

1 of the moisture in the HA. And if you've done it and not
2 included it, I think that should also be included in the
3 final application.

4 DR. GRIFFITH: Okay.

5 CHAIRMAN YASZEMSKI: Thank you, Dr. Griffith.

6 Before we take the next question, I want to remind
7 us all that the FDA is interested in, for this question,
8 whether Sulzer Spine-Tech demonstrated effectiveness with
9 and without the HA coating, and please, let's make sure we
10 do adequate discussion of that issue.

11 Dr. Cheng?

12 DR. CHENG: I have one question to the FDA to
13 clarify this panel question and four questions to the
14 sponsor regarding this issue. Do I have permission to ask
15 them at this time point?

16 CHAIRMAN YASZEMSKI: Yes.

17 DR. CHENG: The first question to the FDA is: Are
18 you referring to effectiveness of the device for 1-level
19 only, 2-levels, or both combined?

20 CHAIRMAN YASZEMSKI: FDA, Ms. Rhodes?

21 MS. RHODES: Go ahead.

22 DR. WITTEN: I was going to say, that's a good
23 question. We asked it generally, but if you have specific
24 comments related to 1-level, 2-level, specifically or both,
25 this would be part of the question. We would like to hear

1 those concerns discussed.

2 CHAIRMAN YASZEMSKI: Dr. Cheng?

3 DR. CHENG: The four questions to the sponsor. My
4 first question is: A number of your patients, as has been
5 pointed out, in the control group dropped out after
6 randomization, and I suspect this has to do with the desire
7 of the patients to obtain the device, and when they're
8 randomized to the control, they decided to drop out.

9 My question is: Were any of those patients--or do
10 you know if any of those patients were re-randomized or re-
11 entered into the study and randomized to the device group,
12 either with the original surgeon or perhaps going to another
13 surgeon at another center in their effort to obtain the
14 device? Because that would affect some bias in the study.

15 MR. MANS: The answer to that question is we did
16 not do a comprehensive investigation to determine whether or
17 not patients who left, for example, one investigator and
18 sought another investigator to be re-randomized. We are not
19 aware that that happened at all. In fact, the patients were
20 not allowed to be re-randomized certainly at that
21 investigational site.

22 DR. CHENG: Okay. The second question is: In
23 your results that you reported, and as Dr. Diaz just
24 mentioned in his summary, there are some differences between
25 the autograft and the allograft used for the ACDF control

1 group. I'm wondering if you did any analysis--at least in
2 your results, the autograft control group did better than
3 the allograft control group, as I recall reading. And did
4 you compare that superior control group with your BAK
5 device?

6 MR. MANS: We did perform some analysis that were
7 not presented to the FDA regarding fusion rates in the
8 autograft control group versus fusion rates in the allograft
9 control group. We also did look at the incidence of graft
10 collapse in those two groups.

11 What we found is that, with respect to the fusion
12 outcome, there was a difference in the rate of fusion
13 between autograft and allograft, as you would suspect. I
14 actually have a slide. If you'd like to look at that data,
15 we could connect up our computer and show you that.
16 However, the difference between autograft and allograft in
17 the control group did not reach the level of statistical
18 significance.

19 As far as graft collapse is concerned, we were
20 somewhat surprised to find out that when you looked at the
21 prevalence of graft collapse in the two groups, there was a
22 similar proportion of autograft and allograft patients.
23 That proportion was the same as the proportion in the
24 control group which were allograft and autograft. So
25 although statistical analysis would be difficult because

1 there were not a large number of graft collapse procedures,
2 the incidence did not appear different for autograft versus
3 allograft.

4 DR. CHENG: So although your results would
5 indicate, at least in my opinion, that at one level the
6 effectiveness has been established compared to a mixture of
7 types of ACDF, perhaps to the optimal method of ACDF, as
8 some surgeons might believe, you have not performed an
9 analysis. Am I correct in that understanding?

10 MR. MANS: You're correct in that understanding.
11 We did not take the highest-performing control group and
12 separately compare its performance to our device.

13 DR. CHENG: Okay. I do have a question for Dr.
14 Larntz, and that is, Kinley, you have been keenly able to
15 discern weaknesses in statistical analyses much better than
16 many of us sitting on the panel, certainly than myself. In
17 your opinion, what are the weaknesses of this study's
18 analysis?

19 DR. LARNTZ: Wow. Thank you.

20 [Laughter.]

21 DR. LARNTZ: If I were looking at the actual
22 weaknesses, I think the main weakness in conclusions--with
23 respect to addressing this question?

24 DR. CHENG: Well, both the analysis, the way it
25 was done, and the conclusions. I guess I'm asking you to

1 criticize your own work.

2 DR. LARNTZ: I don't disagree with Dr. Simon that
3 we could have done some analysis, particularly with the
4 actual scales of measurement and maybe controlled for that.
5 I think that was actually a nice criticism. So there's
6 certainly a criticism that I think is a good criticism.

7 I think with respect to the conclusions, with
8 respect to what we've done, I think the--I'll stand over
9 here in case I have to run out the door. I think that--I
10 worried a great deal about the dropout of the control
11 patients. And I would worry a good deal about the dropout
12 of the control patients that didn't get the device. Now,
13 that's something that we didn't have information on with
14 respect to, you know, characteristics of those, at least to
15 a great extent. I think there are some. But I would say
16 that's an analysis that I couldn't do because I didn't have
17 information.

18 So we'd have to decide how great a difference--you
19 know, did all the patients who were going--let's see, how
20 would the bias go? Have to be careful now, right? If the
21 control patients who dropped out were actually patients who
22 were going to succeed, I think that's where it would be a
23 bias against the device. Right? If the patients who
24 dropped out of the control group were going to succeed,
25 that's the kind of patients that we'd worry about. And so

1 if there was evidence, any evidence of that sort, then I
2 would worry very strongly about that.

3 My understanding--I'm just the statistician, you
4 know. My understanding is that patients who dropped out may
5 have been patients for whom they or the physicians felt that
6 maybe the control device wasn't going to be effective enough
7 for them because their disease was such that they needed a
8 stronger device, maybe a device that--stop me if I'm saying
9 something wrong clinically, but maybe they need plating.
10 They weren't supposed to--but as entry criteria, they
11 weren't supposed to need plating, if I understand the entry
12 criteria correctly. But maybe after they got randomized to
13 the ACDF, they decided, well, maybe they should have had
14 plating. And, you know, we'd take a chance with these
15 patients if we gave them the sponsor--the BAK/C device, but
16 we won't take a chance on the ACDF without doing plating.

17 That actually--I'm not sure. You can evaluate
18 more than I can whether those patients would be more likely
19 to be successful if they're continued through the study or
20 not.

21 Have I answered--have I answered enough?

22 DR. CHENG: I don't know. That's up to you.

23 Maybe just to expand on that, Dr. Simon suggested doing a
24 sensitivity analysis for those patients who dropped out
25 after randomization in the control group. Is that possible

1 to do in this situation?

2 DR. LARNTZ: I guess I could have done that. We
3 didn't--we didn't think of doing that at the time. I could
4 have done something with respect to that. I didn't carry it
5 out.

6 CHAIRMAN YASZEMSKI: Okay. Thanks, Dr. Larntz.
7 Dr. Finnegan?

8 DR. FINNEGAN: I also have a question for you.
9 Don't go away from the microphone. Acknowledging up front
10 that statistics is definitely not one of my virtues, I have
11 some basic concerns actually about your use of the Bayesian,
12 because my understanding was that it would cover any
13 differences between centers as far as--I mean, my basic
14 understanding of your choosing this method was so that if
15 there were differences between centers, they would be
16 covered by this method of statistics. Is that correct?

17 DR. LARNTZ: If there are differences in centers,
18 if there are differences, then what that would do is we
19 would estimate--the analysis would allow us to estimate the
20 size of those differences, and if there are differences in
21 centers, then the effect on those credible intervals is the
22 credible intervals will get larger.

23 DR. FINNEGAN: All right, because my question
24 comes from looking at the data of the input of the various
25 centers, and some centers had exactly or pretty close to the

1 same numbers for each of the three groups. Some centers
2 actually didn't enter patients in specific groups, and there
3 were some centers that had very low numbers, including one
4 center that had one patient in the control group and no
5 patients in the experimental group.

6 How does that minimum data influence your
7 statistics?

8 DR. LARNTZ: In fact, every patient that entered
9 in every center is in the analysis, and the fact there are
10 differential numbers means we have different abilities to
11 estimate the differences among centers. Okay? But, in
12 fact, to the degree to which they are different and we use
13 all the information to the best we can, we incorporate
14 information from centers with small numbers of patients with
15 those with large numbers and include them in the analysis.
16 So they contribute and, you know, I'll have to say as a
17 statistician I always want to include all of them. I always
18 want to include all the patients from all the centers. And
19 I guess--and this is my opinion. I'm not so worried about
20 differentials of that sort as long as I take account of the
21 fact that center differences might be there. And if they
22 are there, then this analysis allows us to estimate and take
23 account of those differences.

24 CHAIRMAN YASZEMSKI: Dr. Larntz, I think Dr.
25 Skinner has a question for you, too, before Dr. Hacker comes

1 up.

2 DR. LARNTZ: Do you have something to comment on
3 in the previous question? I think he wants to comment on--

4 CHAIRMAN YASZEMSKI: Hang in. Let's let you
5 finish first.

6 DR. LARNTZ: Okay. Thank you.

7 DR. SKINNER: Kinley, in your analysis, you
8 concluded, I believe, that the HA-coated and the non-HA-
9 coated were equivalent. Dr. Simon had maybe--and Dr.
10 Pennello had different conclusions. My read on your
11 conclusion was that if the HA-coated and the non-HA-coated
12 are equivalent, then we shouldn't approve the HA-coated
13 because it's only more expensive.

14 DR. LARNTZ: Well, I'm not sure that we have
15 differences of opinion.

16 DR. SKINNER: Were they not--

17 DR. LARNTZ: I'm sorry. I--

18 DR. SIMON: I wasn't challenging whether--this is
19 Dr. Simon speaking. I wasn't challenging that the coated
20 was not equivalent--I wasn't challenging the conclusion that
21 the coated was equivalent to the non-coated. What I was
22 questioning was for both of them, not whether they were
23 equivalent to control but whether they've established that
24 the control was actually effective in this group of
25 patients.

1 DR. LARNTZ: Right, and that goes to the basis of,
2 you know, this study was set up with a control and the
3 protocol approved with that control and carried out with
4 that control, but what was the measurement of effectiveness
5 of the control. I actually think there were in the clinical
6 study some indications that the control--that all the
7 patients got better with respect to pain and radicular
8 symptoms, for instance. But I understand that issue, the
9 issue of the effectiveness of the control.

10 Now, with respect to whether there's a difference
11 between coated and uncoated, Dr. Pennello--you think Dr.
12 Pennello and I said something different, and, Gene, do you
13 want to...

14 DR. PENNELLO: I just noticed some differences
15 mainly for safety in implant-related complications. When
16 they did their Bayesian logistic model, it showed that the
17 coated device seemed to do better than the uncoated device.
18 And there was an indication in radicular symptoms in the
19 effectiveness analysis. The posterior probability wasn't 95
20 percent, but it seemed to be close to that, that the coated
21 device was doing better than the uncoated in radicular
22 symptoms.

23 DR. SKINNER: So the two devices are equivalent?

24 DR. LARNTZ: Well, I mean, what I think Dr.
25 Pennello and I both say--I think we actually have, looking

1 at the same data--is that, in fact, all of the lines for
2 comparing the coated and uncoated, in my picture all cross
3 zero. They all cross zero, which means there's no evidence
4 of difference between the two. So if you wanted to choose
5 between one or the other, it would be inconclusive. That's
6 what was said.

7 What Dr. Pennello just said was, But some of those
8 are close. Okay? Some of those are close. And I actually
9 think I said that, too, in my presentation. I said with
10 respect to 2-level for overall function and radicular that
11 they were shifted--they weren't--they crossed the line, but
12 they were close. And I think we're really saying the same
13 thing.

14 CHAIRMAN YASZEMSKI: Okay. Thanks, Dr. Larntz.

15 Can we give Dr. Hacker a chance to answer? You
16 have an answer to one of the questions posed to the sponsor,
17 Dr. Hacker?

18 DR. HACKER: Thank you, Mr. Chairman. I'm Bob
19 Hacker, and I'd like to amplify on an answer directed in
20 part to the clinical study earlier from Dr. Cheng.

21 This speaks to the dropout of patients in the
22 control group. Discussing with three of other clinical
23 investigators and amplifying from my own experience as a
24 clinical investigator, it should be made clear that none of
25 the investigators here--and it was not our policy to

1 encourage retro-selection, if you will, after patients had
2 been randomized into the study. No investigator was
3 instructed nor do any of us in our practice enter patients
4 into the study who we think we might be unsuitable
5 candidates for either the cage or the control group; rather,
6 as part of informed consent required for all patients who
7 are entered into the study, we would explain the risks and
8 benefits and rationale of both the clinical control and
9 investigational procedure.

10 As part of this, we were obligated to inform the
11 patients that in the control group, autograft harvest would
12 carry a potential risk of chronic iliac crest donor site
13 pain. Also, in the control group, we would have to explain
14 that allograft techniques had been demonstrated to have
15 poorer bone fusion biology and also involve what some people
16 found less tasteful, insertion of cadaver or another
17 person's bony substance into their body.

18 Upon hearing this in my clinical experience, I had
19 patients who would tell me, If I can't get the device, I
20 think I'd rather choose a third option, which I mentioned
21 earlier, which in some of these cases was discectomy and
22 decompression without placement of graft.

23 CHAIRMAN YASZEMSKI: Thank you, Dr. Hacker.

24 What I'd like to do now, if I can, is Drs. Larson
25 and Topoleski had questions, and then I'm going to ask Dr.

1 Simon for his opinion on the question FDA posed to us.

2 Dr. Larson, you had a question?

3 DR. LARSON: Actually, mine related to the HA
4 questions.

5 CHAIRMAN YASZEMSKI: Okay. Thank you.

6 Dr. Topoleski?

7 DR. TOPOLESKI: My question is, I guess, more of a
8 clarification from the FDA, and that is that I had some
9 questions based on the in vitro testing and mechanical
10 integrity of the device. And I was wondering if we wanted
11 to ask them now, or would it be more appropriate to talk
12 about them during the safety question, or at all?

13 CHAIRMAN YASZEMSKI: Well, I think probably not at
14 this time, perhaps later, because I think we want to focus
15 on the question they're asking us.

16 Dr. Simon?

17 DR. SIMON: My own view would be--did they
18 establish effectiveness?--I would say for 2-level patients,
19 I would say the answer is no, that there are two problems
20 with the 2-level patients: one, there was a large
21 percentage of 2-level patients in the control group who
22 dropped out of the study when they found that they were
23 randomized to the control treatment; and, secondly, that the
24 subsequent analyses of the 2-level patients with regard to a
25 number of the endpoints did not establish--given the

1 endpoints that were used, even then they did not establish
2 therapeutic equivalence. And so I think on those two
3 grounds, to me it's fairly clear that they have not
4 established effectiveness of the cage for 2-level patients.

5 For 1-level patients, I think the issue is
6 somewhat more--is different. There were--I think to me
7 there was this issue of the number of control patients, 1-
8 level control patients who refused the randomized treatment-
9 -who were randomized to control and refused the randomized
10 treatment. The percentage was smaller for the 1-level
11 patient than it was for the 2-level patient. We don't know
12 that there was really a bias there. I've suggested that
13 some additional analyses could be performed to sort of try
14 to clarify whether or not there was a bias. But, you know,
15 no study is ever perfect, and at the time you have to give
16 your advice, you never really have all of the analyses you
17 would really like. And so I would not assume that there was
18 a bias, and so I would not sort of base my answer on the
19 fact that I would assume that there was a bias.

20 The other issue, in my mind--so assuming that
21 there is not a bias or that additional analyses can sort of
22 provide no basis for thinking there was a large bias there,
23 I would say they've established pretty well for 1-level
24 patients equivalence of the cage to the control treatment.
25 The other concerns I have about establishing effectiveness

1 is whether we can assume, based on the analyses that were
2 done, that the control treatment was effective, I think
3 that's probably--you know, with regard to fusion, I don't
4 think--you know, I think we can say, well, we can take
5 fusion as a sort of--as meaning effectiveness, and if we
6 take that, then I think they've established--having
7 established equivalence, then I think they've established
8 effectiveness.

9 I think with regard to the other endpoints, like
10 pain relief, I think it would be better to analyze the data
11 just looking at patients who have substantial pain or
12 functional impairment prior to surgery. Some analyses of
13 that type were presented actually earlier today, although I
14 didn't actually see them in the booklet.

15 So, again, it's always difficult when you have to
16 make a recommendation at a time when you haven't seen all of
17 the analysis that you would like. But I think I would come
18 out on the side that for 1-level patients they've pretty
19 well established effectiveness of their device.

20 CHAIRMAN YASZEMSKI: Okay. Thank you, Dr. Simon.

21 Before I summarize the panel's discussion to the
22 FDA, are there any other comments from any other panel
23 members? Dr. Li?

24 DR. LI: Yes. We seem to have reduced this
25 question to whether or not the implant had HA or not. And I

1 guess my question to either the statistician who looked at
2 the data or the petitioner: Is this the only variable
3 that's involved? In other words, for instance, were there
4 size differences? Were all the HAs, for instance, 12-
5 millimeter and the non-HAs some different size?

6 Also, this would apply kind of also in the 1-
7 level, 2-level. In the 2-level ones, were the HA sizes
8 different? In other words, is the only variable that we're
9 looking at here with and without HA? Or did anybody look at
10 any potential other variables like the size of the implant,
11 if one implant was used or two implants were used, with an
12 without HA, if there was any kind of skew there? Or maybe
13 even which level--which cervical level these implants were
14 in?

15 In other words, is this really the only variable
16 that's involved here, or are there a whole bunch of other
17 variables that either they've been looked at and we missed
18 through the seven volumes or have not been looked at?

19 CHAIRMAN YASZEMSKI: Okay. Does somebody from the
20 company want to address that?

21 MR. MANS: This is Dan Mans from the study
22 sponsor. Let me see if I can cover all the questions.

23 The standard or the definition of equivalence that
24 was outline in the protocol did not require that we prove
25 performance of the device by device size or by implant level

1 within the cervical spine. However, there were some
2 analyses that we requested by the FDA. For example--and Dr.
3 Kinley Larntz can perhaps discuss the covariate analysis
4 that was done on number of implants per level.

5 For example, are bilateral implants more or less
6 likely to be effective than single implants at a level? We
7 can comment on the results of some of that if you're
8 interested.

9 Similarly, there was an implant size analysis,
10 which was presented, I believe, to the FDA in a recent
11 amendment, describing whether or not for the 8-millimeter
12 device there were any particular performance
13 characteristics, again, if used as a unilateral device or a
14 bilateral device. As Dr. Griffith pointed out earlier, the
15 6- and 8-millimeter devices could be used either way.

16 I think an important point to make in this regard
17 is that--and I would perhaps invite the clinicians who
18 implant this device and make determinations as to whether or
19 not single devices or bilateral devices as well as size of
20 device should be placed in a given patient situation.

21 The concept of the different sizes is to create a
22 construct within the space which is consistent with the
23 needs of that patient. So there are patients with large
24 disc sizes. Those patients are distracted according to the
25 clinician's feelings as to what kind of distraction is

1 required, and then a cage size is implanted according to
2 that distraction amount. So, therefore, the construct,
3 albeit perhaps a different cage size for a different
4 patient, is what we're evaluating here, and there is
5 variation based primarily on patient need.

6 CHAIRMAN YASZEMSKI: Thank you.

7 Dr. Skinner?

8 DR. SKINNER: Yes, I'd like to address Steve Li's
9 question to some extent. I think the issue is not HA or not
10 HA. The question is effectiveness. And I think the
11 question that Dr. Simon was bringing up is: Is fusion an
12 effective treatment for this process? And probably neither
13 of you have the perspective that the surgeons who have been
14 around for a while have.

15 Over the years, anterior cervical fusion has been
16 a procedure that's been used and has gradually become, I
17 would say, favored over what was previously used, which was
18 anterior cervical discectomy. And the rationale behind
19 that--and Ed and Mike could perhaps correct me--was that
20 when you put in a fusion mass, you separated the frame and
21 you reduced the radicular symptomatology.

22 And I think history has shown with plating and
23 fusion that this has become the preferred procedure. And
24 based on that, I think we can say pretty safely that the
25 effective treatment is fusion. So the question here is:

1 Have we demonstrated effectiveness? And I would put the
2 question back on your shoulders, Dr. Simon. You've agreed
3 that it's okay--it's effective for the 1-level fusion, but
4 has the 2-level fusion demonstrated equal efficacy or equal
5 effectiveness as the fusion, or is it inferior? Because if
6 it's equal, I would say that it's acceptable then.

7 DR. SIMON: Thank you very much for giving your
8 perspective, and I think you stated that very well.

9 I was trying to say that for the 2-level patients
10 I do not think that this study has established equivalency
11 of using the cage to fusion without the cage for the 2-level
12 patients. So there's a problem in interpreting the data
13 because of the large number of 2-level patients who dropped
14 out, who refused the control treatment, and even of those
15 who accepted the control treatment, when you go and analyze
16 your data, the analyses, these confidence intervals, these
17 credible intervals do not establish--I don't believe that
18 they establish equivalence.

19 CHAIRMAN YASZEMSKI: Thank you, Dr. Simon.

20 Dr. Cheng?

21 DR. CHENG: I just want to go back to the fourth
22 question I was planning to ask, and that was one of
23 clarification to the sponsor or by the sponsor. My reading
24 of the history of this is that the PMA was approved in its
25 final form in November 1998, and you had your 24-month data

1 closed November 15, 1999. So I don't quite understand how
2 you obtained 352 cases with 24-month follow-up or possible
3 24-month follow-up by November 1999 when the PMA was just
4 approved in 1998. Was the study going on before the PMA was
5 involved?

6 Part of the reason I ask this is because I think
7 one might argue that the better control in 1998 might have
8 been to consider ACDF with instrumentation, such as a plate,
9 rather than ACDF with a graft only.

10 MS. RHODES: If I can clarify that, the IDE for
11 this study was originally submitted to the agency in 1994,
12 and in December of 1994, the first case was implants. So
13 1998 was when the submission was made to the agency, and
14 then various iterations, more data has been collected. So
15 578 patients implanted since the beginning, since 1994, and
16 the numbers that you have for how many patients have reached
17 the 24-month time point.

18 MR. MANS: If I may, just a follow-up to the other
19 point that you're raising, the reason that you brought that
20 question to bear, I'd like to invite Dr. Hacker to describe,
21 for two reasons, his clinical perspective on the
22 appropriateness of the control. As you brought it up
23 before, allograft and autograft are mixed, and as Dr. Simon
24 pointed out, unless you establish that your comparison group
25 is working and is an acceptable medical practice,

1 establishing equivalence to that may not be saying much.

2 So I think it's an important thing for perhaps one
3 of our clinicians to address.

4 DR. HACKER: Thank you for your question, Dr.
5 Cheng. This is a question that I find personally
6 interesting, and for the panel members, let me digress for a
7 moment about plating.

8 This procedure may be performed with additional
9 stiffness provided to the fusion space by attaching a metal
10 fixation device. This is called cervical plating.
11 Originally, cervical plating was introduced to this country
12 and this city by Dr. Wolfgang Casper in 1988. Since then,
13 there has been a variety of plates. We devolved from
14 bicortical purchased plates to unicortical purchased plates,
15 from non-constrained to constrained plates, locking screw
16 plates, and we now have a new generation of plates offered
17 by three different manufacturers which are called subsidence
18 or dynamized plates.

19 Let's first look at why this control was chosen.
20 At the time of this study's inception in the mid-1990s,
21 there was very little controversy about whether or not
22 additional fixation was required in the performance of 1-
23 level and, for the most part, 2-level anterior cervical
24 fusion. The opinion of neurosurgeons and spine surgeons was
25 that it was not necessary. Additionally, it was recognized

1 that cervical plating carried with it a comorbidity.

2 As studies have evolved and as practice has
3 evolved, although there are no randomized controlled studies
4 save one, which I will mention, which have looked
5 specifically at this issue of plating, stability, and
6 fusion, it has been largely anecdotal evidence that fusion
7 rates are increases with plate application.

8 However, plate application is associated with its
9 own rate of complications. Gary Lowry has published in
10 Spine in 1995 a series of plating patients, and he found a
11 33 percent incidence of hardware failure. Dr. Lowry,
12 interestingly, published a paper two years later in Spine in
13 which he looked at failures of autograft and plating and
14 found that even with a satisfactorily positioned plate
15 construct, and a plate construct that appeared not to have
16 failure, almost 30 percent of his patients would have
17 evidence of failed fusion under the plate. That means that
18 the allograft did not incorporate.

19 This has led Benzel, Haid, and other surgeons in
20 the spine community to move towards dynamized plates. The
21 problem with plate constructs is that we now have not only
22 introduced another variable to our assessment of the
23 efficacy of the cage, but we've also introduced yet another
24 level of potential complication to our treatment arm in the
25 control group which would not be present in the cage group.

1 Specifically, hardware failure is well recognized.
2 Secondly, esophageal injury is also recognized to be more
3 commonly associated with plate placement, and also dysphagia
4 is recognized to be more commonly present with plate
5 placement.

6 None of these, however, as Dr. Cheng mentions,
7 none of these speak to the fact that plates do not increase
8 stiffness and potentially increase fusion. However, it
9 should also be noted that the cage device does increase
10 stiffness over that of the control group and in itself
11 provides a benefit beyond autograft biology.

12 I would summarize my comments by just saying there
13 is shifting sand of the status quo out there, and we all
14 recognize that we move on and progress. At the time the
15 control group was formulated for this study, the standard of
16 care was dominated by autograft and allograft stand-alone
17 fusions, and that was the reason that control was chosen.

18 CHAIRMAN YASZEMSKI: Thank you, Dr. Hacker. I
19 think I'm going to--

20 DR. CHAPMAN: If I may make a comment to Dr.
21 Hacker's comment?

22 CHAIRMAN YASZEMSKI: Go ahead, Dr. Chapman.

23 DR. CHAPMAN: Dr. Hacker quoted the study by
24 Lowry, et al., and this study pertains to carpectomies and
25 not discectomies, and this is a biomechanically different

1 environment, so--

2 CHAIRMAN YASZEMSKI: Thanks, Dr. Chapman.

3 DR. CHAPMAN: --does not necessarily apply here.

4 In the same vein, I'd like to just ask Dr. Hacker
5 whether he's aware of any patients during the course of the
6 study who received a supplemental plating, although it was
7 not part of the protocol. Is he aware of any supplemental
8 plating in the control group or in the cage group that has
9 been implanted?

10 CHAIRMAN YASZEMSKI: Dr. Hacker?

11 DR. HACKER: Thank you, Dr. Chapman. Yes, I am
12 aware, because I had a patient who is one of the 2-level
13 reoperation patients in the cage group. This patient
14 underwent a surgical approach with cage placement at C5-6,
15 C6-7. The patient had ongoing symptoms following the
16 procedure. Studies demonstrated failure of fusion, pseudo-
17 arthrosis at the C5-6 level.

18 I subsequently reoperated, removed the cage at C5-
19 6, positioned an autograft harvested from the iliac crest,
20 and spanned the area of surgical treatment from the C5
21 vertebral body to the C7 vertebral body with a constrained
22 plate.

23 CHAIRMAN YASZEMSKI: Thanks, Dr. Hacker.

24 I think what I'd like to do now is summarize to
25 the FDA our thoughts on this question--go ahead, Ms. Rhodes.

1 MS. RHODES: I just wanted to clarify the second
2 question, which is related to Dr. Cheng, which is, you know,
3 make sure that you're addressing just 1- and 2-level
4 combined data applied to the 2-level patients.

5 CHAIRMAN YASZEMSKI: Thank you.

6 There were some concerns raised by the group
7 regarding the dropout of controls after randomization, and
8 Dr. Simon's statistical analysis indicated that perhaps some
9 additional data could be looked at with different analyses.
10 The group thought, however, that for the 1-level cages there
11 was equivalence to the control group of anterior cervical
12 discectomy and fusion, but that for the 2-level cages,
13 equivalence was not demonstrated.

14 There were thoughts about stratification level,
15 size, and whether HA was the only variable. However, with
16 respect to the question that the FDA asked, the panel
17 discussion seems to indicate there is equivalence for 1-
18 level but not for 2-level.

19 May I ask the FDA if we've adequately discussed
20 and answered your question?

21 DR. WITTEN: Yes. Thank you.

22 CHAIRMAN YASZEMSKI: Thank you. Let's move on now
23 to Question 2.

24 DR. WITTEN: Yes, I think you've covered Question
25 2 in your discussion of Question 1.

1 CHAIRMAN YASZEMSKI: If that's okay, I was going
2 to go through them individually, but I will then go right to
3 the question. FDA, have we adequately answered your
4 concerns regarding Question 2?

5 DR. WITTEN: Yes. Thank you.

6 CHAIRMAN YASZEMSKI: Thank you, Dr. Witten.
7 Let's go to Question 3.

8 MS. RHODES: Okay. Taking into account the same
9 concerns we identified with respect to the effectiveness of
10 the device--missing data, safety and effectiveness being
11 based on different cohorts, and the withdrawal rate of
12 control patients, did Sulzer Spine-Tech demonstrate safety
13 of the BAK/C with and without the HA coating?

14 CHAIRMAN YASZEMSKI: I'm going to ask Dr. Skinner
15 to lead the discussion on this question.

16 DR. SKINNER: Was this my question?

17 [Laughter.]

18 DR. SKINNER: Well, I think that Dr. Larntz's
19 description of the benefits of using the larger cohort was
20 compelling. I thought that--I agree with him that you're
21 more likely to get complications in the first year than you
22 are in the first two years; in other words, the number of
23 complications are going to go down as time goes on. And
24 based on that, I thought it was a good idea to use the
25 larger cohort, and I thought that they did demonstrate

1 safety with and without the HA coating.

2 CHAIRMAN YASZEMSKI: Other discussion on this
3 question, other panel members? Drs. Chapman or Diaz, are
4 you still with us, and have you any comments on this
5 question?

6 DR. DIAZ: I'm still here. I have no comments.

7 CHAIRMAN YASZEMSKI: Thank you, Dr. Diaz.

8 Dr. Chapman?

9 DR. CHAPMAN: Yes, as we know from our lumbar
10 cages, there is a significant concern in terms of late
11 complications of stand-alone cages in terms of implants
12 loosening, subsidence, and non-union. The exact mechanisms
13 are incompletely understood, but probably in part pertain to
14 the very small bone surface that actually grows through the
15 host vertebra into the case. This emphasizes that long-term
16 follow-up, including motion studies, has to be performed on
17 these patients and it cannot be assumed by a, quote, stable
18 vertebra on X-ray, such as at three- or six-month follow-up.

19 CHAIRMAN YASZEMSKI: Thank you, Dr. Chapman.

20 Comments from our sponsor?

21 DR. SHERMAN: Yes, John Sherman, spine surgeon,
22 Minneapolis Medical Director, Sulzer Spine-Tech. I
23 appreciate Dr. Chapman's comments pertaining with the long-
24 term follow-up and certainly would concur that longer-term
25 follow-up is important. But a long-term study looking at

1 lumbar cages, in fact, did show, as the data has carried out
2 at four and then continuing data after six years, that when
3 an arthrodesis has been achieved by the radiographic methods
4 that we do have that the arthrodesis at two years is
5 maintained going out forward. The development of
6 radiolucent lines or evidence of pseudo-arthrosis developing
7 late has not, in fact, occurred.

8 Likewise, both in this study as well as in the
9 study of the lumbar cages, frequently what one sees--and,
10 actually, we saw this more frequently in our cervical cage--
11 there was bridging trabecular bone over time that coincided
12 very, very closely with the lack of motion and the motion
13 studies that were done to assess arthrodesis.

14 CHAIRMAN YASZEMSKI: Thank you.

15 DR. CHAPMAN: May I ask a follow-up question right
16 there?

17 CHAIRMAN YASZEMSKI: Go ahead, Dr. Chapman.

18 DR. CHAPMAN: Did the sponsors perform
19 measurements of subsidence of the vertebra around the cage
20 implants from their initial post-operative follow-up and
21 later-on follow-up? I know this is not part of the
22 radiographic requirements, but I was interested in whether
23 the company's aware of rates of subsidence and differences
24 in rates of subsidence in 1- and 2-level cage.

25 CHAIRMAN YASZEMSKI: Thank you. Dr. Griffith?

1 DR. GRIFFITH: I can address that two ways. First
2 of all, we did not look at that. In this particular
3 clinical trial, one of our investigators in Europe has
4 worked with us to look at subsidence issues around the
5 BAK/C, and through a strict measurement technique that we
6 employed, we were able to determine that it doesn't settle
7 any more than 2 millimeters.

8 Furthermore, that was corroborated by a study done
9 by the German biomechanics group in Wilkie's lab that
10 suggested in vitro on an applied axial load also showed
11 about 2 millimeters in subsidence of the cage into the
12 vertebral body. Interestingly enough, his study also said
13 that that increased the stability of the motion segment when
14 he did that.

15 Does that answer your question?

16 DR. CHAPMAN: Yes.

17 CHAIRMAN YASZEMSKI: Thank you. Thank you, Dr.
18 Griffith.

19 This question on safety, may I ask Ms. Rue, our
20 consumer representative, have you any concerns about the
21 safety from a consumer's perspective?

22 MS. RUE: No, I don't.

23 CHAIRMAN YASZEMSKI: No. Any other questions from
24 the panel? Dr. Cheng?

25 DR. CHENG: This also pertains to the last panel

1 question which you asked me to address, but I'll just bring
2 it up here now since it seems pertinent.

3 I think the hydroxyapatite coating in other
4 locations, there have been concerns about debonding of the
5 coating from the prosthetic device itself for joint
6 implants. And this being relatively new for the cervical
7 spine and untested, I think it does warrant some concern in
8 terms of safety because debonding could add more
9 catastrophic consequences in the cervical spine than around
10 the hip or knee. And so perhaps that could be addressed
11 with some type of post-market surveillance, but I do think
12 that is something which needs to be addressed in this
13 question.

14 CHAIRMAN YASZEMSKI: Thank you.

15 Would anyone from the company like to address the
16 issue of debonding of the HA? Dr. Griffith?

17 DR. GRIFFITH: Can I get a clarification on
18 debonding? You mean debonding in situ or debonding upon
19 insertion?

20 DR. CHENG: Debonding after insertion at a later
21 time point between the layer between the hydroxyapatite
22 coating and the metallic device.

23 DR. GRIFFITH: The only evidence we have right now
24 is actually based on the goat study we did where we
25 implanted HA-coated devices and did see no debonding in the

1 histology, at least at three months. That's the farthest
2 time point we have out.

3 DR. CHENG: Right. But for other locations this
4 has been shown to occur at later dates, and so that's why I
5 think it is something that needs to be looked at.

6 DR. GRIFFITH: Okay.

7 CHAIRMAN YASZEMSKI: Dr. Skinner?

8 DR. SKINNER: I think that what Dr. Cheng is
9 referring to is in primarily total hips, but also total
10 knees to some extent, and I think it's a different issue in
11 that situation because you have a different phenomenon. You
12 have wear debris which is causing loosening of the
13 prosthesis. Then when you have motion of the prosthesis,
14 you have a different situation.

15 When you have, as I picture this, a fused
16 intervertebral segment with a metal cage in it with a white
17 coating on it, it is pretty stable. I doubt that there'd be
18 much to expect after that.

19 CHAIRMAN YASZEMSKI: Thank you. I'd like to
20 summarize--Dr. Li?

21 DR. LI: I'm not quite sure--in these questions,
22 I'm not quite sure I'd interject the comments on in vitro
23 testing, because there doesn't seem to be a space for it,
24 but I'll take the safety issue as a place where I could
25 mention that. So let me interrupt. I misplaced my question

1 from the very first question. I guess I don't see any
2 mechanical data on HA-coated devices in the application, nor
3 do I see any integrity testing of the HA coating after steam
4 sterilization of the device. So those are areas that I see
5 no information on that I believe should be included.

6 CHAIRMAN YASZEMSKI: Comments from the sponsor?

7 DR. GRIFFITH: I know we did fatigue testing of
8 the HA-coated device, 10-millimeter. I also know we did
9 steam sterilization of the--repeat testing of the HA-coated
10 device, and if it's not in the panel pack, we can get you
11 that information.

12 CHAIRMAN YASZEMSKI: Thank you.

13 Dr. Larson?

14 DR. LARSON: With regard to both of these issues,
15 these are pretty well established parameters for HA coatings
16 in general, and assuming that the HA coating source is one
17 of the recognized vendors of HA coatings and that there is a
18 master file on hand, I think all of these questions should
19 be dealt with.

20 CHAIRMAN YASZEMSKI: Dr. Griffith?

21 DR. GRIFFITH: It is an approved HA supplier.
22 It's actually Biocoat, all according to ASTM specifications.

23 CHAIRMAN YASZEMSKI: Dr. Finnegan?

24 DR. FINNEGAN: Maybe I can answer this when I do
25 my question, but it seemed to me that maybe we should divide

1 this into two questions and address the safety of the
2 uncoated and the safety of the coated as two separate
3 questions.

4 CHAIRMAN YASZEMSKI: Let's do it with your
5 question so we can get through this one as listed, if that
6 would be all right, if that would be acceptable to
7 everybody.

8 Dr. Topoleski?

9 DR. TOPOLESKI: A quick question to the sponsor.
10 Did you test in any other loading modes other than the
11 uniform compression? Because I was noticing when you did
12 the stability test there was flexion, extension, rotation,
13 et cetera, which would imply that these devices would be
14 under bending loads, perhaps, or at least non-uniform loads;
15 and given the complex geometry, it's full of holes. There
16 are at least two different types of threads, including the
17 triangular thread that the pure compression might not fully
18 address all of the in vitro--or in vivo loading modes.

19 DR. GRIFFITH: We did not test anything other--
20 just the implant integrity--other than axial compression.
21 And the reason for that is we were basing our testing
22 methodology on a proposed ASTM standard, and in that
23 standard, if you read it, it talks about pure axial
24 compression as well as a 45-degree shear angle. The 45-
25 degree shear angle was put in there mainly for lumbar

1 devices when you look at L5-S1 in the anatomical position.

2 The thing we did do relative to this question is
3 actually look at pullout of these devices, and the pullout
4 strength is well over 500 Newtons, which is a fairly
5 significant load to pull these devices out, at least in
6 shear. Given the fact that that load would probably never
7 be seen by the implant in that mode. So that addresses a
8 little bit of the flexion, extension issue.

9 Does that answer your question, Dr. Topoleski?

10 DR. TOPOLESKI: Yes. So you did not do any other
11 types of fatigue loading.

12 DR. GRIFFITH: We didn't feel it was needed.
13 Didn't feel it was needed.

14 DR. TOPOLESKI: Okay. Thank you.

15 DR. CHAPMAN: I have a question to the
16 manufacturer.

17 CHAIRMAN YASZEMSKI: Go ahead, Dr. Chapman.

18 DR. CHAPMAN: Thank you. Given the relative
19 equivalency of the HA-coated group and the non-HA-coated
20 group, which was implied by the manufacturer itself earlier,
21 does the manufacturer even have a reason to persist in
22 pursuing an HA-coated implant? Again, I did not see any
23 substantial improvement in any of the data group in the HA
24 coating group, so why pursue this, for the manufacturer,
25 more expensive technique any further?

1 CHAIRMAN YASZEMSKI: Comments from the sponsor?
2 Dr. Chapman's question is why pursue the more expensive HA
3 if both the coated and non-coated are equivalent.

4 MR. MANS: There is certainly an important
5 decision to be made here as a manufacturer, and we at one
6 point during this application did not intend to pursue it
7 for that reason.

8 However, we have been encouraged by some who
9 believe that there are some arguments that are mechanistic
10 that can be made about potential benefits of the HA-coated
11 device that perhaps some clinician would use in perhaps some
12 of their patients. And those arguments or those performance
13 characteristics, our study may not have been adequate to
14 detect that particular element. So that would be one reason
15 where perhaps this would have some application.

16 CHAIRMAN YASZEMSKI: Thank you.

17 DR. CHAPMAN: Let me ask a follow-up question.
18 What are the inadequacies of the study, then, if you could
19 point those out?

20 CHAIRMAN YASZEMSKI: That was Dr. Chapman.

21 DR. CHAPMAN: What are the inadequacies that you
22 were mentioning or referring to of your current study?

23 MR. MANS: I didn't mean to imply there were
24 inadequacies. What I meant to say was that the study was
25 not designed specifically to evaluate all elements of the

1 performance of the HA coating that may or may not benefit
2 the patient, and that's all I mean.

3 Let me just say, for example, if we were going to
4 make a very intense evaluation to try and determine the
5 differences, it may take other kinds of testing, and you
6 may, for example, enter a very difficult study or patients
7 with difficulties in whom those clinicians feel that that
8 device would be beneficial, and those patients perhaps who
9 would be more appropriate to determine or see the
10 differences, it would become a different evaluation that
11 we've done.

12 Let me justify, I hope, that the purpose of this
13 evaluation was not to establish equivalency or determine the
14 difference between the devices. The purpose of this
15 evaluation was to compare them to a medically acceptable
16 procedure, which was the control, and that's what was
17 demonstrated in the study.

18 CHAIRMAN YASZEMSKI: Thank you, Mr. Mans.

19 Dr. Topoleski, last question. Then we're going to
20 summarize.

21 DR. TOPOLESKI: A quick question, perhaps, for Dr.
22 Griffith. Given all the complex Bayesian analysis we've
23 seen, I was curious about the fatigue study that was
24 presented in the panel handout. And perhaps you could
25 clarify, but is it true that somebody sort of just hand-drew

1 an average curve and then hand-picked an endurance limit
2 from that data?

3 DR. GRIFFITH: No, that's not correct. We did do
4 a formal SN curve calculation, and we can hook the computer
5 maybe after lunch, if we're going to continue, and I can
6 show you that, if you'd like.

7 I want to make one clarification on the fatigue
8 curve, too. I think you stated--it might have been state in
9 the panel pack at one point we went to 3 million cycles. We
10 indeed went to 5 million cycles, and in doing so, the first
11 fatigue cycle we ran, the 3 million cycles at 300 pounds, we
12 had to lower that, because we ran it out to 5 million cycles
13 and we had one minor fracture, a crack that occurred, and
14 had to lower the runout load to 120 pounds.

15 CHAIRMAN YASZEMSKI: Thank you--

16 DR. GRIFFITH: We took it further out, actually.

17 CHAIRMAN YASZEMSKI: Thank you, Dr. Griffith.

18 For the FDA, then, the panel thinks and concurs
19 that the sponsor did establish safety. There were some
20 concerns raised about perhaps considering the coated and the
21 uncoated devices separately, but we believe that safety has
22 been established.

23 Have we adequately discussed this, FDA?

24 DR. WITTEN: Yes. Thank you.

25 CHAIRMAN YASZEMSKI: Let's move on to the next

1 question. This will be for Dr. Aboulafia.

2 MS. RHODES: Sulzer Spine-Tech proposes a post-
3 approval study to evaluate the long-term, five-year, post-
4 operative outcome of patients implanted with the BAK/C.
5 Clinical assessment parameters in the study presented today
6 are: neck pain, arm/shoulder pain, neurologic assessment,
7 including right and left arm sensation, strength and
8 reflexes, and function.

9 No radiographic assessment is proposed in this
10 post-approval study. No control group is proposed. And
11 there are no plans to evaluate the effect of the HA coating
12 in the post-approval study.

13 Patient success in the post-approval study is
14 defined as freedom from surgical intervention and a rating
15 of excellent or good on the Odom scale.

16 What, if any, long-term questions does the panel
17 think it would be important to answer in a post-approval
18 study?

19 DR. ABOULAFIA: All of the things that I have--and
20 we only just list four--have at least been touched on, if
21 not addressed very directly. I agree that radiographic
22 studies are worthwhile, as are motion studies. What appears
23 to be fused at 12 months may not actually be fused, and if
24 it's not followed further out, that would not become
25 apparent.

1 I'd also like to see what the effect is at other
2 levels. If a C3-4 level is fused, what is the effect a 4-5
3 or 5-6? And that could be calculated by surgical
4 interventions, which I guess is already addressed by the
5 current study. Then what is the effect on revision surgery?
6 They've mentioned that at least one patient had a revision
7 procedure after having a pseudo-arthrosis. What are the
8 clinical results after putting in a cage, and then going to
9 revision operation, be it autograft with plate or not? And
10 then adverse events.

11 Other than that, I have no comment.

12 CHAIRMAN YASZEMSKI: Thank you, Dr. Aboulafia.

13 Other comments from the panel on this question?

14 Ms. Rue?

15 MS. RUE: Depending on how long the post-approval
16 study goes, one question I want to ask is for women who have
17 had this implanted and have become post-menopausal, in the
18 extended study length, how the change in hormone level would
19 affect the bone density. If that was an issue, then it
20 would need to be addressed.

21 CHAIRMAN YASZEMSKI: Thank you.

22 Dr. Li?

23 DR. LI: I don't know if this is the time to
24 interject. Is there a plan to follow or study the outcomes
25 based on the size of the implants, whether or not you use

1 one or two, and what cervical level the devices are used in?
2 Is that--if not, I think that would be something useful to
3 follow.

4 MS. RHODES: I can answer that question. Correct
5 me if I'm wrong, but that was not a part of the currently
6 proposed post-approval study.

7 CHAIRMAN YASZEMSKI: Thank you.

8 Other questions? Dr. Simon?

9 DR. SIMON: Just a comment. Of course, it's
10 always better to have a control for a study than non-
11 control, but sometimes it makes it vastly more difficult to
12 do the study. I think in this particular case, some of the
13 questions that are being asked here, although they might be
14 answered more cleanly with a control, just having the study
15 even without a control group will be, I think, very
16 important, given that we really don't have long follow-up on
17 this study.

18 CHAIRMAN YASZEMSKI: Thank you, Dr. Simon.

19 Dr. Skinner?

20 DR. SKINNER: I'd like to raise the opposite
21 viewpoint. I look at the results that have been presented
22 so far, and I see a relatively low complication rate. And
23 when I think about what might happen over the long term, I
24 see--I suppose there's a possibility that the back could
25 back out. There might be displacement with significant

1 trauma, major trauma perhaps. There might be infection
2 because you have a foreign body. It might stick out. You
3 might get esophageal perforation over a period of time,
4 mediastinitis. And I see all of these things as being very
5 low in incidence, and I don't see the benefit we'd get from
6 a post-approval study unless it ran out long term, like Ms.
7 Rue suggested. I just don't see the benefit of it because
8 the chance of showing something is very small.

9 I would probably, from my viewpoint, be happy to
10 look at the MDRs that came out after it had been on the
11 market.

12 CHAIRMAN YASZEMSKI: Dr. Finnegan?

13 DR. FINNEGAN: I am going to disagree with my
14 esteemed colleague here. When you look at the complications
15 that were discussed, spinal stenosis occurs only in the BAK
16 group. It does not occur in the--or I did not see it,
17 anyway, in the control group. And this is in a relatively
18 early, short follow-up. As well, if you look at their
19 complications, per complication they talk of new development
20 of symptoms which mainly are radicular, which would suggest
21 also that there's some spinal stenosis. So I think that
22 definitely would need to be included in long-term follow-up.

23 My other comment comes from trauma surgeons in
24 that removing titanium anytime after 10 to 12 months is an
25 experience you don't want to have if you can avoid it. And

1 I would be very interested if there has been any experience
2 moving titanium after 12 months and what kind of problems
3 they expected.

4 CHAIRMAN YASZEMSKI: Comments from the sponsor?
5 The issues were titanium removal, number one, and the spinal
6 stenosis, number two. Is there spinal stenosis because of
7 protrusion of the cage or bone growth after surgery? Maybe
8 you could address that.

9 MR. MANS: I'll ask two of our clinicians to come
10 up and address these points. Two of them have had
11 opportunity to remove cages as part of follow-up to
12 complications that developed. And I can also address the
13 specifics of the spinal stenosis case.

14 DR. HACKER: I'd make comments on two points.
15 One, on the titanium cage removal, as I mentioned earlier,
16 the case in which I had a pseudo-arthrosis and performed a
17 revision with cage removal.

18 The cage is, for lack of a better word, a
19 relatively small investment of titanium, and I found it
20 quite easy, actually, to remove the case. Having never done
21 this before or talked to anyone who had before I performed
22 it, I had some apprehension. However, the cage was easily
23 removed in my particular case by simply slotting the sides
24 with a high speed burr and then simply pulling the cage out.

25 I wanted to make one comment regarding the post-

1 approval study, and I'd like to buttress some of Dr.
2 Skinner's comments.

3 In the October 2000 issue of the Journal of
4 Neurosurgery, I published my particular results, my
5 particular performance of this procedure. I have the
6 benefit in Oregon of having a rather captive audience. Once
7 people move there, they don't move out.

8 What I found was in my patients my average follow-
9 up was over 36 months, and it ranged from two years to four
10 years in my study. We did not see late complications. Our
11 fusion rates were usually by two years, what was seen as a
12 solid fusion was well maintained at distant follow-up.

13 CHAIRMAN YASZEMSKI: Thank you, Dr. Hacker.

14 Are there other comments? Dr. Chapman? Dr. Diaz?

15 DR. DIAZ: Not from me.

16 CHAIRMAN YASZEMSKI: Thank you.

17 DR. CHAPMAN: Yes, this is Dr. Chapman. I do
18 find--

19 CHAIRMAN YASZEMSKI: Dr. Chapman, I'm sorry.
20 There was another surgeon from the sponsor who wanted to
21 make a comment. May I ask you to hold for just a second,
22 please?

23 DR. CHAPMAN: Yes.

24 CHAIRMAN YASZEMSKI: Sorry. Go ahead.

25 DR. CAUTHEN: I'm Joseph Cauthen, neurosurgeon

1 from Florida. Regarding the question about removal of a
2 cage, there was one instance where the cage had bonded to
3 the superior vertebral inplate but not to the inferior
4 inplate, requiring reoperation. It was relatively easy to
5 fracture the attachment of the top of the cage to the
6 superior inplate. So it was not a problem in that single
7 case.

8 Thank you.

9 CHAIRMAN YASZEMSKI: Thank you.

10 Go ahead, Dr. Chapman.

11 DR. CHAPMAN: I do find a merit of a post-approval
12 study, and I would insist that we do need to learn more
13 about these implants in a living and moving creature, as
14 just exemplified and underscored by the colleague from
15 Florida, it was relatively easy for him to crack loose the
16 cage on the healed site, even, indicating that the actual
17 cross-trabeculation from the host bone into the cage might
18 not be as strong as we hoped it to be. Therefore, we do
19 have to perform--we should learn more about these cages, but
20 the flexion, extension films, even at two-year post-op
21 follow-up, and we should assess for subsidence on a later-
22 date basis to account for the phenomenon of occult non-
23 union, which is, again, something that is emerging in the
24 stand-alone cage environment in the lumbar spine.

25 CHAIRMAN YASZEMSKI: Thank you, Dr. Chapman.

1 I'd like to, if I might, then summarize for the
2 FDA that the discussion was that although perhaps there
3 might not be a need for a study, most of the panel thought
4 that there was a need for a study, and things that should be
5 looked at are radiographic studies to assess the longevity
6 of a fusion, degeneration at other levels, and perhaps
7 subsidence of the fused level, to look at revision surgery
8 rates over the long term, to look at the effect in post-
9 menopausal women, to perhaps consider a control group, even
10 for the long-term study, to look at the issue of titanium
11 debris.

12 FDA, have we adequately discussed this?

13 DR. WITTEN: Yes. Thank you.

14 CHAIRMAN YASZEMSKI: Thank you. Let's move on to
15 the next question.

16 MS. RHODES: The next question, really, you've
17 just answered by identifying various parameters to include
18 in a post-approval study. At this point, however, you
19 haven't really talked about the duration of the study. The
20 sponsor proposed five years. Do you think that's adequate?

21 CHAIRMAN YASZEMSKI: Dr. Finnegan?

22 DR. FINNEGAN: Actually, I would like to also
23 touch a little bit on the design of the study. I think that
24 it cannot be less than three years, and I think that the
25 five years that was suggested is, in fact, fairly

1 reasonable. Certainly most of the implant studies that are
2 being done now, looking between five and tens years is when
3 you are running into some surprises that were not
4 anticipated in the first 24 months.

5 I think that there is no question that
6 radiographic studies are needed, both--and there are several
7 things that have been brought up that I think are very
8 important. Motion is obviously one of them. The effect on
9 adjacent discs is one. Subsidence is one. And then peri-
10 disc stenosis is another one.

11 I read the Odom's article that was in the packet
12 that was sent to us, and I really could not find the
13 criteria for good or excellent on the Odom scale, number
14 one. And, number two, I think that if you want to compare
15 these results long term, you need to use the same parameters
16 that you used originally. And the only thing I did not see
17 for originally is if these clinical assessments were done by
18 a research nurse or if they were, in fact, done by the
19 operating surgeon. And I think there are problems if you
20 pick the operating surgeon, with deference to the surgeons
21 included, who I'm sure were not like a lot of other people
22 in the country, but I do think having somebody who is not
23 attached to the surgery would be the best way to do it.

24 Finally, I do think that the HA needs to be
25 followed as a subset.

1 CHAIRMAN YASZEMSKI: Thank you, Dr. Finnegan.

2 Other comments from panel members concerning this
3 question?

4 [No response.]

5 CHAIRMAN YASZEMSKI: FDA, we discussed the aspects
6 of this question considerably in the last question and had
7 the addition by Dr. Finnegan. Have we adequately addressed
8 this issue?

9 DR. WITTEN: Yes. Thanks.

10 CHAIRMAN YASZEMSKI: Thank you. Let's move on to
11 the last question.

12 MS. RHODES: This one also relates to a potential
13 post-approval study. Well, you've answered this one, too.
14 Are there any questions which relate to the effect of the HA
15 coating that the panel believes need to be addressed in a
16 post-approval study?

17 CHAIRMAN YASZEMSKI: Dr. Cheng, would you have any
18 further comments on this? We did discuss it somewhat, but
19 if you have--

20 DR. CHENG: Yes, I think I made my comments
21 already, and more in line with what Dr. Finnegan just
22 mentioned about identifying this as a separate group, and
23 for the reason identified earlier, studying them five years
24 seems entirely reasonable.

25 CHAIRMAN YASZEMSKI: Thank you.

1 Dr. Li, you had comments regarding the HA. Have
2 you any additional comments about it at this time?

3 DR. LI: No, just the earlier comments that I
4 made.

5 CHAIRMAN YASZEMSKI: Additional comments from the
6 panel?

7 MS. RHODES: Could I ask for a clarification?

8 CHAIRMAN YASZEMSKI: Ms. Rhodes, go ahead.

9 MS. RHODES: Is there anything in particular that
10 we should be looking for in terms of either adverse events
11 or other outcomes for the HA group compared to the uncoated
12 group?

13 CHAIRMAN YASZEMSKI: Comments from the panel?

14 DR. ABOULAFIA: No.

15 CHAIRMAN YASZEMSKI: Dr. Skinner?

16 DR. SKINNER: I would be concerned--and that's why
17 I asked the question--about having hydroxyapatite crack off
18 the coating and then abrade the titanium. So I'd be looking
19 for titanium wear problems.

20 DR. LI: And I guess I would re-emphasize the--
21 unless they already have the test data, about the steam
22 sterilization and then subsequent use.

23 CHAIRMAN YASZEMSKI: FDA, we, again, had
24 considerable discussion of this question while going over
25 the last questions. Have we adequately discussed this?

1 DR. WITTEN: Well, I do have one follow-on to
2 this, which is, this question actually asks specifically
3 about the post-approval study, and there has been discussion
4 about other bench testing that needs to be done. I'm just
5 wondering if there are any other comments or any other
6 suggestions for pre-clinical testing that the panel wants to
7 comment on that would be desirable to have the sponsor
8 perform on this.

9 CHAIRMAN YASZEMSKI: Okay. Dr. Chapman?

10 DR. CHAPMAN: As mentioned previously, I believe
11 by Dr. Mans, the current study, in his own words, seemed to
12 not allow us to identify the efficacy of HA coating in
13 contrast to the BAK/C without coating. So by the sponsor's
14 own admission, it seems that the current data shows at least
15 an impasse between the two implants, but certainly not a
16 benefit.

17 Beyond being a possible marketing gimmick,
18 obviously I'd like to ask the sponsor what specific study
19 proposals they had in mind to show that this is actually to
20 some benefit, aside from just having a certain intuitive
21 appeal to some surgeons, again, I'm going to say a marketing
22 appeal.

23 CHAIRMAN YASZEMSKI: Comments from the sponsor?

24 MR. MANS: I would not propose any further study
25 to characterize the performance benefit of coated versus

1 uncoated and just reiterate that the purpose of this PMA
2 application has been to establish the equivalence of the two
3 devices to the control.

4 CHAIRMAN YASZEMSKI: Thank you, Mr. Mans.

5 FDA, the further discussion has once again brought
6 up the issue of perhaps considering the HA-coated separate
7 from the uncoated. And with that in mind, have we
8 adequately discussed this?

9 DR. WITTEN: Yes. Thanks.

10 CHAIRMAN YASZEMSKI: Thank you.

11 We're going to break for lunch now, everybody.
12 Thank you. It's been a long morning.

13 What I'd like to say, however, is that we're going
14 to try to break for 15 minutes, so let's everybody try to be
15 quick and get our lunch done and get back in here. It's
16 now--well, let's call it 25 after. Let's start at 20
17 minutes to 2:00, and everybody please be in your seat and
18 ready to go.

19 Drs. Chapman and Diaz, 15 minutes.

20 [Whereupon, at 12:25 p.m., the meeting was
21 recessed, to reconvene at 1:40 p.m., this same day.]

AFTERNOON SESSION

[1:45 p.m.]

CHAIRMAN YASZEMSKI: Let's get started with the second session of the meeting. If we can ask everybody to take their seats, please, we'll get started in a moment.

We will now proceed with the open public session of this meeting. I would ask at this time that all persons addressing the panel come forward and speak clearly into the microphone as the transcriptionist is dependent on this means of providing an accurate recording of the meeting.

We're requesting that all persons making statements during the open public session of the meeting disclose which company they represent--our transcriptionist isn't ready. I'm going to hold on a second here.

[Pause.]

CHAIRMAN YASZEMSKI: We're requesting that all persons making statements during the open public session of the meeting disclose which company they represent and whether they have financial interests in any medical device company. Before making your presentation to the panel, in addition to stating your name and affiliation, please state the nature of your financial interest, if any.

Is there anyone at this time wishing to address the panel?

[No response.]

1 CHAIRMAN YASZEMSKI: At this time then, seeing no
2 one, I'd ask Sulzer Spine-Tech if they have any final
3 comments before the panel proceeds with voting for the BAK/C
4 premarket approval application.

5 MR. MANS: My final comment is related to the 2-
6 level approval situation. Panel members may have noticed
7 that in the presentation of material in the panel packet,
8 there is a draft package insert which attempts to deal with
9 this issue, and specifically it suggests approval for both
10 1- and 2-levels and then a precaution statement which
11 reflects the fact that the 2-level data standing upon their
12 own do not establish safety and effectiveness.

13 The reason this was done--and perhaps it's a
14 little bit contradictory and there could be some changes to
15 it worked out, but the rationale behind this was that there
16 is still a pretty substantial body of evidence coming out of
17 this clinical study that could be useful to clinicians as
18 they're making determinations as to how to treat their 2-
19 level patients.

20 Obviously, they are making decisions based on
21 their own experiences and based on published (?) within the
22 literature, which oftentimes are less substantial than a 90-
23 patient series, which is what our 2-level data represents.

24 We agree approval for 1- and 2-levels straightaway
25 is not an appropriate approval, but we think addressing it

1 in this way, with a precaution and allowing the clinician to
2 review that data by making it available in the package
3 insert, would be very appropriate from a regulatory point of
4 view.

5 That's it.

6 CHAIRMAN YASZEMSKI: Thank you.

7 I'd now like to ask Mr. Hany Demian to read the
8 voting instructions for the panel.

9 MR. DEMIAN: I will now provide you the panel
10 recommendation options for premarket approval applications.
11 The Medical Device Amendments to the Federal Food, Drug, and
12 Cosmetic Act require that the Food and Drug Administration
13 obtain a recommendation from an outside expert advisory
14 panel on designated medical device premarket approval
15 applications that are filed with the agency. The PMA must
16 stand on its own merits, and the recommendations must be
17 supported by safety and effectiveness data in the
18 application or by applicable publicly available information.

19 Safety is defined in the act as reasonable
20 assurance based on valid scientific evidence that the
21 probable benefits to health under the conditions of use
22 outweigh any probable risks. Effectiveness is defined as
23 reasonable assurance that in a significant portion of the
24 population, the use of the device for its intended uses and
25 conditions of use when labeled will provide clinically

1 significant results.

2 Your recommendation options for the vote are as
3 follows:

4 Approval, there are no conditions attached.

5 The second one, approvable with conditions. You
6 may recommend that the PMA be found approvable subject to
7 specified conditions such as resolution of clearly
8 identified deficiencies that have been cited by you, the
9 panel, or FDA staff. All the conditions are discussed by
10 the panel and elicited by the panel Chair and then voted on
11 one by one.

12 For example, you may specify what type of follow-
13 up information the panel or FDA should evaluate prior to or
14 after approval. Panel follow-up is usually done through a
15 homework assignment by one or two panel primary reviewers of
16 the application or to other specified members of this panel.
17 A formal discussion of the application at a future panel
18 meeting is not usually held.

19 If you recommend post-approval requirements to be
20 imposed as a condition of approval, then your recommendation
21 should address the following points: the purpose of the
22 requirement, the number of subjects to be evaluated, and the
23 type of reports that should be submitted.

24 The third option is not approvable. Of the five
25 reasons the act specifies for denial of approval, the

1 following three reasons are applicable to your panel
2 deliberations: the data do not provide reasonable assurance
3 that the device is safe under the conditions prescribed,
4 recommended, or suggested in the proposed labeling;
5 reasonable assurance has not been given that the device is
6 effective under the conditions of prescribed, recommended,
7 or suggested in the labeling; and based on a fair evaluation
8 of all material facts in your discussions you believe the
9 proposed labeling to be false or misleading.

10 If you recommend that the application is not
11 approvable for any of these stated reasons, then we ask that
12 you identify the measures that you think are necessary for
13 the application to be placed into approvable form.

14 Traditionally, the consumer representative and the
15 industry representative do not vote, and Dr. Michael
16 Yaszemski as panel chairman votes only in the case of a tie.

17 Dr. Yaszemski?

18 CHAIRMAN YASZEMSKI: Before beginning the voting
19 process, I'd like to mention both for the benefit of the
20 panel and for the record that votes taken are votes in favor
21 of or against the motion and not the product.

22 Is there a motion? And at this time I might ask
23 our lead clinical reviewer, Dr. Diaz, if he has a motion.

24 Dr. Diaz?

25 DR. DIAZ: Yes, I do.

1 CHAIRMAN YASZEMSKI: May I ask you to read your
2 motion?

3 DR. DIAZ: The motion is to approve with
4 conditions.

5 CHAIRMAN YASZEMSKI: And what are those
6 conditions?

7 DR. DIAZ: The conditions would be that the use of
8 the cages be limited to patients with 1-level fusion; that
9 further review is required to assess fully the value and
10 potential safety requirements for the 2-level fusion; and
11 that a further analysis needs to be completed regarding the
12 potential benefit of cage fusion as opposed to purely the
13 simple decompression of the levels involved.

14 CHAIRMAN YASZEMSKI: Thank you, Dr. Diaz.

15 Before I ask for a second, I'm going to make a
16 note about process here. Once we have a second, we're going
17 to vote simply for approval with conditions, and then
18 depending upon the result of that, if it were to pass, we
19 will discuss and vote upon each of those conditions
20 separately. So I'm going to ask now for a second to vote
21 for approval with conditions. Is there a second?

22 DR. SKINNER: Second.

23 CHAIRMAN YASZEMSKI: Dr. Skinner has seconded it.

24 It's been moved and seconded that the premarket
25 approval application for BAK/C be approved with conditions.

1 I'm going to ask now that all those in favor raise their
2 hands.

3 DR. CHENG: Clarification, please?

4 CHAIRMAN YASZEMSKI: Yes, Dr. Cheng.

5 DR. CHENG: The motion is approval with conditions
6 for 1-level usage. Is that correct?

7 CHAIRMAN YASZEMSKI: We will vote on the
8 conditions separately. If the panel members believe that
9 this is approvable with conditions, which are as of this
10 moment unspecified, then the vote is yes. If you believe
11 that it is not approvable with conditions, then your vote is
12 no. If it passes as approvable with conditions, we will
13 then vote on each of those conditions independently.

14 Dr. Finnegan?

15 DR. FINNEGAN: A question perhaps to you and Dr.
16 Diaz. Would you consider to split the motion into two, one
17 motion for or against 2-level and one a motion for or
18 against 1-level, and then go from there?

19 CHAIRMAN YASZEMSKI: Those will be conditions.
20 You can raise that as a condition.

21 DR. FINNEGAN: Okay. But you won't split the
22 motion.

23 CHAIRMAN YASZEMSKI: No. I'm going to ask now for
24 a vote. All those who would favor approval with conditions,
25 as yet unspecified, please raise your hand.

1 [A show of hands.]

2 DR. CHAPMAN: This is Jens Chapman raising his
3 hand.

4 [Laughter.]

5 CHAIRMAN YASZEMSKI: Thank you. Dr. Diaz, may I
6 assume, since you made the motion, that you're voting yes?

7 DR. DIAZ: I am raising my hand, too.

8 CHAIRMAN YASZEMSKI: Okay. The motion passes
9 unanimately.

10 We will now entertain any motions to introduce
11 conditions, and we'll take them one at a time. Conditions,
12 Dr. Cheng?

13 DR. CHENG: The conditions which I would propose
14 would be, as Dr. Diaz has already indicated, for 1-level
15 usage only and not for 2-level usage. Second would be for
16 the performance of the sensitivity analysis for the missing
17 data due to patient dropout in the control group. And the
18 third would be performing the post-market surveillance as we
19 just discussed in our previous discussion.

20 CHAIRMAN YASZEMSKI: We will list the conditions
21 now. Then we're going to go over them one at a time. Are
22 there additional conditions?

23 DR. CHAPMAN: I couldn't hear whether
24 hydroxyapatite was listed, but, again, I would suggest
25 splitting that up.

1 CHAIRMAN YASZEMSKI: How would you word that, Dr.
2 Chapman?

3 DR. CHAPMAN: The need for addition of
4 hydroxyapatite coating on a BAK/C device needs to be further
5 clarified. Its utilization, its benefits, and its risks
6 should be established further.

7 CHAIRMAN YASZEMSKI: Okay. Thank you.
8 Are there any additional motions? Dr. Li?

9 DR. LI: Yes, I'd like to see additional
10 mechanical testing on the HA-coated devices, both in terms
11 of the mechanical static and fatigue tests as well as the
12 integrity of the HA coating after steam sterilization.

13 DR. CHAPMAN: I second that.

14 DR. LI: And also, for the non-HA-coated devices,
15 there's only four sizes, and the geometries are not the same
16 in all four sizes. They differ in the number of holes, the
17 threads have a different taper, and the stress fields are
18 quite complicated. Without seeing the FDA analysis, I don't
19 really think there's much of an excuse for not running the
20 mechanical tests for all four sizes.

21 CHAIRMAN YASZEMSKI: Any additional motions?

22 [No response.]

23 CHAIRMAN YASZEMSKI: We'll now go through these
24 one at a time and vote on each of them independently. The
25 application has been approved with conditions, and what

1 we're going to do now is vote on and then list those
2 conditions.

3 The first is a condition of 1-level usage. There
4 has been a motion raised to have 1-level approval only
5 versus 2-levels. Is there a second to that motion? And
6 then we'll have discussion. There's a second, Dr. Finnegan.

7 Discussion? Dr. Skinner?

8 DR. SKINNER: I would recommend adding to the
9 motion that the package insert changes suggested by the
10 company be included.

11 CHAIRMAN YASZEMSKI: Thank you. Other discussion?
12 Dr. Simon?

13 DR. SIMON: In some clinical trials, I mean, it's
14 not practical to demonstrate effectiveness in every subset,
15 and so to what extent you need to demonstrate effectiveness
16 and safety separately by patient subsets really depends sort
17 of on your a priori view of to what extent these were really
18 subsets that should be evaluated separately.

19 Everything I saw about the presentation of the
20 data in these eight books indicated to me that, from the
21 outset, the viewpoint was that these are really different
22 subsets of patients, and that you really couldn't assume
23 that effectiveness for one subset implied effectiveness for
24 the other subset.

25 I really felt that the data for the 2-level

1 patients was really unevaluable because of the number of
2 control patients who refused the treatment; therefore, I
3 believe that the condition of approving it only for the 1-
4 level patients is the appropriate one.

5 CHAIRMAN YASZEMSKI: Thank you, Dr. Simon.

6 Dr. Skinner?

7 DR. SKINNER: I agree totally with Dr. Simon. The
8 reason I suggested adding the package insert is that the FDA
9 doesn't regulate medical practice, and I know surgeons are
10 going to put these in more than one level. And I am working
11 out for the surgeon to give him a little bit of background,
12 a little bit of justification for doing that when he has to
13 stand up in court.

14 CHAIRMAN YASZEMSKI: Thank you. Other discussion
15 on this condition?

16 [No response.]

17 CHAIRMAN YASZEMSKI: We're now going to vote on
18 this condition. The condition is to make the approval for
19 1-level usage and to include those changes recommended by
20 the sponsor in the package insert with respect to surgeons'
21 considering 2-level usage.

22 I'll call for a vote now. All those in favor of
23 this condition, please raise your hand.

24 [A show of hands.]

25 DR. CHAPMAN: Jens Chapman reports his right hand

1 is raised.

2 CHAIRMAN YASZEMSKI: Dr. Diaz?

3 DR. DIAZ: I vote yes.

4 CHAIRMAN YASZEMSKI: The vote is unanimous. This
5 condition passes.

6 We'll now move to the second condition. The
7 second condition was to perform a sensitivity analysis of
8 the dropout patients in the control group. Discussion on--
9 first, let me hear, is there a second for this condition?

10 DR. DIAZ: Second.

11 CHAIRMAN YASZEMSKI: The second has been raised.
12 Discussion, please? Dr. Simon?

13 DR. SIMON: I believe that that's the weakest
14 point of the analysis, that is, the dropouts, and I think
15 that the best effort should be made in terms of trying to
16 assure that those dropouts have not biased the conclusions.
17 And I think from the analysis presented so far, that
18 analysis is really not the best effort that can be done.

19 CHAIRMAN YASZEMSKI: Thank you.

20 Dr. Aboulafia?

21 DR. ABOULAFIA: I think what industry did do was
22 they gave a worst-case scenario and said even--

23 DR. SIMON: That was the worst-case scenario for
24 patients who accepted their treatment, but then did not--
25 were not evaluated later. This is a sensitivity--this is

1 running a sensitivity analysis for patients who actually
2 refused the randomized treatment.

3 CHAIRMAN YASZEMSKI: Thank you.

4 Dr. Cheng?

5 DR. CHENG: Although I proposed that condition, I
6 did not propose a threshold criteria as to what the
7 sensitivity analysis must show. And I'm wondering if Dr.
8 Simon might have some thoughts on that.

9 CHAIRMAN YASZEMSKI: Dr. Simon?

10 DR. SIMON: I think it would be difficult to
11 really establish that at this point, really.

12 CHAIRMAN YASZEMSKI: I would take it from that,
13 then, we'll leave it up to the sponsor to determine the
14 levels.

15 PARTICIPANT: Up to the FDA.

16 CHAIRMAN YASZEMSKI: Agreed.

17 Other discussion?

18 [No response.]

19 CHAIRMAN YASZEMSKI: I'll call for a vote on this
20 condition. The condition is that a sensitivity analysis
21 will be performed on the dropouts from the control group.
22 All in favor?

23 [A show of hands.]

24 DR. CHAPMAN: In favor.

25 DR. DIAZ: In favor.

1 CHAIRMAN YASZEMSKI: All opposed?

2 The vote is one opposed. Dr. Aboulafia has
3 opposed. All others are in favor. This motion passes.

4 We'll move on to the third condition. This was
5 for the post-approval study. A second for this condition?
6 Seconded by Dr. Finnegan.

7 Discussion? Dr. Skinner?

8 DR. SKINNER: Well, I know I'm in a minority here,
9 but I still think that it's going to be such a large study
10 conducted for such a long period of time that to get
11 statistically meaningful data, it's going to be expensive
12 and onerous, and I'm not sure that it's going to be
13 beneficial. So I'm really against it, but I know where it's
14 going.

15 [Laughter.]

16 CHAIRMAN YASZEMSKI: I might for purposes of
17 clarification, this post-approval study will be as described
18 in the discussion of the six questions.

19 Other discussion? Dr. Simon?

20 DR. SIMON: I would just say, you know, my
21 impression has been that when you do a study, even if it's a
22 study without a control group, it really establishes that
23 you do follow those patients, you have a built-in evaluation
24 at built-in times, with built-in criteria. And it really
25 gives you a whole lot more information than if you depend on

1 adverse event reporting.

2 CHAIRMAN YASZEMSKI: Thank you.

3 Other discussion?

4 [No response.]

5 CHAIRMAN YASZEMSKI: I'm now going to call for a
6 vote on a condition of a post-approval study consistent with
7 the discussion of Questions 4 through 6 that the FDA posed
8 to the panel earlier. All in favor?

9 [A show of hands.]

10 DR. CHAPMAN: Favor.

11 CHAIRMAN YASZEMSKI: Dr. Diaz?

12 DR. DIAZ: Favor.

13 CHAIRMAN YASZEMSKI: The vote is unanimous. This
14 condition passes--excuse me, I'm sorry. I didn't look close
15 enough to my right, and Dr. Skinner has voted no. There is
16 one dissenting vote to this. Pardon me, Dr. Skinner. This
17 motion passes.

18 The next condition--there are two left--is to have
19 an evaluation of the risks and benefits of the hydroxy-
20 apatite coating. Dr. Chapman, you raised this. I'm going
21 to ask for a second, and then I'm going to ask you to lead
22 the discussion. Is there a second to this motion?

23 DR. FINNEGAN: Second.

24 CHAIRMAN YASZEMSKI: Dr. Finnegan has seconded it.
25 Dr. Chapman?

1 DR. CHAPMAN: Again, the sponsor's identified
2 ample data that shows seeming equivalency of this new
3 technology in terms of spine implants. We know very little
4 about it. There seems to be an awareness on the part of the
5 sponsor's methods of how to investigate whether it actually
6 provides a benefit, a true benefit, or whether it is a
7 simple marketing ploy more or not--more or less. Therefore,
8 I suggest that (?) mechanical testing, suggested by Dr.
9 Cheng, be performed, including shear testing, and that
10 further assessment criteria should be resolved and proposed
11 in order to further clarify its actual utility and efficacy.

12 CHAIRMAN YASZEMSKI: May I ask you to--since the
13 last condition is going to deal with mechanical testing, can
14 I ask you to separate those out? We'll discuss those under
15 mechanical testing and ask you to focus on which things you
16 would like to see in the clinical testing in the post-
17 approval testing.

18 DR. CHAPMAN: Sure. Specifically in terms of
19 clinical testing, rate of integration of the cages and any
20 differences in terms of ingrowth should be assessed and
21 would also be included in the post-approval study, and
22 methods such as apparently have been applied to the European
23 arm of the sponsor's undertakings should also be made known
24 to us and possibly utilized.

25 CHAIRMAN YASZEMSKI: Thank you.

1 Other discussion on this condition? Dr.
2 Aboulafia?

3 DR. ABOULAFIA: Yes, my impression was--and I went
4 over the data pretty strongly--was that the HA-coated and
5 the non-HA-coated devices were substantially equivalent to
6 each other, which were also substantially equivalent or
7 better than for the control group, which is what the study
8 trial was and what was asked of sponsor in their initial
9 plan. So I'm not sure we can change the rules.

10 CHAIRMAN YASZEMSKI: Other discussion? Dr.
11 Larson?

12 DR. LARSON: I think if there is to be a clinical
13 criterion for showing a difference between HA-coated and
14 non-HA-coated, I think that will be statistically an
15 extremely difficult thing to do. Generally, HA coatings are
16 used, and I think the wisdom is that they're used to ensure
17 in very difficult situations. But statistically you
18 generally don't see that difference. So I think that to
19 require that would be excessive.

20 Basically, the sponsor has made the position that
21 they've shown that there's equivalence between HA-coated
22 ones and the control, and they've shown equivalence between
23 uncoated ones and the control. And that's the regulatory
24 requirement.

25 CHAIRMAN YASZEMSKI: Thank you.

1 Other discussion? Dr. Simon?

2 DR. SIMON: I'm just a little confused

3 procedurally in the sense that--are we really dealing with
4 an issue of sort of marketing claims and whether--I mean,
5 will this take care of itself if we're worried about
6 undocumented marketing claims? Do we have to worry about
7 that, or is that something--in other words, if we approve it
8 coated or uncoated, and if the company marketed it as having
9 some advantage which wasn't demonstrated, won't the FDA take
10 care of that?

11 CHAIRMAN YASZEMSKI: I think what we're going to
12 have to limit ourselves to now is whether we're going to put
13 the stipulation that, for approval, one of the conditions
14 for approval will be that the company has to do some follow-
15 up on HA- versus non-HA-coated. And I think the vote will
16 take care of that.

17 Dr. Larson?

18 DR. LARSON: Let me clarify. I was not suggesting
19 that there not be follow-up, but I was suggesting that there
20 not be a requirement that there be a statistically
21 significant difference shown.

22 CHAIRMAN YASZEMSKI: Okay. Other discussion?

23 DR. CHENG: Could you read that condition again?

24 CHAIRMAN YASZEMSKI: The condition refers to
25 making a distinction in the post-approval study between the

1 HA-coated implants and the non-HA-coated implants, and that
2 the sponsor look at the clinical outcome variables that they
3 are going to gather separately for HA versus non-HA.

4 Other discussion?

5 [No response.]

6 CHAIRMAN YASZEMSKI: I'm going to call for a vote
7 on it now. All in favor?

8 [A show of hands.]

9 DR. CHAPMAN: Aye. Chapman in favor.

10 CHAIRMAN YASZEMSKI: Dr. Diaz?

11 DR. DIAZ: Favor.

12 CHAIRMAN YASZEMSKI: Unanimous for approval.

13 The last one concerns the requirement to perform
14 further mechanical testing of the HA, and I'll for the
15 particulars of that after we see if we have a second. Is
16 there a second to this motion?

17 DR. CHAPMAN: Second.

18 CHAIRMAN YASZEMSKI: There's a second.

19 Discussion? Dr. Li, specifically what would you like to
20 have them do? I know you mentioned it before, but let's
21 hear it.

22 DR. LI: Yes, I went through it before. I could
23 say the same thing. I would like to see mechanical testing
24 of the same sort they did on the non-HA-coated devices for
25 the HA-coated devices, and I would like to see that testing

1 done on all sizes, actually, for the coated and uncoated.
2 And I also for the HA-coated would like to see results of
3 the HA integrity post-steam sterilization as recommended by
4 the sponsor.

5 CHAIRMAN YASZEMSKI: Thank you.

6 Discussion? Dr. Topoleski?

7 DR. TOPOLESKI: I would also like to see that the
8 test method, the loading, et cetera, is more relevant to the
9 clinical loading.

10 CHAIRMAN YASZEMSKI: And specifically what would
11 you ask them to do? How would you word that if we give them
12 directions as to how to do it?

13 DR. TOPOLESKI: To test--to reproduce the loads in
14 flexion, extension, rotation, and lateral movement.

15 CHAIRMAN YASZEMSKI: Thank you.

16 Other discussion? Dr. Skinner?

17 DR. SKINNER: Regarding the integrity of the
18 coating, I would like to exclude from that requirement
19 anything that shows up in the master file for John Kay's
20 coating. Floyd, maybe you'd address that.

21 DR. LARSON: It's Biocoat's coatings.

22 DR. SKINNER: Bio?

23 DR. LARSON: Biocoat. Rick Georgette's.

24 DR. SKINNER: That's Rick Georgette's coating?

25 DR. LARSON: Yeah.

1 CHAIRMAN YASZEMSKI: Other discussion?

2 [No response.]

3 CHAIRMAN YASZEMSKI: Okay. I'm going to read what
4 the motion for this condition is. It's that further testing
5 of the HA-coated BAK/C be done to include mechanical testing
6 similar to the testing that was done on the non-coated
7 BAK/C, to include fatigue testing, testing after
8 sterilization, testing of all four sizes; that the test
9 method reproduce clinically relevant loads, but that these
10 tests exclude any data already included in the master file
11 for this HA.

12 I'm going to call for a vote now. All in favor?

13 [A show of hands.]

14 DR. CHAPMAN: Aye, Chapman.

15 CHAIRMAN YASZEMSKI: Dr. Diaz?

16 DR. DIAZ: Favor.

17 CHAIRMAN YASZEMSKI: The motion passes.

18 This concludes the conditions to the main motion.
19 We have one last vote to take now. Considering that the
20 approval is for approval with conditions, we ask for a last
21 vote to approve this application with all the conditions
22 that we just went over and approved individually, and I'll
23 call for that vote now. All in favor?

24 [A show of hands.]

25 DR. CHAPMAN: Aye.

1 CHAIRMAN YASZEMSKI: Dr. Diaz?

2 DR. DIAZ: Favor.

3 CHAIRMAN YASZEMSKI: Unanimous. The vote is for
4 the motion with the conditions just listed, and the panel is
5 recommending that this premarket approval application for
6 BAK/C be approved with conditions that we just listed and
7 voted upon.

8 Mr. Demian?

9 MR. DEMIAN: I would like to thank all the panel
10 members for their time and their effort and energy in
11 reviewing this material and participating in this FDA panel
12 meeting. All your efforts are truly appreciated.

13 At this time I would like to remind all panel
14 members if you want the material destroyed in front of you,
15 just leave it where it is and I'll take of it.

16 This meeting is adjourned.

17 [Whereupon, at 2:20 p.m., the meeting was
18 adjourned.]