

1 Yes, Leon, that is correct, that basically we did an
2 evaluation of the CT in all of the patients in whom
3 CTs were available and that was a vast majority.

4 DR. LENCHIK: Since you're up there,
5 Harry, what about the issue of artifact coming off the
6 metallic cage on CT, were there any patients in whom
7 you thought you simply couldn't tell whether there was
8 bridging across or this is a hypothetical that just
9 exists in my head and not in real life?

10 DR. GENANT: Well, indeed, that is an
11 issue. Although that we recognize that in this case
12 we're dealing with titanium cages and clearly if we
13 had other metal alloys that would be -- would almost
14 preclude the evaluation. But nevertheless, we found
15 that with the combination of the axial images with the
16 coronal and with the sagittal reformations, that we
17 were able to make an estimate of the intracage
18 ossification in virtually all the cases.

19 CHAIRPERSON FINNEGAN: Okay, thank you.
20 Dr. Larntz?

21 DR. LARNTZ: Just one question. The one
22 question is, was any analysis done to adjust the

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1 laparoscopic results for the difference in baseline
2 variables?

3 DR. LIPSCOMB: The answer is yes. In
4 anticipation of your question, Dr. Larntz, we did do
5 a co-variant adjustment analysis comparing the
6 investigation of lap group to the control group. Next
7 slide, please. We looked at 25 demographic and
8 preoperative conditions and also some of the surgical
9 variables to get out base of what other possible co-
10 variants and from a logistic regression, we identified
11 eight that seemed to be -- that had the most
12 significant effect.

13 Next slide, please. And those are the
14 eight that came up from the logistic regression. Some
15 of them obviously, make a lot of sense when you start
16 thinking about what maybe would effect the outcome.
17 Next slide. And then when you do the Bayesian
18 analysis, comparing the lap to the control with the
19 adjustments, you see that an equivalence is
20 established in all the major categories; fusion,
21 Oswestry, neuro and overall success and in fact,
22 superiority could be claimed in three of them,

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1 Oswestry, neuro and overall, so yes, we did.

2 DR. LENCHIK: Thank you.

3 CHAIRPERSON FINNEGAN: Ms. Rue.

4 MS. RUE: I think my other questions and
5 comments were pretty much discussed but I do have one.
6 You had a very nominal amount of patients that had
7 hepatitis. Was there anything specifically different
8 about their outcomes?

9 DR. LIPSCOMB: I'd have to look to see if
10 there's anything. I think there's only just one or
11 two patients that had that and if you can give us a
12 second, we can --

13 MS. RUE: I think there was like three in
14 one and two in the other. It was just nominal.

15 DR. LIPSCOMB: Yeah, if you can give us a
16 second we can check.

17 CHAIRPERSON FINNEGAN: Ms. Maher?

18 MS. MAHER: I have nothing further to add.

19 CHAIRPERSON FINNEGAN: All right, if you
20 will all -- while he's looking that up -- hang on a
21 second. Yes.

22 DR. KOSTUIK: May I ask a question?

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1 CHAIRPERSON FINNEGAN: Microphone.

2 DR. KOSTUIK: It's John Kostuik. It's my
3 understanding that there was statistically significant
4 difference in urological or urogenetic problems between
5 the InFUSE™ group and the controls and that these
6 were mainly retention and that they all resolved, but
7 I do have some concerns. It's my understanding,
8 probably wrong, that there may be some influence BMPs
9 in the prostate. I would like to know the breakdown
10 between sexes and ages as to who had the significant
11 problems with urinary retention because this could
12 lead in the older population to some difficulties.

13 DR. MATHEWS: Hal Mathews. Thank you, Dr.
14 Kostuik. We did not urogenital issues in the patients
15 in the investigational group. We tried to look at
16 specific mechanisms for that and we didn't really come
17 up with anything specific to that but Dr. Kostuik's
18 point is well-taken. We're currently searching for
19 the distribution of age and sex.

20 We discussed this clinically amongst the
21 investigators and we thought that there were two
22 issues which were really pretty obvious in treating

1 these patients. Number one was the fact that the
2 patient that received the investigational control
3 device did not have a bone graft harvest; and hence,
4 when the surgery was over, if they were treated
5 laparoscopically, they were going home in 45 percent
6 of those patients.

7 If they were treated as an open surgical
8 patient, they wanted to get up because they didn't
9 have much pain. They didn't have the iliac crest
10 harvestation. And hence if one is up and mobile, one
11 will typically ask the nurse, "May I have my catheter
12 removed", because as you know, the catheter insertion
13 and Foley catheter drainage during and a lift procedure
14 (ph) is paramount to that procedure. You want to have
15 the bladder deflated.

16 And hence, if you didn't have an iliac
17 crest harvestation, you had your catheter taken out
18 very early and you were up and mobile. However, we
19 still always know that that's an anterior procedure
20 and that anterior approach still has the risk of
21 having ileus and also urogenital complications just
22 from being there and hence those patients may have had

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1 reinsertion of a Foley catheter later because of this.

2 However, it is important to note that all
3 of these retention issues did resolve before they went
4 home and no patients needed additional catherizations.

5 CHAIRPERSON FINNEGAN: All right, thank
6 you. We're going to have to proceed to questions, to
7 the FDA questions but I think Dr. Li had one question.

8 DR. LI: I just have one question I failed
9 to ask earlier. In one of the summaries, it compares
10 the results of nine of the investigators who had a
11 financial interest in the product versus the
12 investigators that did not have a financial interest.
13 And I was taken by the fact that the surgeons that had
14 the financial interest had a better overall success
15 rate in both your control and your test group, almost
16 by a factor of two in the test group, versus those
17 physicians that did not have a financial interest.

18 So I don't really raise this at all to
19 impugn anybody's integrity but my question is, is
20 there something that we can learn about that? Was
21 there something that your nine investigators that had
22 a financial interest, did they have a higher

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1 experience level, did they have a better technique?
2 Is there something that we can take away from that
3 that you could put into the labeling or instruction or
4 manuals than that would basically make everybody's --
5 or you could give everybody a financial --

6 (Laughter)

7 DR. LIPSCOMB: Well, what a question. The
8 only thing I can say about that is we did the
9 analysis, as you had in your packet, and it just
10 speaks to the beauty of having a prospective
11 randomized control trial because if you look at the
12 results that were presented, yes, those with the
13 financial interest did better than those that didn't
14 on the numerical -- different numerical parameters,
15 but they also did equally well in the control group as
16 well. So when you start making those comparisons,
17 that's where those kind of wash out.

18 DR. LI: Yeah, I guess my question is, did
19 you investigate why that was? I mean, was there
20 something that we could take from that to teach
21 everybody across the board to have the same --

22 DR. LIPSCOMB: We didn't specifically look

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1 past that point, no.

2 CHAIRPERSON FINNEGAN: Time out. If you
3 will bear with me, we need to actually officially have
4 a second open public session, so I would like to
5 proceed with that at this time. I would ask that all
6 persons addressing the panel come forward and speak
7 clearly into the microphone so that the
8 transcriptionist can have a valid means of providing
9 an accurate record of this meeting.

10 And we request that all persons making
11 statements during the open public session of the
12 meeting disclose which company they represent and
13 whether they have financial interests in any medical
14 device company. Before making your presentation to
15 the panel, in addition to stating your name and
16 affiliation, please state the nature of your financial
17 interest, if any. Is there anyone wishing to address
18 the panel? Please.

19 DR. PATEL: I'm Tushar Patel. I'm a
20 service consultant to Depuy Acromed as well as Striker
21 Biotech. And I'm here with my travel expenses paid
22 for by Depuy Acromed. I'm a clinical assistant

1 professor at Yale University and a private practice
2 spine surgeon, limited to spine surgery, orthopedics.

3 This is a two-part question, a follow-up
4 of that to Dr. Finnegan, who commented upon the
5 endless resourcefulness of orthopedic surgeons. I
6 plead guilty. How does one insure, given Dr.
7 McCullough's comments earlier about off-label
8 application, different carriers, et cetera, and this
9 is a particularly important question. I would be
10 delighted to see BMPs approved in the sense that I
11 think that's a tremendous advance in treating spinal
12 disorders, but I think it is important to address the
13 off-label issue.

14 The second is for the people from Integra
15 Life Sciences, in which the question was asked, have
16 any antibodies been seen. Knowing that it's been
17 approved 29 years ago, were any tests done to look for
18 the antibodies? I understand that nobody's ever
19 reported any immune response but did anybody ever look
20 for an immune response and specifically the
21 antibodies? Thank you.

22 CHAIRPERSON FINNEGAN: Would you guys like

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1 to answer the first question?

2 MR. DEMIAN: He's just giving a comment.
3 You don't have to specifically answer the questions.
4 This is open public session where he's providing his
5 comments to the panel, so that's it.

6 CHAIRPERSON FINNEGAN: All right, at this
7 time I would like to ask the sponsors, Medtronic
8 Sofamor Danek if they have any final comments before
9 we proceed with reviewing the questions.

10 MS. RUE: Dr. Finnegan, I'd like them to
11 answer the question about --

12 CHAIRPERSON FINNEGAN: Oh, certainly,
13 hepatitis.

14 DR. LIPSCOMB: We did a quick analysis of
15 the patients that had hepatitis and if you'll just
16 look at the overall success, bear with us, the data
17 that we could garner quickly, three out of five of the
18 open investigation patients were successes at their
19 last visit, overall successes. Sixty-six percent or
20 virtually 60 versus 66 percent in the control were
21 successes and then 100 percent in the lap group were
22 successes.

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1 MS. RUE: Thank you.

2 CHAIRPERSON FINNEGAN: Would you like to
3 make any final comments?

4 DR. LIPSCOMB: No.

5 CHAIRPERSON FINNEGAN: Oh, thank you.
6 Aric, if you would go ahead and put up the questions,
7 please.

8 MR. KAISER: Okay, the first question has
9 to do with reproduction and teratogenicity and we
10 would like the panel to discuss the potential for an
11 immune response in the mother to effectively block
12 BMP-2 in the developing fetus.

13 CHAIRPERSON FINNEGAN: Comments from the
14 panel.

15 DR. DIAMOND: I think we have to say it's
16 a potential hazard and that this study so far doesn't
17 prove the null hypothesis, so it's a potential
18 concern.

19 CHAIRPERSON FINNEGAN: Any other comments?

20 DR. LENCHIK: I've got one.

21 CHAIRPERSON FINNEGAN: Yes.

22 DR. LENCHIK: We're talking about the

1 pregnancy registry. Why not just make it a contra-
2 indication in women who are pregnant, no one has
3 brought that up as an option.

4 CHAIRPERSON FINNEGAN: All right.

5 DR. WITTEN: Can I provide some
6 clarification to that question, just in response to
7 that, which is as Peter Hudson explained during his
8 presentation, it's not the -- what we're concerned
9 about potentially is a potential concern, it's not
10 something demonstrated in the study. It's not that
11 the product itself when administered is causing a
12 problem in developing fetus but that the problem --
13 that the product may cause an immune response in
14 another that could at some time, not necessarily
15 related to you know, the time point at which it was
16 implanted, cause a problem.

17 So then, you know, the question would be
18 if a woman had it which would be suggesting a contra-
19 indicating event. So that's just something to keep in
20 mind, you then contra indicate it or -- you know,
21 there's a sort of -- it's not clear what the time
22 limit would be of that contra-indication.

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1 DR. BOYAN: Madam Chairman?

2 CHAIRPERSON FINNEGAN: Yes, Dr. Boyan.

3 DR. BOYAN: The -- I guess I would argue
4 against that contra-indication because I don't think
5 we have enough information one way or the other except
6 to say that the incidents of an immune response in the
7 mother was exceedingly low in the clinical trial and
8 based on the information that was given to us would be
9 very low in the general population, but I don't think
10 we should ignore it.

11 I think that we need to make it clear in
12 the labeling somewhere that it's a potential issue and
13 that I guess I might even go as far as to say that
14 there may be some wording to suggest that the patient
15 be made aware of that not just in some vague
16 discussion but should they then get a second or a
17 third treatment using BMP-2 in some sort of device,
18 that they maybe want to pre-test to see if they have
19 antibody titer at that time.

20 DR. KIRKPATRICK: Dr. Finnegan, may I
21 comment?

22 CHAIRPERSON FINNEGAN: Go ahead.

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1 DR. KIRKPATRICK: John Kirkpatrick. I
2 would just suggest that as a surgeon, and I hope my
3 colleagues would agree but I can't read their minds,
4 that I would not plan to do an elective surgery on a
5 pregnant woman anyway. So putting it as a contra-
6 indication is kind of not relevant to medical
7 practice.

8 DR. DIAMOND: I think the concern, the
9 caution would be for women who want to get pregnant,
10 who plan to get pregnant and I think that maybe there
11 should be some post-marketing continued studies of
12 these antibodies in gestating animals.

13 CHAIRPERSON FINNEGAN: And actually I
14 strongly support that as well. One of my questions,
15 Dr. Witten, is that one of the studies that is
16 proposed or no, because I don't see that as a --

17 DR. WITTEN: That's actually one of the
18 studies that we're asking you to make a recommendation
19 on. If you do propose such a study, we'd like to know
20 that and what it would look like.

21 CHAIRPERSON FINNEGAN: Okay. You can go
22 ahead.

1 MR. KAISER: All right, the next question,
2 same topic, discuss the potential that the fetal
3 expression of BMP-2 could restimulate a maternal
4 immune response and cause adverse effects in the
5 mother, which was the question that Dr. Witten had
6 brought up.

7 CHAIRPERSON FINNEGAN: All right. Dr.
8 Diamond, do you have any comment on this being as you
9 are our resident immunologist?

10 DR. DIAMOND: You know, I think that I
11 don't know if that transplacental model that we heard
12 about goes in both directions and whether you can
13 actually see whether fetal protein goes into the -- I
14 mean, I think it's an interesting question. I'm more
15 concerned the other way.

16 CHAIRPERSON FINNEGAN: Okay. Dr. Miller.
17 You need a microphone.

18 DR. MILLER: There certainly are data that
19 suggests in mouse models that the decidua is they're
20 producing tremendous amounts of RNA about day seven
21 and perhaps, influencing where implantation will be
22 occurring in that process, Dr. Day out at the

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1 University of Kansas in a group. So it may not just
2 be fetal. It may be maternal reaction to generating
3 a large amount. It may not be transplacental.

4 DR. BOYAN: I guess I would be worried
5 about it going the other way. I mean, I also would be
6 in favor of worrying about unborn fetuses but there's
7 lots of us that are like already born and there is a
8 certain amount of use of BMPs in normal fracture
9 healing even in micro-fractures. I think it is
10 important to know that and since the company is more
11 than willing to investigate that and FDA is willing to
12 let it be investigated after a post-approval moment,
13 I think we should encourage them to do so and suggest
14 that study -- I have to admit this is not my field, so
15 I don't know how to suggest a study, but I'm willing
16 to put my thoughts to it.

17 CHAIRPERSON FINNEGAN: Thank you. Okay.

18 MR. KAISER: With respect to
19 tumorigenicity, we would like you to discuss the
20 potential for rhBMP-2 to stimulate growth of
21 transformed cells.

22 DR. DIAMOND: You already recommended the

1 study of primary isolates that are receptor positive
2 and receptor negative, correct?

3 CHAIRPERSON FINNEGAN: So the question is
4 do we agree with the proposed study?

5 DR. DIAMOND: I think that's a good study.

6 CHAIRPERSON FINNEGAN: Dr. Reddi, did you
7 have any comment on that?

8 DR. REDDI: No, I think I'm very -- I'm
9 not enthusiastic on wasting time on looking at
10 transformed cells. Cell lines are a dime a dozen. It
11 only enriches the contractors who do research for
12 Genetics Institute and it doesn't give any useful
13 information. I would like to see in vivo data.
14 Although Dr. Riedel has mentioned that he has done
15 some dog studies, I still would like him to keep his
16 eyes open, ears open and senses open to see if
17 anybody's talking about it and it should be brought t
18 the attention of FDA and it's the duty of every one of
19 us in this room, like Dr. Miller here, he has Dr.
20 Day's studies in Kansas City. It should be brought to
21 the attention, especially our hard working colleagues
22 in FDA.

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1 CHAIRPERSON FINNEGAN: Okay.

2 MR. KAISER: With respect to radiographic
3 effectiveness, we'd like your comment on the
4 interpretation of the radiographic findings at various
5 time points in view of the following; the presence and
6 absorption rate of the ACS, the progression of bone
7 repair and the presence or absence of rhBMP-2 and the
8 relative ability of bone formed at various time points
9 to withstand the applied loads.

10 CHAIRPERSON FINNEGAN: Well, actually, I
11 think I'm going to take this and I think that Dr.
12 Kostuik and Dr. Hanley and Dr. Lenchik probably all
13 together have told us that none of them work and it's
14 probably not worth fussing about.

15 DR. KIRKPATRICK: If I could add, John
16 Kirkpatrick, with regard to the last point that you
17 had about to withstand applied loads, I believe that
18 the loads will be shared between the graft and the
19 titanium cage. The titanium cage is more than
20 adequate to withstand the loads even after the graft
21 is formed.

22 DR. LENCHIK: Can I just make a comment?

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1 I think the way you have the questions broken down
2 don't make a lot of sense to me because we've heard
3 from the sponsor that the ACS is gone by six weeks or
4 two months and the first set of radiographic studies
5 were at six months. So I'm not really sure how we can
6 answer the first part.

7 The second part, I think, we can answer.
8 I think you can see bone ingrowth at the rate that you
9 would expect to see it. I think that has been shown
10 with both plain films and with CT. So whether they
11 included the CT in the study or not I think the
12 efficacy of the system would have still been proven.
13 The fact that they included CT is interesting. I
14 don't think it makes any difference from the
15 standpoint of patient evaluation and some people will
16 still use CT. Other people will still use plain
17 films.

18 I wouldn't regulate how you evaluate
19 radiographic fusion in the labeling of the device. So
20 I agree with everything that's been said previously.
21 I think the third question you simply can't answer
22 from any of the data that's been provided because

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1 nobody's really told us what kind of loads were
2 applied at what time points, so I'm not exactly sure
3 how to answer that third sub-question.

4 CHAIRPERSON FINNEGAN: That's a no, Dr.
5 Witten.

6 DR. WITTEN: Okay, thank you.

7 MR. KAISER: Okay, instructions for use.
8 We would like you to provide suggestions for adequate
9 instructions for use with respect to radiographic
10 interpretation and also to discuss any other specific
11 training that should be implemented with the product.

12 CHAIRPERSON FINNEGAN: Go ahead, Dr.
13 Hanley.

14 DR. HANLEY: These questions are part of
15 the normal clinical practice of medicine and are not
16 specific to any particular device. I don't see the
17 relevance for this particular issue personally.

18 CHAIRPERSON FINNEGAN: Can we address
19 packaging or not? I have some serious concerns about
20 packaging but you haven't actually asked about that
21 and I was going to try and cheat and put it under
22 instructions for use but I don't know if that will

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1 work.

2 The question has been brought up by our
3 toxicologist about the volume inside the cage,
4 basically what he's saying is the amount of medication
5 or drug that's available. You have different sizes of
6 cages, you have different sizes of sponges, you have
7 different concentrations of BMP and they're all going
8 to be packaged separately and somebody gets to figure
9 out how much of what they put in where and I have
10 serious concerns about that.

11 DR. WITTEN: And the concern is --

12 CHAIRPERSON FINNEGAN: The concern is that
13 the amount of BMP that gets to a specific disc space
14 may be inadequate, may be over adequate or may be
15 appropriate and there's no guidance to the user. It
16 would seem to me to make much more sense to package a
17 size of cage with an associated size of sponge with an
18 associated size of BMP as one package that came
19 together because then you know you've got a controlled
20 amount of everything.

21 MS. MAHER: Dr. Finnegan, can I actually
22 give a response to that? I'd also like the sponsor to

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1 help out.

2 CHAIRPERSON FINNEGAN: Sure.

3 MS. MAHER: I think by having them
4 packaged together, you would be adding a tremendous
5 extra expense to the consumers because of the
6 sterilization methods of the different products,
7 because of the different sizes and how they're going
8 to be used, but I think Medtronic Sofamor Danek can
9 better answer the question as to how it will be
10 controlled.

11 DR. BODEN: This is Scott Boden. From the
12 standpoint of an operating surgeon and in the interest
13 of patient care, the reality of it is that you need
14 the ability to mix and match cage sizes and sometimes
15 you change something. You think you're going to use
16 a certain size and while we template these patients,
17 it's hard to predict in advance what we're going to
18 actually need and sometimes you need a different cage
19 size on one side than on the other depending on the
20 shape of the spine.

21 So the practicality of having that
22 together would be difficult in terms of feasibility,

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1 in terms of what goes on in the operating room. I
2 should mention that once you've figured it out, then
3 the 15-minute wait for reconstitution. The reality of
4 it is there's only actually one concentration of
5 recombinant BMP-2 and that's 1.5 milligrams per
6 milliliter and the instructions to rehydrate the
7 lyophilized powder (ph) are effectively the same.

8 The only variable is what size the sponge
9 is and that's based on the size of the cage and the
10 little, you know, template that says how to cut it,
11 and then therefore, the volume that appropriately
12 fills up the size of the sponge, based on the sponge.
13 It is difficult, if not impossible, to -- the sponge
14 can only hold so much volume. So in terms of putting,
15 you know, large excess, full, too much on, it's
16 technically not really possible.

17 I mean, this thing ends up like a wet
18 little, sort of mushy thing, cigar, and even if you
19 went and doubled the volume you put in, it wouldn't
20 hold it. The volume that it's designed for is a
21 wetting volume that's appropriate for the sponge so
22 that when you handle it, it doesn't go squeezing out

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1 all over the place and all those have been worked out.

2 CHAIRPERSON FINNEGAN: But then what would
3 stop someone from taking, once you've squeezed it up
4 to put two of those sponges in? I mean, the cage, it
5 does really compress down and so the cage could take
6 two of them. I mean, I really don't see that you're
7 controlling dose exposure.

8 DR. BODEN: I guess it's based on
9 concentration and so if you take 1.5 milligrams per
10 milliliter and put it in half the size of the cage, it
11 will make bone in that half of the cage. And if you
12 take another sponge and put it in the other half of
13 the cage, then it would still make the bone. I guess
14 I'm not sure why a surgeon would try and use twice as
15 much of something that's been shown to work using the
16 instructions. I mean, I don't understand how this is
17 different than --

18 CHAIRPERSON FINNEGAN: You've never --

19 DR. BODEN: -- any other drug, you know,
20 where you have instructions, and you know, if you use
21 twice as much of an anti-inflammatory you might get an
22 ulcer risk. I don't know why -- if you're getting,

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1 you know, effectively a 100 percent bone induction,
2 why even would in the mind of a creative orthopedic
3 surgeon, which I'll subscribe also to that group of
4 people, it just wouldn't go through my mind to think
5 to use more of something that's not inexpensive.

6 CHAIRPERSON FINNEGAN: Any other comments?
7 Okay, next.

8 MR. KAISER: In the area of post-market
9 studies, the first question has to do with
10 reproduction and teratogenicity. FDA believes that
11 additional animal models may be useful for assessing
12 an immune response effect on fetal growth and
13 development. And we'd like your comment on the need
14 for these studies and if you believe they're
15 necessary, the type of studies to be performed and the
16 type of animal models.

17 CHAIRPERSON FINNEGAN: So comments.

18 MR. REDDI: I'm Hari Reddi. I just want
19 to echo the comments made by Dr. Betty Diamond from
20 Albert Einstein College of Medicine. I hope I'm sort
21 of giving sort of combined views, but if you have good
22 antibodies for recombinant BMP-2 that it be used to

1 study in a mouse model to see, number one, does it
2 effect after administering it, prior to implantation,
3 which is four to five days, after implantation between
4 nine days and 10 days when the first skeletal elements
5 begin to form and then again after implantation and
6 after limb bud formation, and during the joint
7 formation such as -- and also spine formation in the
8 embryo, say 16 days or 17 days to see what it does.
9 Can you agree, Dr. Diamond?

10 DR. DIAMOND: Yes.

11 CHAIRPERSON FINNEGAN: All right, that
12 sounds like that's --

13 MR. KAISER: Okay. In the area of
14 tumorigenicity, FDA and the sponsor have agreed to
15 conduct additional non-clinical studies to evaluate
16 the potential for rhBMP-2 to stimulate transformed
17 cells. We'd like your comment on the need for any
18 other non-clinical studies and if you believe they're
19 necessary, the types of studies and the appropriate
20 models.

21 CHAIRPERSON FINNEGAN: Dr. Reddi, if I
22 understand you correctly, you feel that there are some

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1 clinical studies that should be done.

2 DR. REDDI: Non-clinical studies.

3 MR. KAISER: Non-clinical.

4 DR. REDDI: Yes, I would like to -- I
5 didn't want to speak up first. I wanted somebody else
6 in the panel to -- I have very strong views, I think
7 people already know, at the risk of repeating, adding
8 these substances to 60 other transformed cell lines is
9 worthless. It should not be done. But instead I
10 recommend to these sponsors a very careful study be
11 done using again simple animal like mouse and
12 administer -- the studies about tumorigenicity is not
13 that you give one big bolus and go off to Miami for
14 vacation.

15 You've got to take these mice and you have
16 to see these mice every day. You've got to have such
17 good technicians and they should be administered the
18 dose equally distributed over about three to six
19 months. If the mouse has a longevity of two years, I
20 don't buy the study in which they say we give 1000
21 times the dose and the mouse was fine at six months.
22 That's not a useful study in cancer research.

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1 Cancer research is the dose distributed
2 over a period of time and see what happens. This
3 should be done and I strongly recommend such a non-
4 clinical study be implemented.

5 DR. DIAMOND: But I think the study that
6 you suggested -- they're really are two questions.
7 One is promoting tumor growth and one is inducing
8 tumors and the question Dr. Reddi is addressing is
9 inducing tumors.

10 Promoting tumor growth would also be an
11 unfortunate outcome. So I think, I agree that tumor
12 cell lines are not the way to go. Primary isolates
13 are and to have them identified as receptor positive
14 so because it may be that of the 71 primary isolates
15 looked at or whatever, only three were receptor
16 positive.

17 DR. BOYAN: I would agree with both of you
18 except that I'm not sure I would limit it to receptor
19 positive primary isolates because BMP induces its own
20 receptors. So it can be that you just take your best
21 and --

22 DR. DIAMOND: But identified --

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1 DR. BOYAN: The you know one way or
2 another if it was or not.

3 DR. DIAMOND: Yes, yes.

4 DR. BOYAN: And I must stress again no
5 more cell lines because we could take -- just the
6 people sitting at this table could pick one cell line
7 each and we could get the cells to proliferate or not
8 proliferate or inhibit or whatever we wanted them to
9 get depending on how confluent they were in the
10 culture, how we set up the experiment. I think an
11 animal study is the only acceptable way to go.

12 MS. MAHER: Can I just ask Genetics
13 Institute to give on one-sentence response to Dr.
14 Reddi's comments on the cell --

15 CHAIRPERSON FINNEGAN: Well, I think this
16 is basically for the panel to make its decision, so
17 you can go onto the next.

18 MR. KAISER: Okay. We'd like you to
19 comment in the use of ongoing post-market registry
20 data bases to further assess the potential for
21 congenital abnormalities and if you agree that
22 registries are recommended, discuss the types of data

1 to be captured.

2 CHAIRPERSON FINNEGAN: Any comments on
3 this?

4 DR. LARNTZ: Registries are just hard to
5 do. They're hard to follow. Hard for people to --
6 it's a serious undertaking and you have to be very
7 specific about what you want to find out. It would
8 seem like for this particular issue it's going to be
9 difficult to get enough patients to make it
10 worthwhile.

11 DR. DIAMOND: I think that's the point.
12 You won't get enough numbers to get statistical
13 significance.

14 DR. LARNTZ: But it's hard to do anyway
15 and if you're not going to get enough people, why
16 bother?

17 CHAIRPERSON FINNEGAN: Any other comments
18 around the table?

19 All right, I need the panel to listen very
20 carefully because this gets really complicated. Do I
21 want to ask her if we've adequately answered the
22 questions? I don't think she wants to hear us any

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1 more.

2 DR. WITTEN: Yes.

3 CHAIRPERSON FINNEGAN: Dr. Witten, have we
4 adequately answered the questions?

5 DR. WITTEN: Yes, thank you.

6 CHAIRPERSON FINNEGAN: All right, we are
7 now going to move to a vote. For the panel, your
8 instructions; the options are that we do not approve
9 the PMA. Second option is that we approve with
10 conditions and the third option is that we approve
11 with no conditions. The first and the third are
12 obvious. The second one for each condition, we have
13 to vote, so this is -- it's actually -- if you've been
14 here before, this is a very good way to deal with this
15 -- if this is the way we go, a good way to deal with
16 the conditions, but you have to be patient and you
17 have to understand that for each new condition, we
18 have to have another vote.

19 So I would ask Dr. Kirkpatrick, who is the
20 panel's clinical reviewer for this, if he would like
21 to make a motion.

22 DR. KIRKPATRICK: I'd like to move that

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1 it's approvable with conditions.

2 CHAIRPERSON FINNEGAN: All right, we will
3 go around the table and see if that is comfortable
4 with people and if it is, that's fine. If not, if you
5 could give your reasons. Dr. Li.

6 DR. LARNTZ: He needs a second for that
7 before we --

8 CHAIRPERSON FINNEGAN: He needs a second,
9 all right.

10 DR. LARNTZ: I second it.

11 CHAIRPERSON FINNEGAN: All right. Dr. Li?

12 DR. LI: I concur.

13 CHAIRPERSON FINNEGAN: Dr. Doull?

14 DR. DOULL: I concur.

15 CHAIRPERSON FINNEGAN: Dr. Diamond?

16 DR. DIAMOND: Also.

17 CHAIRPERSON FINNEGAN: Dr. Hanley?

18 DR. HANLEY: Non-voting.

19 CHAIRPERSON FINNEGAN: Oh, he's -- you're
20 not voting. Dr. Siegal?

21 DR. SIEGAL: I concur.

22 CHAIRPERSON FINNEGAN: I concur -- I don't

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1 vote. Dr. Naidu?

2 DR. NAIDU: I concur.

3 CHAIRPERSON FINNEGAN: Dr. Boyan?

4 DR. BOYAN: And are we actually voting
5 here because I would have wanted to vote for no
6 conditions.

7 CHAIRPERSON FINNEGAN: You're allowed to
8 say that you would like to vote against this and vote
9 for no conditions.

10 DR. BOYAN: Well, I don't want to not vote
11 for approval. Let me just give this a thought a
12 second.

13 CHAIRPERSON FINNEGAN: All right, let me
14 go around you and come back. Dr. Reddi?

15 DR. REDDI: Yeah, I would like to proceed
16 with the rest of the group.

17 CHAIRPERSON FINNEGAN: All right, Dr.
18 Lenchik?

19 DR. LENCHIK: Concur.

20 CHAIRPERSON FINNEGAN: Dr. Larntz.

21 DR. LARNTZ: I concur.

22 CHAIRPERSON FINNEGAN: Dr. Boyan?

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1 DR. BOYAN: Oh, yeah, the crowd is for
2 this. I'm going with approvable with conditions.

3 CHAIRPERSON FINNEGAN: Thank you. All
4 right, we have approvable with conditions. Dr.
5 Kirkpatrick, would you like to add conditions or would
6 you like others to add conditions?

7 DR. KIRKPATRICK: Can I defer and then
8 come back?

9 CHAIRPERSON FINNEGAN: You can defer. Dr.
10 Diamond, would you like to add a condition?

11 DR. DIAMOND: I would like to add the
12 condition that there be some testing of the effect of
13 anti-BMP-2 antibodies on all stages from implantation
14 to birth in a rodent model for fetal development.

15 CHAIRPERSON FINNEGAN: All right, so your
16 condition is that there be further studies on the
17 reproduction teratogenicity and you're comfortable
18 with the studies that were proposed?

19 DR. KIRKPATRICK: Dr. Finnegan, if I may.

20 CHAIRPERSON FINNEGAN: You may.

21 DR. KIRKPATRICK: We've already passed
22 notes on exactly how to word the condition.

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1 CHAIRPERSON FINNEGAN: Go for it.

2 DR. KIRKPATRICK: Assess the potential for
3 BMP-2 to promote growth of primary tumor isolates
4 which have been analyzed for BMP-2 reception
5 expression.

6 CHAIRPERSON FINNEGAN: Okay.

7 DR. DIAMOND: That's a different one.

8 DR. KIRKPATRICK: Sorry, that was a
9 different one. I missed the first one.

10 CHAIRPERSON FINNEGAN: All right, would
11 you like to reword the first one?

12 DR. DIAMOND: Okay, to assess the
13 potential for anti-BMP-2 antibodies to cause
14 reproductive problems with -- problems with
15 implantation or fetal development.

16 CHAIRPERSON FINNEGAN: All right.

17 DR. KIRKPATRICK: I'm sorry, I read the
18 wrong line. Can I make sure we've got it the way we
19 want it?

20 CHAIRPERSON FINNEGAN: Okay.

21 DR. KIRKPATRICK: Study anti-rhBMP-2 in
22 systemic administration mouse model for antibodies at

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1 conception, implantation and limb bud formation time
2 points.

3 DR. DIAMOND: That's fine.

4 CHAIRPERSON FINNEGAN: All right. Do we
5 have a second for that condition?

6 A VOICE: I second it.

7 CHAIRPERSON FINNEGAN: All right, Dr. Li?

8 DR. LI: Concur.

9 CHAIRPERSON FINNEGAN: Dr. Doull?

10 DR. DOULL: Yeah, I like that.

11 CHAIRPERSON FINNEGAN: Dr. Diamond, you'd
12 better like it. Dr. Siegal?

13 DR. SIEGAL: I concur.

14 CHAIRPERSON FINNEGAN: Dr. Kirkpatrick?

15 DR. KIRKPATRICK: I agree.

16 CHAIRPERSON FINNEGAN: Dr. Naidu?

17 DR. NAIDU: Concur.

18 CHAIRPERSON FINNEGAN: Dr. Boyan?

19 DR. BOYAN: I concur.

20 CHAIRPERSON FINNEGAN: Dr. Reddi?

21 DR. REDDI: I concur.

22 CHAIRPERSON FINNEGAN: Dr. Lenchik?

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1 DR. LENCHIK: Concur.

2 CHAIRPERSON FINNEGAN: Dr. Larntz?

3 DR. LARNTZ: Concur.

4 CHAIRPERSON FINNEGAN: All right. Next
5 condition, Dr. Kirkpatrick.

6 DR. KIRKPATRICK: I believe it was Dr.
7 Reddi's condition. Study the mouse model with equal
8 dosing and multiple dosing over long periods of time
9 to compliment the large dose at a single time data.
10 Is that correct, Dr Reddi?

11 DR. REDDI: Yes.

12 CHAIRPERSON FINNEGAN: Do I have a
13 seconder for that, Dr. Reddi?

14 DR. REDDI: I would second it.

15 CHAIRPERSON FINNEGAN: All right.

16 DR. KIRKPATRICK: He can't move and second
17 the same thing so I'll second it for him.

18 CHAIRPERSON FINNEGAN: All right. Dr. Li?

19 DR. LI: Concur.

20 CHAIRPERSON FINNEGAN: Dr. Doull?

21 DR. DOULL: Could you read it again? I
22 want to hear that again.

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1 DR. KIRKPATRICK: Study the mouse model
2 with equal dosing of the rhBMP-2 and multiple dosing
3 over a long period of time to compliment the data
4 we've already heard which was single large dose at a
5 single time.

6 DR. DOULL: Yeah, I agree.

7 CHAIRPERSON FINNEGAN: Dr. Diamond?

8 DR. DIAMOND: Yes.

9 CHAIRPERSON FINNEGAN: Dr. Siegal?

10 DR. SIEGAL: Yes.

11 CHAIRPERSON FINNEGAN: Dr. Kirkpatrick,
12 you already seconded it. Dr. Naidu?

13 DR. NAIDU: I concur.

14 CHAIRPERSON FINNEGAN: Dr. Boyan?

15 DR. BOYAN: I concur.

16 CHAIRPERSON FINNEGAN: Dr. Lenchik?

17 DR. LENCHIK: Concur.

18 CHAIRPERSON FINNEGAN: Dr. Larntz?

19 DR. LARNTZ: Concur.

20 CHAIRPERSON FINNEGAN: All right. Dr.
21 Doull, did you want to make a condition on toxicity?

22 DR. DOULL: No, I think that issue has

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1 been covered by that condition. The question is
2 whether the previous chronic studies they've done were
3 adequate to indicate reasonable assurance of safety
4 and I think this study clearly would strengthen that
5 position a lot.

6 CHAIRPERSON FINNEGAN: And Dr. Siegal, do
7 you have any conditions on pathology?

8 DR. SIEGAL: I do not except to say as a
9 friendly suggestion that those studies be done with
10 the use of a pathologist who has expertise in those
11 areas, especially a perinatal pathologist with those
12 embryo/fetal studies.

13 DR. LIPSCOMB: Dr. Finnegan, can I just
14 ask one point of clarification? Are these post-
15 approval recommendations or are these -- I mean,
16 what's the --

17 CHAIRPERSON FINNEGAN: These are the
18 conditions attached to the approval.

19 DR. LIPSCOMB: I know, but are they post-
20 approval conditions, post-PMA approval conditions?

21 CHAIRPERSON FINNEGAN: I think we give the
22 FDA the freedom -- they're post-approval, right.

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1 DR. WITTEN: I'm assuming you're
2 recommending them from the way they've been worded as
3 post-approval.

4 DR. KIRKPATRICK: It was my understanding
5 that these would be -- you would have the approval and
6 then these studies would be required of you after the
7 approval.

8 DR. LIPSCOMB: I just wanted
9 clarification.

10 CHAIRPERSON FINNEGAN: All right, Dr.
11 Naidu, did you have any conditions that you were
12 concerned about?

13 DR. NAIDU: No, I just have a quick
14 question. This is strictly for single level fusion,
15 am I correct? I just want to clarify that.

16 CHAIRPERSON FINNEGAN: That's being done.
17 Dr. Boyan?

18 DR. BOYAN: I have nothing further.

19 CHAIRPERSON FINNEGAN: Dr. Lenchik, any --
20 Dr. Larntz?

21 DR. LARNTZ: I have nothing further.

22 CHAIRPERSON FINNEGAN: All right, Dr.

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1 Kirkpatrick, your next one?

2 DR. KIRKPATRICK: Yeah, I'd like to
3 propose two conditions that would be regarding -- one
4 is regarding the labeling and one is regarding the
5 packaging. One is that the labeling be specific for
6 the anterior approach and I guess it's in there
7 already as I understand it and a single level is in
8 there, as I recall.

9 I would like to restrict it to only
10 tapered cages and I believe that that will prevent a
11 majority of surgeons from applying this from a
12 posterior lumbar interbody fusion perspective and
13 therefore getting in the canal bone formation. Not
14 many of us would try and put in a tapered cage from
15 the back and give induced lordosis, so I would trust
16 that judgment of surgeons would prevent that because
17 that is a concern that I have. And I think if we
18 restrict it to the tapered cage, we'll solve that, so
19 we'll leave it at that specific thing and then I have
20 another one after that.

21 DR. WITTEN: Can I just point out the
22 device is a three-component device that includes a

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1 lumbar tapered cage.

2 CHAIRPERSON FINNEGAN: But it's the
3 tapered cage that is his concern.

4 DR. KIRKPATRICK: I'm making sure it's a
5 tapered cage.

6 DR. WITTEN: That's a component of the
7 product.

8 CHAIRPERSON FINNEGAN: So that's
9 officially in the title and does not need to be a
10 condition?

11 DR. WITTEN: Well, it's officially -- that
12 is the description of the product that's under
13 consideration.

14 CHAIRPERSON FINNEGAN: Will it upset
15 anybody if --

16 DR. WITTEN: No, you can put it in.

17 CHAIRPERSON FINNEGAN: All right, okay.
18 Do I have a seconder for that?

19 DR. SIEGAL: I'll second it.

20 CHAIRPERSON FINNEGAN: Thank you. Dr. Li?

21 DR. LI: I'll just raise this issue even
22 though I know the rest of the panel members may

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1 disagree, but with all due respect to Dr. Larntz, the
2 idea of not doing a registry because it's difficult in
3 this case is a little peculiar to me. I understand
4 the difficulties of that but the alternative right now
5 is to do a mouse study, which I agree with, but at the
6 end of that mouse study, even if it turns out to be an
7 immune response it's going to be, well, that was a
8 mouse, will it happen in a human.

9 So I think if you don't do some kind of
10 registry, if you don't look for sure you're not going
11 to find anything. And if you have some sort of
12 registry where you make an honest attempt to look for
13 a certain set of conditions and the immunologist and
14 biologist could probably set the type of things to
15 look for, I don't really understand how you could not
16 do it in this case where you have a small potential
17 for not a very good effect.

18 CHAIRPERSON FINNEGAN: Why don't -- I'm
19 going to ask you to make that as a condition but we'll
20 vote on this condition about the tapered cage first.

21 DR. LI: Sorry.

22 CHAIRPERSON FINNEGAN: No, perfect. I'm

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1 glad you brought that up.

2 DR. LI: So do you want me to make that a
3 condition?

4 CHAIRPERSON FINNEGAN: Isolated to the
5 tapered cage.

6 DR. LI: Well, for the device that's
7 described in the application, I would like a post-
8 market surveillance registry of -- I guess you want a
9 definition of what the registries would include; is
10 that correct, or what you should look for?

11 CHAIRPERSON FINNEGAN: I'm going to come
12 back to you on that.

13 DR. WITTEN: Right now, Dr. Finnegan is
14 asking for --

15 CHAIRPERSON FINNEGAN: A vote on the
16 condition.

17 DR. WITTEN: -- a vote on the condition --

18 CHAIRPERSON FINNEGAN: -- of only using
19 the tapered cage.

20 DR. LI: Oh, well, fine.

21 CHAIRPERSON FINNEGAN: I need a yes, is
22 what I need.

1 DR. LI: Yes.

2 CHAIRPERSON FINNEGAN: Thank you.

3 DR. LI: Yes, sorry, I got all excited.

4 CHAIRPERSON FINNEGAN: Dr. Doull?

5 DR. DOULL: Yeah, does that include
6 information on the dose?

7 CHAIRPERSON FINNEGAN: No, no. That's
8 just trying to keep it out of there.

9 DR. DOULL: I agree.

10 CHAIRPERSON FINNEGAN: Dr. Diamond?

11 DR. DIAMOND: That's fine.

12 CHAIRPERSON FINNEGAN: Dr. Siegal?

13 DR. SIEGAL: Yes.

14 DR. DOULL: Dr. Naidu?

15 DR. NAIDU: Yes, I concur.

16 CHAIRPERSON FINNEGAN: Dr. Boyan?

17 DR. BOYAN: Yes.

18 CHAIRPERSON FINNEGAN: Dr. Reddi?

19 DR. REDDI: I concur.

20 CHAIRPERSON FINNEGAN: Dr. Lenchik?

21 DR. LENCHIK: Yes.

22 CHAIRPERSON FINNEGAN: Dr. Larntz?

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1 DR. LARNTZ: Yes.

2 CHAIRPERSON FINNEGAN: Okay. Now, Dr. Li,
3 your condition?

4 DR. LI: My suggested condition is that
5 the sponsor does conduct a post-market surveillance by
6 way of a registry and I'll let, perhaps, some
7 biological colleagues determine what they should look
8 for in that registry.

9 CHAIRPERSON FINNEGAN: All right.

10 DR. SIEGAL: Can I ask just a point of
11 information?

12 CHAIRPERSON FINNEGAN: Yes.

13 DR. SIEGAL: Isn't there going to be a
14 required adverse reporting to the FDA anyway?

15 CHAIRPERSON FINNEGAN: Do you want to
16 touch that with a 10-foot pole, Dr. Witten or --

17 DR. WITTEN: Sorry, I missed the context
18 but the question was is adverse event required?

19 CHAIRPERSON FINNEGAN: Reporting to the
20 FDA.

21 DR. WITTEN: Adverse event reporting for -
22 - is required and it will happen for things that are

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1 recognized to be related to the product.

2 CHAIRPERSON FINNEGAN: Problem but not --
3 yeah, but not -- yes, Dr. Li.

4 DR. LI: Yeah, can I comment on that? I
5 guess in total hips and total knees which is subject
6 to the same adverse reporting schedule, it's estimated
7 that somewhere only about one or two percent of actual
8 adverse events actually get reported in that system.
9 So my own experience is in the absence of a separate
10 pre-determined mandated sort of post-market
11 surveillance, it isn't going to happen.

12 DR. LARNTZ: Can I ask a question?

13 CHAIRPERSON FINNEGAN: Do I have a -- go
14 ahead.

15 DR. LARNTZ: No, the question is you're
16 talking about a registry of all patients? I wasn't
17 clear on that before. Is it an all patient registry?

18 DR. LI: That's a good question. I guess
19 in the context of our discussion today, it would
20 obviously be a registry that would at least be of --
21 minimally would be of women of child bearing ages.

22 CHAIRPERSON FINNEGAN: Do I have -- go

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1 ahead.

2 DR. KIRKPATRICK: I have just a question
3 about kind of thing we're asking them to do. Are we
4 basically asking them as the sponsor to maintain sales
5 records on who gets the implant because they are not
6 going to be responsible for following up those
7 patients once they've had the implant.

8 DR. WITTEN: Well, they're not
9 responsible, no, for following up patients who've got
10 an implant that's commercially distributed, no. To do
11 a registry you'd -- it's similar to doing a study.
12 They'd have to design it and describe how they would
13 be recruiting patients and what kind of data they
14 would be collecting. I mean, that's the kind of thing
15 we'd want recommendations from you all on.

16 CHAIRPERSON FINNEGAN: How long would you
17 like them to do this registry?

18 DR. LI: I guess the biologist and
19 radiologist would have to tell me what a reasonable
20 time course would be.

21 MS. MAHER: Can I make a comment? I think
22 that we need to be careful and I know you haven't

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1 gotten a second yet, so I'm going to throw my two
2 cents in a little early. But if you're going to -- I
3 mean, I saw the numbers they threw up there. I'm not
4 sure that a registry would capture any information but
5 it would be very expensive for the company to maintain
6 and I think as a panel we need to be very careful not
7 to throw cost, which ultimately goes down to the
8 consumer, there's no way around it, the consumers bear
9 the cost in the long run, that aren't going to provide
10 any relevant information at all. So I just would like
11 you all to think about that as you're deciding whether
12 to second it.

13 CHAIRPERSON FINNEGAN: But with
14 information systems on the internet that's available
15 now, the registry may not be as difficult as it was
16 say five or 10 years ago.

17 DR. LARNTZ: I would disagree totally.
18 It's very difficult to do a registry, do it right. So
19 many registries are so sloppily done and then you get
20 our garbage at the end and someone says, "Nothing
21 happened" but there wasn't good enough -- it's very
22 difficult to do. It's important to do it right and I

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1 just have to say a registry is a study. Dr. Witten
2 said that and she's right, it's a study, so we're
3 requiring another study to be done. It's a serious
4 effort. It requires serious work.

5 I don't -- I like registries if they can
6 be done well, but I see too many that are done so
7 poorly and then the information misused out of them,
8 that that's my concern.

9 DR. BOYAN: I actually -- I mean, we
10 haven't had too much discussion after any of these
11 conditions and it hasn't been good. This is good that
12 we're having this. I would like to go ahead and
13 second it so we can vote it down or just -- or agree
14 not to do it. And I really would -- while I
15 appreciate your reasons for doing it, Steve, I have to
16 say that I think it's something that is -- we're going
17 to get the answer we want from the mouse study.

18 If something comes out of the mouse study
19 -- this company has distinguished itself by being
20 willing to get a tremendous amount of science done
21 before they've come forward with the product. I don't
22 think that we would run in -- I don't foresee a

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1 problem developing. If the data should come out from
2 the mice in an unfortunate way, I think that the rest
3 will follow naturally.

4 DR. LI: Are you comfortable then that
5 just as a follow-up question, if you do the mouse
6 study, and it turns out there's no negative effects of
7 the BMP-2, then you would be comfortable that we will
8 never see an effect in humans?

9 DR. DIAMOND: I think the issue is that it
10 will take more than five years, more than 10 years
11 with the kinds of numbers of patients to be able to
12 see what are generally small -- I mean, they can be
13 two-fold increments, but you still need to look at
14 thousands and thousands to see. And so I think the
15 problem is that it's very costly and very difficult to
16 keep the effort going over that time frame and the
17 chance of actually reaching numbers where you can say
18 with confidence it's not teratogenic is vanishingly
19 small. I think that's the issue.

20 DR. LI: Well, and again, I just throw
21 this out, number one, so we could have the
22 conversation and if you want to vote it down --

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1 CHAIRPERSON FINNEGAN: It's on the record.

2 DR. LI: Okay, and that's fine. I guess
3 my only negative on this product is this potential
4 problem for which we actually have no evidence for.
5 Right? And I'm just not completely comfortable that
6 the only way we're going to answer that is with a
7 bunch of mice.

8 CHAIRPERSON FINNEGAN: All right, Dr.
9 Kirkpatrick, your next condition.

10 DR. KIRKPATRICK: Actually, it's not my
11 next condition. I just want to amend a condition that
12 we've already talked about because Dr. Reddi provided
13 me with specifics on the studying of the mouse model
14 with equal dosing and multiple over a long period of
15 time. He suggests monthly over a one-year period and
16 since we're going to add that, I need to make sure
17 that everybody agrees with that.

18 CHAIRPERSON FINNEGAN: Well, we don't want
19 to tell them how to do their study, do we?

20 DR. KIRKPATRICK: Or we can delete it,
21 yeah. I'm just saying he provided me with this extra
22 information. Okay.

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1 CHAIRPERSON FINNEGAN: I don't think we
2 want to tell them how to do their study.

3 DR. LI: Madam Chairman, I think Dr. Boyan
4 actually seconded my condition. If nobody else wants
5 to vote on it, that's okay, but --

6 DR. BOYAN: I only seconded it in the
7 event that we were going vote for it and then I was
8 going to suggest in my seconding that we vote
9 negatively, but --

10 DR. LI: That's okay, that's okay.

11 DR. BOYAN: But if there's no second, we
12 don't have to vote.

13 DR. LI: That's okay, I just want you to
14 put me away on this one. That's okay.

15 DR. BOYAN: Great.

16 CHAIRPERSON FINNEGAN: Are you formally
17 seconding --

18 DR. BOYAN: No, no, if there's no other
19 second, then we don't have to worry about it.

20 DR. DIAMOND: Can I ask, did we actually
21 vote on assessing the potential for promoting tumor
22 growth?

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1 CHAIRPERSON FINNEGAN: We did, yes. All
2 right, Dr. Kirkpatrick, your next one.

3 DR. KIRKPATRICK: Okay, I do have another
4 condition which in all due deference to inventory
5 issues and the difficulty that will require my implant
6 supplier to come into the operating room with an
7 entire tote full of product, I would like to propose
8 the condition that the cage and the infused must be
9 packaged together.

10 CHAIRPERSON FINNEGAN: Do I have a
11 seconder for that? Am I allowed to second?

12 A VOICE: No.

13 CHAIRPERSON FINNEGAN: Okay, do I have a
14 seconder for that?

15 DR. DIAMOND: Well, I'll second so there
16 can be discussion but I don't --

17 CHAIRPERSON FINNEGAN: All right.
18 Comments?

19 DR. KIRKPATRICK: Would you like me to --

20 CHAIRPERSON FINNEGAN: Go ahead.

21 DR. KIRKPATRICK: In order to give a
22 rationale to this, we've already heard several

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1 instances that surgeons will vary from the indications
2 on the package insert. In addition, we have heard the
3 vice president of the company indicate not directly
4 but between the lines that while he would not
5 encourage off-label use of the InFUSE™ by itself, it
6 sounds like he would welcome its use because it would
7 be an issue where people would be able to use the
8 InFUSE™ without the cage. I'm not sure that they
9 would be adequately policing that.

10 MS. MAHER: I never heard them say that,
11 sir.

12 DR. KIRKPATRICK: Between the lines he
13 mentioned that they would be packaged separately as
14 separate components and we'd have to match them in the
15 operating room. We'd have to match our cage with the
16 appropriate dose. What I am suggesting is, is that if
17 they know the dose for each cage that's right, they
18 can package the two together and that way we don't
19 have the burden in the operating room of saying, "I
20 need a 14 millimeter by 20 cage, what dose do I need
21 to apply to it".

22 If it's already pre-determined and pre-

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1 packaged that way, we don't have that problem. You
2 also will stop the problem of a surgeon taking just
3 the InFUSE™ without the cage and applying it in an
4 off-label use if that is a concern at this time.

5 DR. BOYAN: May I comment on that?

6 CHAIRPERSON FINNEGAN: Uh-huh.

7 DR. BOYAN: I would like to see us not do
8 that for another reason and that's because things
9 happen and as a consumer myself, I'm thinking right
10 now but things do happen in the operating room and
11 there is a change in the cage size, a dropping on the
12 floor of the sponge. I think it's important that the
13 surgeon have the opportunity to buy the sponge with
14 the BMP as a separate entity just because of the sheer
15 -- the complexities of this, the end stage
16 sterilizing.

17 I was very much taken with the fact that
18 they explained how they decided to prepare the BMP
19 under sterile conditions rather than ethylene oxide.
20 That's very important to me as a biologist and it
21 means that they're able to use a lower dose of BMP
22 than they would have had to have done if they

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1 sterilized it another way and these are large doses
2 but they're not as large as they could be if they had
3 to start off with the ethylene oxide sterilizing.

4 So there are some really compelling
5 reasons for me that they be able to package them
6 separately and --

7 CHAIRPERSON FINNEGAN: But they can
8 actually sterilize them differently and package them
9 together.

10 DR. BOYAN: Well, okay, I'll just go on
11 record as saying that it would be my intent to vote
12 against that.

13 CHAIRPERSON FINNEGAN: How do you address
14 the volume concern, then?

15 DR. BOYAN: How do I address it?

16 CHAIRPERSON FINNEGAN: Yeah, I mean --

17 DR. BOYAN: Well, I --

18 CHAIRPERSON FINNEGAN: -- as a scientist
19 how would you address the fact you don't know what
20 concentration you're getting to --

21 DR. BOYAN: Well, you would. I mean, I
22 just can't believe that the surgeons are not -- and

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1 their staff are not intelligent enough to say, "I have
2 a cage from column A and I'm going to match it with a
3 package from column B that is B_A. I think they can do
4 that, but I also think there is times when they have
5 to make decisions and sometimes those -- they need the
6 flexibility of that decision.

7 Now, I agree with you, there is a
8 potential for off-label use and I've already been
9 sitting over here thinking of the 15 ways I would do
10 it if I had the opportunity, you know, once that went
11 into my brain, but I also think that there's
12 consequences for making those decisions and they know
13 what they are. And we have to trust that they would
14 use their brain activity.

15 MS. MAHER: You also have to consider that
16 if you package them together if something falls on the
17 floor and it becomes contaminated, you're going to
18 open up a whole new package which is -- from an
19 industry standpoint, that's another sale, but I don't
20 think that the hospitals are going to be particularly
21 happy with that. Or if you open them up and say, "Oh,
22 damn, I need another size", it's going to mean that

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1 you go back and you have to open everything up again
2 as opposed to one at a time. So I think that's
3 another problem.

4 DR. KIRKPATRICK: With regard to the
5 second issue about sizing, do we not use a size before
6 we open the implant? In other words, are we not doing
7 a specific tapered reaming and a specific tapping for
8 this implant? I haven't reviewed the specifics of the
9 implantation protocol, but I believe that you do size
10 it before you open the implant.

11 DR. MATHEWS: Hal Mathews. In general,
12 you're correct. However, there are times when the
13 position of the cage for some reason isn't optimal,
14 the anatomy of the approach isn't optimal and for some
15 reason the cage will tend to migrate towards one side
16 of the intervertebral space. That migration may cause
17 the need to up-size the cage after you've already
18 opened the cage. And that up-sizing would then
19 generate a whole another second BMP being brought onto
20 the table that wouldn't have had to happen if you
21 could do it individually with cage sizing and then
22 once you determine the appropriate cage size, then

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1 actually getting the BMP and putting it in
2 secondarily.

3 DR. KIRKPATRICK: Can you provide me with
4 an incidence of when that happens or how often that
5 would happen because I can provide you with the
6 relative incidence of dropping things in our ORs being
7 very low fortunately.

8 DR. MATHEWS: Well, I would love to know
9 that incidence historically in the study. I can tell
10 you that it happened to me. I was not able to use a
11 double-barrel cage insertion device which for the
12 panel members is a device that actually lets you come
13 down on the spine and actually have the channels for
14 the reaming already established. We had to use what's
15 called a free-hand technique which, in my hands, being
16 somewhat more experienced than others, it did not
17 allow for that cage size to go in and I had to up-size
18 the cage on the table.

19 Now, I've never dropped one on the floor,
20 I can give you that, but I've had to up-size a cage.

21 DR. KIRKPATRICK: And you had that cage
22 open before you recognized that?

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1 DR. MATHEWS: I had that cage open, saw
2 the migration in the insertional process and had to
3 make an adjustment during surgery.

4 DR. KIRKPATRICK: And roughly how many of
5 the cases were in your hands?

6 DR. MATHEWS: There were 13 of the
7 investigational patients in my hands.

8 DR. KIRKPATRICK: So we're talking less
9 than 10 percent at least.

10 DR. MATHEWS: That happened in my hands.

11 DR. KIRKPATRICK: Yeah, but less than 10
12 percent.

13 DR. MATHEWS: That is the math, correct.

14 DR. KIRKPATRICK: Okay.

15 DR. NAIDU: Can I just make a comment?
16 You know, I don't think that packaging together is
17 going to discourage off-label use because, you know,
18 if the guy wants to use the BMP off-label, he's going
19 to use it anyway. For example, in fact, it could turn
20 out to be a more expensive proposition because if you
21 look at the small finger joints that we use nowadays,
22 they package it with titanium grommets which they

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1 double the price of the implants. And a lot of us
2 don't even use the grommets and we throw them out.

3 We just put in the implants for finger
4 joints. I mean, you know, the lower end on the totem
5 pole, but still the suggestion that the guy's not
6 going to use that BMP off-label by packaging them
7 together is probably not a good, you know, issue to
8 package them together.

9 CHAIRPERSON FINNEGAN: Actually do we have
10 a second for this before we go any farther.

11 DR. DIAMOND: Yes, I believe I seconded
12 it.

13 CHAIRPERSON FINNEGAN: Oh, you seconded
14 it, okay. Yes, Dr. Witten?

15 DR. WITTEN: Yeah, I just want to make one
16 comment because people keep mentioning off-label use
17 which is we're really asking you to focus your
18 discussion on this product and its safety and
19 effectiveness as the label indication --

20 CHAIRPERSON FINNEGAN: Okay.

21 DR. WITTEN: -- and not, you know,
22 speculate on what other uses might not be safe of, you

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1 know, a portion of the product or some other product.

2 CHAIRPERSON FINNEGAN: All right, we will
3 do a vote on the packaging. Dr. Li? Sir.

4 DR. TREHARNE: May I make one point?

5 CHAIRPERSON FINNEGAN: I guess, yeah.

6 DR. TREHARNE: My name is Rick Treharne.
7 I'm with the sponsor and I just want to remind the
8 panel that this cage is already commercially
9 available. It's already in hundreds of hospitals
10 around the country and if this is packaged together
11 then people who have those cages would not be able to
12 use those. They'd have to throw them away and buy a
13 new one, so it's just not practical. There's a lot of
14 other -- a number of other reasons why this can't be
15 done, different shelf lives. They have different
16 methods of sterilization and it's just not a practical
17 thing to do. I just wanted to add that.

18 CHAIRPERSON FINNEGAN: Okay. Dr. Li?

19 DR. LI: No.

20 CHAIRPERSON FINNEGAN: Dr. Doull?

21 DR. DOULL: I guess I could support the
22 idea of a recommendation but conditions are mandates

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1 and I don't -- would not approve of a mandate.

2 CHAIRPERSON FINNEGAN: Okay. Dr. Siegal?

3 DR. SIEGAL: No.

4 CHAIRPERSON FINNEGAN: Dr. Naidu?

5 DR. NAIDU: I disagree.

6 CHAIRPERSON FINNEGAN: Dr. Boyan?

7 DR. BOYAN: No.

8 CHAIRPERSON FINNEGAN: Dr. Reddi?

9 DR. REDDI: This is to package --

10 CHAIRPERSON FINNEGAN: Package, yes.

11 DR. REDDI: -- in one single package?

12 CHAIRPERSON FINNEGAN: Yes.

13 DR. REDDI: I disagree with that.

14 CHAIRPERSON FINNEGAN: All right, Dr.

15 Lenchik?

16 DR. LENCHIK: No.

17 CHAIRPERSON FINNEGAN: Dr. Larntz?

18 DR. LARNTZ: No.

19 CHAIRPERSON FINNEGAN: All right, so are

20 there any other conditions to attach that the panel

21 wishes to attach to this? If not, we'll do our final

22 vote which will be approvable with the listed

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1 conditions and I'll ask Dr. Kirkpatrick to list the
2 conditions.

3 DR. KIRKPATRICK: Summarizing the approved
4 conditions, number one was study anti-rhBMP-2 in
5 systemic administration mouse model for antibodies at
6 conception, implantation and limb bud formation time
7 points. This was approved as a post-approval study.
8 The next was study mouse model with equal dosing and
9 multiple dosing of rhBMP-2 over long time to
10 compliment the large dose at a single time, also
11 approved as a post-approval study.

12 Assess the potential of BMP-2 to promote
13 growth of primary tumor isolates which have been
14 analyzed for BMP-2 receptor expression, also a post-
15 approval study. And tapered cages only was the other
16 condition. The other two that were brought up were
17 not approved.

18 CHAIRPERSON FINNEGAN: All right, so Dr.
19 Li, we are voting on whether we approve with
20 conditions and with all of the conditions that were
21 just listed.

22 DR. LI: I vote to approve the device with

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1 all the conditions just listed.

2 CHAIRPERSON FINNEGAN: Dr. Doull?

3 DR. DOULL: That's three conditions.

4 CHAIRPERSON FINNEGAN: Three conditions.

5 Four.

6 DR. KIRKPATRICK: Three studies and one
7 tapered.

8 CHAIRPERSON FINNEGAN: You're still a yes?

9 DR. DOULL: Yes.

10 CHAIRPERSON FINNEGAN: Dr. Diamond?

11 DR. DIAMOND: Yes.

12 CHAIRPERSON FINNEGAN: Dr. Siegal?

13 DR. SIEGAL: Yes.

14 CHAIRPERSON FINNEGAN: Dr. Kirkpatrick?

15 DR. KIRKPATRICK: Yes.

16 CHAIRPERSON FINNEGAN: Dr. Naidu?

17 DR. NAIDU: Yes.

18 CHAIRPERSON FINNEGAN: Dr. Boyan?

19 DR. BOYAN: Yes.

20 CHAIRPERSON FINNEGAN: Dr. Reddi?

21 DR. REDDI: Yes.

22 CHAIRPERSON FINNEGAN: Dr. Lenchik?

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1 DR. LENCHIK: Yes.

2 CHAIRPERSON FINNEGAN: Dr. Larntz?

3 DR. LARNTZ: Yes.

4 CHAIRPERSON FINNEGAN: Dr. Witten, are you
5 happy?

6 DR. WITTEN: I'm happy. I think, does the
7 panel need to go around and state their reasons? Yes,
8 I'm happy except you still have that one last step to
9 do.

10 CHAIRPERSON FINNEGAN: State our reasons
11 for --

12 DR. WITTEN: State your reasons for your
13 vote. Is that right?

14 CHAIRPERSON FINNEGAN: We haven't spent
15 like the last eight hours talking about the reasons
16 for our vote?

17 DR. WITTEN: You -- well, yes, you have
18 and if someone summarizes them, other people can --
19 you know, don't have to repeat the same reasons. I
20 mean, you can --

21 DR. LI: I'll start if you want.

22 CHAIRPERSON FINNEGAN: Okay, go ahead.

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1 DR. LI: I voted for approval because a
2 method criteria for safety and effectiveness for this
3 device.

4 CHAIRPERSON FINNEGAN: And the conditions?

5 DR. LI: And the conditions are
6 appropriate to make the device safe and effective.

7 CHAIRPERSON FINNEGAN: All right. Dr.
8 Lenchik, if you agree, we can just agree.

9 DR. LENCHIK: Agreed.

10 CHAIRPERSON FINNEGAN: Dr. Reddi?

11 DR. REDDI: I agree.

12 CHAIRPERSON FINNEGAN: Dr. Boyan?

13 DR. BOYAN: I agree.

14 CHAIRPERSON FINNEGAN: Dr. Naidu?

15 DR. NAIDU: I agree.

16 CHAIRPERSON FINNEGAN: Dr. Kirkpatrick?

17 DR. KIRKPATRICK: I agree.

18 CHAIRPERSON FINNEGAN: Dr. Siegal?

19 DR. SIEGAL: I agree.

20 CHAIRPERSON FINNEGAN: Dr. Diamond?

21 DR. DIAMOND: I agree.

22 CHAIRPERSON FINNEGAN: Dr. Doull?

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1 DR. DOULL: I agree.

2 CHAIRPERSON FINNEGAN: Dr. Li.

3 DR. LI: I agree.

4 CHAIRPERSON FINNEGAN: Dr. Witten?

5 DR. WITTEN: And I thank you. I thank all
6 the panel members here, the guests of the panel, the
7 sponsors and particularly the FDA staff and also the
8 chairperson.

9 (Whereupon, at 5:30 p.m. the above-
10 entitled matter was concluded.)

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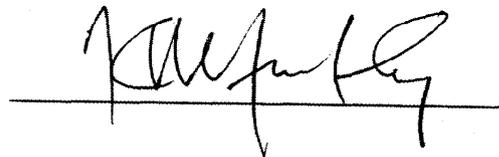
This is to certify that the foregoing transcript in the
matter of: Orthopedics and Rehabilitation Devices
Advisory Panel

Before: DHHS/FDA/CDRH

Date: January 10, 2002

Place: Gaithersburg, MD

represents the full and complete proceedings of the
aforementioned matter, as reported and reduced to
typewriting.



A handwritten signature in black ink, appearing to read "K. M. [unclear]", is written over a horizontal line.