3 million  
3 cycles.

4           Stability testing. The first type of stability  
5 testing was performed by the Harrington Arthritis Research  
6 Center. They used fresh-frozen spine segments between C3  
7 and C7. Five spines were used for the actual test; one  
8 spine was used to set up the fixtures and whatnot. And they  
9 tested in flexion, extension, left and right lateral  
10 bending, and left and right rotation, pretty much using  
11 three different test loads at 0.5, 1.0, and 1.5 Newton  
12 meters, and tested the different specimens, starting with  
13 the intact spine and then a 10-millimeter BAK at C4-C5,  
14 testing bone graft at C5-C6, and then a bilateral 6-  
15 millimeter, that is, two 6-millimeter implant at C6-C7, and  
16 then one spine was tested after discectomy. And they  
17 measured a range of motion neutral zone, what they called  
18 the elastic zone, and the results from those tests show that  
19 the average range of motion decreased in the flexion,  
20 extension, lateral bending, and rotation, and the average  
21 neutral zone decreased.

22           The second stability testing was performed at  
23 McGill University, and that was to compare the single  
24 implant versus the paired implants, and in this case they  
25 used 11 C4-C5 segments and 13 C6-C7 spinal segments,

1 compared the single implant versus the paired implant. They  
2 had 12 specimens of each, again, testing axial rotation,  
3 lateral bending, flexion, extension. And the results showed  
4 that the only difference between the single implant versus  
5 the paired implant was that there was an increase in the  
6 neutral zone for the single implant versus the intact spine,  
7 and there was no change for the paired implant.

8 Briefly, the surgical implantation instrumentation  
9 study was looked at by three surgeons, and the surgeons--one  
10 surgeon actually was participating in the goat study, which  
11 we'll talk about in a second, and other surgeons I believe  
12 used pig spines. And, in general, it looks like the  
13 surgeons found the instrumentation to be adequate and  
14 offered some suggestions on improvement.

15 Finally, there were two animal studies that  
16 specifically used the devices. The first that I'll talk  
17 about was a goat study performed at the University of  
18 Wisconsin-Madison, and ultimately, I believe there are going  
19 to be 21 animals to be tested. Right now there are 14, I  
20 believe. And they are tested with the uncoated BAK/C with a  
21 bone autograft, tested with a hydroxyapatite coating, also  
22 with the autograft, and I believe it's planned to test the  
23 uncoated with BMP2, bone morphological protein 2. The  
24 studies were 3-level fusions, that is, three spinal segments  
25 were fused with the implants, and they used 10-millimeter

1 size implants.

2           After the term of the study was complete, they  
3 performed mechanical testing and axial compression, torsion,  
4 flexion, extension, and lateral bending, and evaluated the  
5 fusion via histology.

6           The results showed that there were no difference  
7 in the biomechanics, the mechanical testing, between the two  
8 groups, that is, the coated versus uncoated, both at  
9 autograft. And there were some slight differences in the  
10 fusion rate: 48 percent without the hydroxyapatite and 62  
11 percent with the hydroxyapatite.

12           The sheep study was performed at the Union  
13 Memorial Hospital in Baltimore. They looked at 12 sheep and  
14 performed fusions at C3-C4 segments and C5-C6 segments and  
15 compared mechanical testing and also looked at histology for  
16 trabecular bone formation and again found no differences in  
17 stability between the three different types of implants,  
18 which I forgot to mention, and they are bone graft alone, a  
19 bone graft tested with a locking plate, and also the BAK/C  
20 implant with a bone graft. Sorry about that. And the  
21 fusion rates were four out of six with the autograft alone,  
22 six out of six with the autograft plus the plated fusion,  
23 and two out of six with the current implant.

24           CHAIRMAN YASZEMSKI: Thank you, Dr. Topoleski.

25           We'll now proceed with Dr. Diaz's clinical review.

1 Dr. Diaz, are you with us?

2 DR. CHAPMAN: Excuse me. This is Dr. Chapman. I  
3 just wanted to confirm that I have been back in my room on  
4 the telephone since 8:30 my time, 11:30 your time.

5 CHAIRMAN YASZEMSKI: Thank you, Dr. Chapman. We  
6 hear you loud and clear.

7 Go ahead, Dr. Diaz.

8 DR. DIAZ: This is Fernando Diaz. I was given the  
9 duty of reviewing the clinical aspects of the study. I am  
10 not going to go into great detail of all the things that  
11 have already been discussed, but I am going to emphasize  
12 some points that I think are important on the clinical  
13 assessment of the study.

14 This is a multi-center, randomized study of,  
15 assessment of the BAK cage as compared to the use of a  
16 conventional anterior cervical discectomy and fusion with  
17 autograft. Two-thirds of the patients received autografts,  
18 and only one-third received allograft.

19 From my personal clinical experience and that  
20 reported in the literature, it is known that the iliac crest  
21 graft is a soft graft and the probability that there will be  
22 collapse is greater than with other types of bone. Iliac  
23 bone does not hold the pressure as well as patellar  
24 allograft would. Autograft is much softer, especially iliac  
25 bone graft.

1           The study presents the analysis of fusion, neck  
2 pain, radicular pain, function evaluation, and an overall  
3 assessment of all four areas of concern, and then reviews  
4 possible complications and additional data which is of a  
5 subjective nature.

6           One conclusion that I can make from the clinical  
7 analysis of this data is very much what was presented in the  
8 statistical review, that the only benefit that I can  
9 determine in any of these areas is for the 1-level BAK  
10 fusion, and I did not see any significant difference between  
11 the simple BAK cage versus the one with the hydroxyapatite.  
12 In reality, from the analysis, the only concern there is  
13 whether one would be superior to the other, and I see no  
14 real benefit of one over the other.

15           The analysis of the fusion rate to me is perhaps a  
16 little unreasonable. I believe that the analysis of fusion  
17 at periods less than nine months is probably not proper.  
18 Bony fusion does not take place completely for nine months,  
19 and the analysis of movement prior to this to me reflects  
20 that the fusion is not complete, which is what would be  
21 expected from the natural process of healing of the bone.

22           Long-term, the fusions in the 12-month and after  
23 evaluations are no different for the BAK group or the  
24 anterior cervical fusion group. In my mind, this is really  
25 the only truly objective analysis of the benefit of the user

1 of the BAK cage versus the anterior cervical fusion group.

2           The other levels of assessment are more of a  
3 subjective nature. The improvement of neck pain, the  
4 improvement of radicular symptoms, the overall feeling of  
5 the patients, the functional assessment is much of a softer  
6 analysis compared to the objectivity of seeing a fusion  
7 actually take place.

8           The safety concerns in my mind are well presented  
9 and well analyzed. I see no difference in the use of the  
10 BAK cage compared to the control, which proves the safety of  
11 the procedure. The graft collapse is predictable based on  
12 what I discussed earlier regarding the use of iliac bone  
13 graft and the use of bone that is softer than what the cage  
14 would be. So the results are predictable and expected.

15           The patient perception is that of improvement, and  
16 there is no significant difference between the patients that  
17 received the cages versus the patients that were treated  
18 with conventional surgery. Return to work was no different,  
19 and the iliac bone donor graft pain is also expected. For  
20 those patients that were grafted, being those for the iliac  
21 bone graft, specifically for the ACDF, versus those that  
22 received a cage and were supplemented with donor graft from  
23 the iliac bone area are things that have been well  
24 established and predictable. Using patellar allograft would  
25 be a better comparison to see the long-term results of one

1 versus the other treatment approach.

2           The outcome expectations of superiority in my mind  
3 are only viewed really in the 1-level fusion comparing the  
4 BAK versus the autograft. Problems that I see with the  
5 study have already been mentioned. A large number of  
6 patients withdrew from study follow-up, especially in the 2-  
7 level fusion. The overall efficacy analysis in my mind,  
8 grouping the four types of evaluation, the fusion, the neck  
9 pain resolution, the radicular pain, and the functional  
10 improvement, I think creates a wastebasket analysis of all  
11 of these things into one big lump from which I cannot really  
12 derive any major beneficial assessment.

13           I have a concern with the overall improvement of  
14 radicular symptoms based on the different sizes that were  
15 used for the grafts. One of the major benefits of an  
16 anterior cervical fusion and decompression is stability,  
17 which is what the graft or the cage provide. But another  
18 one that was not accounted for and must be assessed is the  
19 benefit of the decompression. The actual removal of bone  
20 and/or disc varies with the different type cages used.  
21 There were four different sizes used for the analysis, and  
22 the numbers are small to really determine overall benefit of  
23 one over the other. I think we need to exclude the  
24 beneficial effect of the decompression alone compared to the  
25 effect of the actual fusion and fixation of the area.

1           In summary, my concerns are that the only benefit  
2 that I see is that for cages at 1-level over the actual  
3 cervical fusion as a group. The rest I think it is  
4 inconclusive and perhaps not significant.

5           Thank you.

6           CHAIRMAN YASZEMSKI: Thank you, Dr. Diaz.

7           We'll finish the panel presentations now with Dr.  
8 Simon's statistical review. Dr. Simon?

9           DR. SIMON: Well, since I'm sure everyone on the  
10 panel went through all eight books in great detail, I  
11 probably don't need to say too many things in summary.

12           There were, I think, some points that were  
13 particularly important in my review. One was the way the  
14 endpoints were defined: success or failure. Success, for  
15 example, for neck pain, I think that the pain score was  
16 three or less pre-surgical, then a success on neck pain  
17 meant that it did not get worse; whereas, if the score was  
18 four or greater, then success meant it had to decrease by  
19 two points. And I think the other endpoints were similarly  
20 sort of defined success or failure.

21           To me, analyzing this data in that way with  
22 success or failure is somewhat problematic. This is what  
23 we'd call an active control trial. We want to establish the  
24 effectiveness of the cage device, and the approach to  
25 establishing effectiveness is by comparing it to a control

1 and showing essentially equivalence.

2 Well, you don't just really have to show  
3 equivalence, you also have to show that your control is  
4 effective, or you have to know, based on previous evidence,  
5 that your control is effective. Having something that's  
6 equivalent to something that's ineffective doesn't let you  
7 conclude that your device is effective.

8 Now, I think it's a problem, then. I would have  
9 liked to have seen analyses--and maybe I missed it, but I  
10 didn't see it--where the analysis, for example, if we're  
11 talking about neck pain as restricted to patients who had  
12 neck pain at the start, and showing that for those patients  
13 you were getting improvement in the active control treatment  
14 and similar improvement here. If you sort of mix those  
15 patients with some proportion of patients who are  
16 essentially not having much in the way of neck pain at the  
17 start and you show equivalence, you really haven't--unless  
18 you can assume that in the absence of the control surgical  
19 approach there would have been deterioration in neck pain,  
20 you can't really assume that your control treatment is  
21 effective with regard to that endpoint.

22 So I basically would have liked to have seen those  
23 other analyses, and I didn't see them. So I think that's a  
24 problem in establishing effectiveness.

25 The second issue that other people have sort of

1 mentioned that is a potential concern is the number of  
2 control--patients randomized to the control treatment who  
3 then dropped out of the study. This was particularly  
4 substantial proportion for the 2-level patients. There's a  
5 principle of clinical trials that clinical trials try to  
6 adhere to, and that's the intention-to-treat principle; that  
7 is, when you do a randomized study, you sort of include in  
8 your analysis everyone who's randomized, and you include  
9 them as members of the group to which they were randomized,  
10 even if they did not receive that treatment.

11 Now, you can really only do that if you have those  
12 patients evaluated, even if they refused the treatment  
13 assigned. So this principle, intention-to-treat principle,  
14 was not preserved here, presumably because those patients  
15 were not followed and were not evaluated.

16 And so then the issue becomes, well, you know, how  
17 can we really assure ourselves, at least for the level one  
18 patients, that no great bias was introduced by those  
19 dropouts. And I think there's two potential ways of doing  
20 that. One is by looking for comparability, comparability  
21 issues.

22 Now, the sponsor did look at comparability with  
23 regard to a large number of factors of the patients who were  
24 available for analysis who did not drop out. I guess I  
25 would have liked also to have seen comparability in the

1 control group of those who dropped out versus those who  
2 didn't drop out, because that I think will be a more  
3 sensitive approach to seeing whether there are any  
4 incomparability issues. Also, when you're doing  
5 comparability, it's not really an issue of whether it's  
6 statistically significant or not, but whether there are  
7 differences that look problematic.

8           The other thing is some of the comparability  
9 analyses or many of them that were done just gave means of  
10 the evaluable patients in the control group and the  
11 experimental treatment groups. And it's pretty hard by just  
12 looking at the means to say whether there's any  
13 comparability effect, difference.

14           The other analysis I didn't see--maybe I missed  
15 it--was a sensitivity analysis not based on individuals who,  
16 in terms of not being available for long-term follow-up, but  
17 sensitivity with regard to refusing the randomized treatment  
18 to sort of assure that that was not biasing results.

19           I think the Bayesian versus non-Bayesian issue  
20 basically--I don't know that it's worthwhile. We've had so  
21 much presentations on it now. My own view is that this has  
22 really been overly emphasized. Most of the analyses that I  
23 saw that the sponsor presented can be viewed as non-Bayesian  
24 analyses. They're using what are called sort of non-  
25 informative priors on pretty much everything. And so if you

1 take what they're calling credible intervals and just  
2 reinterpret them as confidence intervals, it's essentially a  
3 non-Bayesian analysis. So I don't--I really won't go into  
4 that unless anyone has any questions.

5 I think the other big issue for me was are enough  
6 patients available for follow-up, and I think, you know,  
7 it's obviously very difficult to maintain patients over--the  
8 further out you go, and I think the sponsor, you know, did  
9 what they could to try to do that. But that was the only  
10 other major issue that I could see.

11 CHAIRMAN YASZEMSKI: Thank you, Dr. Simon.

12 We're going to proceed now with resuming the  
13 discussion aimed at answering the FDA's questions, and as I  
14 ask our FDA colleagues to perhaps come up and get the first  
15 question on the overhead, what we'll do here, there are six  
16 questions that the FDA has asked the panel to consider.  
17 During the discussion we'll have an opportunity for  
18 everybody on the panel to comment on every one of the six  
19 questions and ask questions of either the FDA reviewers, the  
20 industry presenters, or the panel presenters. And when we  
21 feel that the discussion has been appropriate, we'll move on  
22 to the next question.

23 If I might say, to get things started, I'll ask  
24 different of the panel colleagues to perhaps just lead off  
25 with their impressions on each of the questions. And I'd

1 like to ask you all now so you can be prepared for what  
2 we're going to do. And, Dr. Simon, since the first two are  
3 somewhat statistical, as I go around, I'll maybe ask you to  
4 be the first commenter on Questions 1 and 2, and I'll ask  
5 Dr. Skinner to comment on Question 3, and Dr. Aboulafia on  
6 Question 4, Dr. Finnegan on Question 5, and Dr. Cheng on  
7 Question 6, if that would be okay. And after we get each of  
8 their thoughts, we'll ask everybody else for their input.

9 FDA, may we ask you--Ms. Rhodes, thank you--to put  
10 the first question up.

11 MS. RHODES: Okay. Taking into account the amount  
12 of missing data, that effectiveness and safety are based on  
13 two different cohorts, and that a disproportionate number of  
14 control patients discontinued study participation after  
15 randomization but prior to surgery compared to either  
16 treatment group, did Sulzer Spine-Tech demonstrate  
17 effectiveness of the BAK/C with and without the HA coating?

18 CHAIRMAN YASZEMSKI: And, Dr. Simon, if you need a  
19 couple moments, I'll--because I put this on you quite  
20 quickly. If anybody else has something burning while Dr.  
21 Simon's thinking of his comments from a statistical  
22 perspective, please identify yourself in the microphone and  
23 speak up on the panel. Dr. Li?

24 DR. LI: Steve Li, special surgery. Would this be  
25 a time I could interject a question about some--

1 CHAIRMAN YASZEMSKI: Please do.

2 DR. LI: --in vitro testing about these  
3 components?

4 CHAIRMAN YASZEMSKI: Please do. And anything  
5 related to the discussion on this question, please do.

6 DR. LI: Okay. I have a couple of questions on  
7 the HA-coated devices. Actually, maybe you can help me  
8 answer a general question on this. Does the applicant or  
9 petitioner or any of the panel members have any experience  
10 with an implant that's actually mechanically failed? I know  
11 there's only a few hundred in this particular series, but I  
12 read there's maybe 10,000 in Europe that have been placed  
13 in. Has anyone ever seen an implant, coated or not coated,  
14 that's actually mechanically failed in the term of a  
15 fracture or overly deformed or something like that?

16 CHAIRMAN YASZEMSKI: A representative from the  
17 company? Dr. Griffith, can you take that one?

18 DR. GRIFFITH: Sure. This is Steve Griffith from  
19 the sponsor. We don't have any indication outside the U.S.  
20 or inside the U.S. of a failure of either the BAK/C or any  
21 of our lumbar cages as well.

22 DR. LI: Okay. Thank you.

23 CHAIRMAN YASZEMSKI: Thanks, Dr. Griffith. Dr.  
24 Skinner--

25 DR. CHAPMAN: Excuse me. This is Dr. Chapman. I

1 couldn't hear the answer. We had--

2 CHAIRMAN YASZEMSKI: Dr. Griffith said there were  
3 no failures.

4 DR. GRIFFITH: The answer was no.

5 DR. CHAPMAN: Okay.

6 CHAIRMAN YASZEMSKI: Dr. Griffith, I think Dr.  
7 Skinner might ask a question of you. May I ask you to stay?  
8 Dr. Skinner?

9 DR. SKINNER: Just to follow up on that, in any of  
10 these implants that have been put in, have you see the  
11 hydroxyapatite come off the implant during insertion or  
12 during your mechanical tests or during your animal studies?

13 DR. GRIFFITH: The answer to that is also no. We  
14 did some in vitro testing, which I can share some data if we  
15 get our computer hooked up, that suggested--upon insertion  
16 we looked at the coating, the thickness coating on  
17 metallography before insertion and after insertion, and  
18 there were very few instances where we could identify  
19 microscopically any flaking off of the coating.

20 CHAIRMAN YASZEMSKI: Thank you, Dr. Griffith.

21 DR. CHAPMAN: This is Dr. Chapman with, again, a  
22 biomechanical question. Has the manufacturer or the sponsor  
23 tested load failure of the various cage diameters, meaning  
24 6, 8, 10, 12? And are there any significant differences in  
25 terms of ultimate load failure due to, for instance,

1 differences in wall thickness?

2 DR. GRIFFITH: As Dr. Topoleski pointed out, there  
3 were differences based on which size implants you do test,  
4 and that was based on the Von Mesey stress on the finite  
5 element analysis. It suggested that 6 millimeters was the  
6 worst-case scenario with the highest Von Mesey stresses.

7 DR. CHAPMAN: Okay.

8 CHAIRMAN YASZEMSKI: Thank you. Also, I might ask  
9 everybody who's speaking, please speak close to the  
10 microphone. Dr. Griffith, the transcriptionist was having a  
11 little difficulty hearing you. So people who come up to the  
12 mike, please speak close to the microphone.

13 Dr. Li?

14 DR. LI: On the HA-coated devices, did you do any  
15 mechanical testing of an HA-coated device?

16 DR. GRIFFITH: No.

17 DR. LI: I guess my concern would be this is a  
18 plasma-sprayed technique, so--

19 DR. GRIFFITH: That's correct.

20 DR. LI: --somewhere between 5 and 800 degrees  
21 Centigrade plasma spray.

22 DR. GRIFFITH: Yes.

23 DR. LI: So although that's relatively below what  
24 we normally would call a temperature where we'd worry about  
25 the titanium, nonetheless it's still 800 degrees on a 1-

1 millimeter-thick component. It would seem prudent to at  
2 least do some mechanical testing. I think zero is maybe  
3 below the standard of what we would need.

4 DR. GRIFFITH: We did do limited fatigue testing  
5 on HA-coated cages.

6 DR. LI: Was that included--

7 DR. GRIFFITH: The 10-millimeter cage. I can pull  
8 that data up if you'd like.

9 DR. LI: Okay. Then while I've got you here, one  
10 final question. I notice, I think, in one of the comments  
11 that you allow essentially flash steam sterilization of the  
12 component should something happen to the component after  
13 they open the package but they still want to use the  
14 component.

15 DR. GRIFFITH: We also did repeat sterilization  
16 testing on the HA-coated device as well for that very reason  
17 and--

18 DR. LI: So you did test the mechanical integrity  
19 of the HA coating after steam sterilization?

20 DR. GRIFFITH: Can I get back to you that after  
21 the break? I think we did, but I'd have to check with my  
22 engineer.

23 DR. LI: Okay, because I didn't see it in the  
24 inclusion. If you have not done it, I think you would want  
25 to do that because of the potential sensitivity, obviously,