

1 group.

2 Another very important effectiveness  
3 parameter that was assessed was graft site harvest  
4 pain. This was measured in autograft patients using  
5 two numerical rating scales, one for pain intensity  
6 and the other for duration. The composite pain score  
7 ranged from zero to 20 with a lower number signifying  
8 a better outcome. This slide shows a mean graft site  
9 pain for autograft patients from time of hospital  
10 discharge to 24 months post-operatively. At hospital  
11 discharge the mean score was 12.7 and approximately 80  
12 percent of patients had scores of at least 10. As  
13 expected, the harvest site pain improved over time.

14 However, nearly 15 percent of patients had  
15 a score of at least five at 24 months post-  
16 operatively. Aside from the pain approximately 16  
17 percent of patients indicated they were still bothered  
18 by the appearance of the graft site at one and two  
19 years following surgery. When these rates are coupled  
20 with the adverse events associated with harvesting the  
21 bone, a very compelling case can be made for using  
22 infused bone graft in spinal fusion procedures since

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1 it eliminates the negatives of graft site appearance,  
2 pain and morbidity.

3 There is additional good news about the  
4 InFUSE™ bone graft. Another clinical trial was  
5 performed examining the laparoscopic implantation of  
6 the device and the results are just as compelling as  
7 for the open study. The data from the laparoscopic  
8 study augments the safety profile of the device and  
9 support approval of that surgical method of cage  
10 implantation. The laparoscopic study had one  
11 treatment group, those patients treated with the  
12 InFUSE™ bone graft and the LT-cage device. Other  
13 than this, the protocol was identical to that of the  
14 open study.

15 A total of 134 patients received the  
16 investigational laparoscopic treatment. Fourteen  
17 centers contributed the patients. There was no  
18 overlap in surgeons between the open and laparoscopic  
19 studies. On average the hospital stay for  
20 laparoscopic patients was approximately two days  
21 shorter and statistically different than for patients  
22 of either treatment group of the open study.

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1 Further, nearly 45 percent of laparoscopic  
2 patients were treated on an outpatient basis as  
3 compared to virtually none in the open study. The  
4 laparoscopic patients also returned to work some 20  
5 days sooner than for the open study patients. These  
6 surgery, hospital stay and return to work findings for  
7 the laparoscopic patients may suggest that there is a  
8 synergistic effect of the use of the InFUSE™ bone  
9 graft and the laparoscopic insertion of the LT-cage  
10 device.

11 The overall success rate at 24 months  
12 following surgery for laparoscopic patients was more  
13 than 68 percent and nearly 12 percentage points higher  
14 than for the autograft rate of 56 percent. This rate  
15 was not only statistically equivalent to the  
16 autograft, but statistically superior, a finding that  
17 more than satisfies a primary objective of the  
18 laparoscopic study.

19 The safety profile of the laparoscopic use  
20 of the device was also comparable to the open surgical  
21 treatment groups. As expected retrograde ejaculation  
22 rate was higher than with the open surgical treatment

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1 due to the transperitoneal approach for laparoscopic  
2 patients. However, the rate was lower than previously  
3 noted in other large studies using the laparoscopic  
4 implantation of the LT-cage device.

5 The effectiveness results for the  
6 laparoscopic investigational patients were also  
7 impressive. This slide shows statistical equivalence  
8 can be claimed for all comparisons to the autograft  
9 group from the open study. At 24 months the fusion  
10 rate was virtually identical to that for the open  
11 InFUSE™ bone graft treatment at approximately 94  
12 percent, these compared to an 88.7 percent value for  
13 the autograft group. Again, bridging bone was noted  
14 in all evaluated patients at 12 and 24 months  
15 radiographically.

16 Since seeing is believing, I want to spend  
17 the next few minutes showing a few slides of some  
18 study patients using CT. According to the protocol  
19 criteria, these patients had not responded to non-  
20 operative treatment for at least six months prior to  
21 being included in this study and had significant  
22 amounts of pain. The first case is an example of a

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1 successful radiographic fusion in an autograft  
2 patient.

3 The patient is a 37-year old female that  
4 had an L5/S1 fusion procedure. Since cortico  
5 cancellous autogenous bone chips are placed in this  
6 autograft patient's cages, it appears radio-opaque  
7 immediately after surgery. Over time the bone chips  
8 begin to bridge and consolidate to form bridging bone  
9 through the cages. The second patient was a 38-year  
10 old female who had an L5/S1 fusion procedure. This  
11 particular patient's cage were filled with autograft.  
12 The patient was not a successful fusion.

13 As a result of the failed fusion and lack  
14 of stabilization across the disc space, the  
15 surrounding bone undergoes some absorption that  
16 becomes evidenced by radiolucencies and black lines  
17 around the cages. The third patient is a 42-year old  
18 female who had an L4/5 fusion procedure with the  
19 InFUSE™ bone graft placed inside the cage. In  
20 contrast to the autograft filled cages, when InFUSE™  
21 bone graft is placed into the cage, it is not  
22 initially radio-opaque. The InFUSE™ bone graft

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1 starts out as a dark appearance within the cage, so as  
2 to increase whiteness, this is due to new bone  
3 formation.

4 The CT scan clearly shows evidence of new  
5 bone formation at six months, evidenced by the radio-  
6 opacity. And over time this bone becomes denser. In  
7 addition, anterior bridging bone can be seen in front  
8 of the cage and around the sides of the cage. This is  
9 further evidence of mechanical stabilization across  
10 the disc space.

11 One question you may be considering is do  
12 these impressive CT scans infusion results hold up  
13 over time and the answer is yes, and this is based on  
14 four-year post-operative CT scans from the same  
15 InFUSE™ treatment that Dr. Boden previously  
16 presented. So to summarize, as demonstrated in both  
17 animal and human studies CT scans are the most  
18 practical and definitive method of detecting new bone  
19 formation within cages and determining fusion status.

20 The scientific data I have presented has  
21 been impressive and we believe the results certainly  
22 support approval of the product. Science aside,

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1 patients need to be satisfied with their results. So  
2 study patients were asked at their post-operative  
3 visits to respond to three questions related to  
4 satisfaction. This slide vouches for the high levels  
5 of satisfaction at 24 months following surgery for  
6 both InFUSE™ bone graft LT-cage device treatments and  
7 for the autograft group.

8 Generally 75 to 82 percent of the patients  
9 offered positive responses which are very gratifying  
10 findings considering the complex nature of low back  
11 pain and degenerative disc disease. In conclusion,  
12 the primary objective of the prospective randomized  
13 study of the open surgical implantation of the  
14 InFUSE™ device was met. The overall success rate of  
15 the InFUSE™ bone graft LT-cage device was found to be  
16 statistically equivalent to the autograft treatment.

17 The InFUSE™ treatment was associated with  
18 shorter operative times, less blood loss than their  
19 autograft control patients. Two of the primary  
20 benefits of InFUSE™ bone graft are that it induces  
21 bone formation and that it eliminates the need to  
22 harvest autogenous bone graft in spinal fusion

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1 procedures. The autograft group results attest to the  
2 need for InFUSE™ bone graft treatment since 80  
3 percent of the patients had significant perioperative  
4 graft site pain and nearly six percent of these  
5 patients had an adverse event associated with graft  
6 harvesting.

7 Further, the laparoscopic implantation of  
8 the infused device produced very positive clinical  
9 results as well. The overall success rate was  
10 statistically higher than the autograft group. In  
11 addition, the patients had hospital stays that were  
12 two days shorter than the autograft group and they  
13 returned to work some 20 days sooner. Therefore, the  
14 results of this study of the open and laparoscopic  
15 implantation of the InFUSE™ bone graft with the LT-  
16 cage lumbar taper fusion device showed the device to  
17 be safe and effective in the treatment of degenerative  
18 disc disease.

19 Thank you very much.

20 DR. LIPSCOMB: Members of the panel, in  
21 conclusion as clearly demonstrated in these  
22 presentations, and in the information that was

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1 submitted in the PMA application, more than a  
2 reasonable assurance of the safety and effectiveness  
3 of InFUSE™ bone graft with the LT-cage device has  
4 been presented. We understand that following our  
5 presentations the FDA will pose several questions to  
6 this panel. We believe that our presentations have  
7 provided much information to address FDA's questions.

8 For the sake of clarity, let me summarize  
9 what you have just heard as it relates to some of  
10 these questions. One question pertains to a  
11 theoretical issue of rhBMP-2 stimulating cell  
12 proliferation from existing tumor. A comprehensive  
13 review of the literature provides a preponderance of  
14 evidence that rhBMP-2 has either no effect or an  
15 inhibitory effect on tumor cell proliferation.

16 We believe that ongoing laboratory testing  
17 at Wyeth-Genetic Institute as well as precautionary  
18 labeling statements will address any remaining  
19 theoretical concerns. Again, to emphasize, this issue  
20 pertains solely to the effects of rhBMP-2 on an  
21 existing tumor and there is no scientific evidence to  
22 suggest that rhBMP-2 transforms a normal cell into a

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1 tumor cell.

2 Another FDA question to the panel involves  
3 an immunology issue, specifically, what effects, if  
4 any, do antibodies to rhBMP-2 have on a developing  
5 fetus and the mother. Again, this is a theoretical  
6 issue that has not been manifested in either animal  
7 studies or in our human clinical trials. The rate of  
8 authentic rhBMP-2 antibody response was less than one  
9 percent and was similar to that in the control group  
10 in our InFUSE™ clinical trials that you heard about  
11 this morning.

12 We do believe that this issue can be  
13 adequately addressed via precautionary labeling  
14 statements and instructions to females of child  
15 bearing age. Also we intend to discuss further with  
16 FDA the necessity for a pregnancy register.

17 Another line of questioning to the panel  
18 pertains to radiological issues. One aspect, is there  
19 functioning bone inside the cage? The answer is yes.  
20 Histological results from animal studies have verified  
21 that InFUSE™ bone graft causes normal bone to form  
22 and that accompanying CT scans show that the

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1 appearance of the bone radiologically. Our clinical  
2 study CT scans similarly reveal the presence of bone  
3 where none existed before in the InFUSE™ bone graft  
4 patients. This bone also remains intact and dense  
5 over time as evidenced from the CT scans that have  
6 been presented to you some of which are out as far as  
7 four years following surgery.

8 Finally, the major panel consideration, is  
9 the use of InFUSE™ bone graft with the LT-cage safe  
10 and effective in the treatment of symptomatic  
11 degenerative disc disease? The valid scientific  
12 evidence presented here today unquestionably provides  
13 an affirmative response to that question. A multitude  
14 of pre-clinical in vivo and in vitro studies attest to  
15 the safety of InFUSE™ bone graft. Functional animal  
16 model testing and clinical data from a pilot study as  
17 well as two large scale pivotal studies demonstrate  
18 InFUSE™ bone graft safely stimulates the formation of  
19 bone.

20 The data from nine animal species and from  
21 humans are consistent. They are compelling and they  
22 are convincing. InFUSE™ bone graft can safely form

1 normal bone where none existed before and is an  
2 effective substitute for autograft bone. These data  
3 provide more than a reasonable assurance that the  
4 device is safe and effective for its intended use and  
5 this is the criterion for PMA approval. We believe  
6 that you will acknowledge the importance and the  
7 validity of this information and make this  
8 breakthrough technology available to surgeons and  
9 their patients by recommending approval of this PMA  
10 application.

11 This concludes Medtronic Sofamor Danek's  
12 presentations. We are available to respond to any of  
13 your questions. Thank you.

14 CHAIRPERSON FINNEGAN: Thank you.  
15 Actually, I think we'll do the questions later on  
16 today. We are going to take a 10-minute break. We  
17 will return at 12:00 o'clock for the FDA's  
18 presentation and then we will break for lunch.

19 (A brief recess was taken.)

20 CHAIRPERSON FINNEGAN: We are going to  
21 have the FDA presentation and this is in two parts.  
22 The first part is the FDA panel. Those are the

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1 members of the FDA staff who will give their  
2 presentations and the second portion will be three  
3 guest reviewers that the FDA has asked to look at  
4 particular portions of this PMA. And the FDA  
5 presentation will be started by Dr. Aric Kaiser.

6 DR. KAISER: Good morning. I'm Aric  
7 Kaiser, an expert reviewer in orthopedics and the lead  
8 reviewer for the PMA. I would like to first introduce  
9 the other members of the primary review team for this  
10 PMA who will be making the FDA presentations this  
11 morning. Peter Hudson was the lead pre-clinical  
12 reviewer, Barbara Buch, the clinical reviewer and  
13 Telba Irony, the statistical reviewer. I'd also like  
14 to acknowledge the expertise and efforts of a number  
15 of other people involved in this project both from the  
16 Center for Devices as well as valuable input from the  
17 Center for Biologics.

18 The sponsor has gone into detail  
19 describing the product, their pre-clinical data and  
20 the clinical results. And I'd like to remind the  
21 panel that the device that we're seeking your  
22 recommendations on today is the InFUSE™ bone graft

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1 LT-cage lumbar tapered fusion device which is a three-  
2 component spinal fusion device that consists of a  
3 spinal implant, a growth factor and a carrier.

4 The first component, the cage component,  
5 is a titanium alloy tapered spinal fusion cage and as  
6 the sponsor has already mentioned, it has received PMA  
7 approval for use in the treatment of degenerative disc  
8 disease when filled with autograft. The other two  
9 components, the InFUSE™ bone graft consists of rhBMP-  
10 2, the growth factor which is soaked into the ACS  
11 collagen sponge carrier.

12 From a pre-clinical standpoint, there were  
13 two areas that we looked at, those having to do with  
14 the cage itself and those having to do with the BMP  
15 and carrier. Since the fusion cage has already  
16 received PMA approval and has not been changed since  
17 that approval, there was no additional review  
18 necessary and we will not be presenting any  
19 information that the sponsor has not already  
20 presented.

21 The BMP and carrier will be the focus of  
22 the FDA presentations and our presentation will focus

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1 primarily on the issues having to do specifically with  
2 our questions and not repeat the full review that the  
3 sponsor has already given. The same thing will occur  
4 for our analysis of the clinical and statistical data.  
5 The sponsor has given a detailed presentation and  
6 we'll focus our comments on those issues having to do  
7 with the questions.

8 After the last FDA presentation, I'll get  
9 up and go through an overview of what our questions  
10 are, but beforehand, I'd like to just give you an idea  
11 of the general areas of concern so that when you're  
12 listening to our presentations, you have some idea of  
13 where to focus. We will be asking you for your input  
14 on issues having to do with reproduction and  
15 teratogenicity with tumorigenicity, radiographic  
16 effectiveness, end point interpretation, issues having  
17 to do with instructions for use and we'll also be  
18 looking for some input on potential post-market  
19 studies.

20 And with that, I'd like to introduce Peter  
21 Hudson, who will be giving the pre-clinical  
22 presentation.

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1 DR. HUDSON: Hello, I'm Peter Hudson and  
2 I'm the lead pre-clinical reviewer for FDA regarding  
3 this product. I'd like to acknowledge the  
4 collaborative effort of colleagues in the Center for  
5 Drugs, Biologics and Devices for review of this  
6 application. They have provided critical input into  
7 the review of the pre-clinical and manufacturing  
8 information. It's important to note that review of  
9 the manufacturing information of this application has  
10 met the full standards of review that the Center for  
11 Biologics uses for review of recombinant reproduced  
12 growth factors. I'm going to briefly go over the pre-  
13 clinical evaluations and identify the issues that FDA  
14 believes need further evaluation.

15 The sponsor has been informed of FDA's  
16 concerns and in part has either begun to address some  
17 of these concerns or is committed to addressing some  
18 of the concerns as post-market commitments. As you  
19 know, we would greatly appreciate your input and  
20 guidance regarding the issues that remain as concerns.

21 I'll first go over the extensive  
22 toxicology and biocompatibility testing conducted on

1 the produce although not as detailed as Dr. Riedel has  
2 done. Then I will discuss the experiments used to  
3 demonstrate bone inductive ability of the product.  
4 Finally, I will present questions that have arisen in  
5 the course of review of the pre-clinical test  
6 information. I would like to stress that these  
7 questions did not arise specifically due to the  
8 experimental observations from the sponsor's pre-  
9 clinical or clinical studies. We have posed the  
10 questions in consideration of relevant research  
11 literature.

12 As has already been described, part of the  
13 device consists of recombinant human bone morphogenic  
14 protein 2 in an absorbable collagen sponge or matrix.  
15 The rhBMP-2 ACS is placed within the lumbar tapered  
16 cage or fusion device. RhBMP-2 alone was evaluated in  
17 acute single and multiple dose general toxicology  
18 experiments. The results of those studies indicated  
19 that the cytokine did not cause toxicity except for  
20 the occurrence of injection-site related tissue  
21 thickening.

22 To assess the chronic toxicity of the

1 cytokine in sponge, a six-month canine mandibular  
2 maxiofacial defect study and a one-year rat femur  
3 onlay study were conducted. No toxic effects were  
4 observed. The cytokine sponge combination as well as  
5 the fusion cage itself was tested in accordance with  
6 internationally recognized standards of  
7 biocompatibility testing. The cytokine sponge product  
8 passed all the tests shown here.

9 Studies of the ability of rhBMP-2 on a  
10 collagen carrier to induce bone included critical size  
11 defect repair models and fracture repair models on  
12 various entopic sites in rabbits, rats, dogs and  
13 monkeys. Histologic analysis of a monkey ulnar defect  
14 model and other studies suggest that bone formation in  
15 response to rhBMP-2 ACS occurs through a process of  
16 spindle or mesenchymal cell infiltration, vascular  
17 invasion and a combination of endochondral and direct  
18 bone formation.

19 Histologic analysis indicated that the  
20 bone formation process temporally extended from the  
21 outside of the implant towards the center until the  
22 implant was replaced by trabecular bone. Many of the

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1 animal bone induction studies included dose ranging  
2 studies and from these results a broad therapeutic  
3 dose range was identified. The effective dose range  
4 is bordered on one side by inadequate bone formation  
5 and on the other by excessive bone formation.

6 The therapeutic rhBMP-2 concentration  
7 range shifts with the animal species tested. Higher  
8 concentrations are required in canines than in rats  
9 and higher concentrations are required in non-human  
10 primates. The ability of rhBMP-2 ACS contained within  
11 the fusion cage to cause interbody fusion was  
12 evaluated in non-human primates, sheep and goat  
13 studies. The cytokine collagen and fusion cage  
14 combination device cause more fusion in comparison to  
15 autograft control and the fuse bone was not  
16 significantly different mechanically than autograft  
17 fused bone. These results indicate that the bone  
18 induced by rhBMP-2 in combination with ACS and/or the  
19 fusion cage is comparable to autograft induced bone  
20 and mechanically is not significantly different.

21 As I have summarized the sponsor has  
22 conducted a number of studies to establish the

1 biocompatibility and safety of the product and has  
2 used various animal, non-human models to demonstrate  
3 bond inducing capability of the product. However, the  
4 FDA has two questions related to the safety. Again,  
5 these questions don't arise due to pre-clinical and  
6 clinical observations of adverse effects due to the  
7 product but due to consideration of the potential for  
8 adverse effects that might occur.

9 The questions regard the potential for  
10 rhBMP-2 to stimulate transformed cells bearing BMP  
11 receptors to proliferate and the potential for an  
12 immune response to rhBMP-2 to cause adverse effects in  
13 developing fetuses in pregnant women. I'll first go  
14 over the question for the potential for rhBMP-2 to  
15 stimulate transferring cells in a patient's body.

16 Bone morphogenetic proteins form a sub-  
17 family within a transforming growth factor a super  
18 family of cytokines. Cytokines within the TGF beta  
19 family and BMP specifically have been shown to play  
20 crucial roles in embryogenesis. In addition members  
21 of the BMP sub-family have been shown to influence  
22 growth, differentiation and apoptosis of various cell

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1 types including osteoblasts, condroblasts, neuro cells  
2 and epithelial cells. BMP is type 1 and type 2, serum  
3 kinase receptors in order to induce cellular signal  
4 transduction.

5 Like other members of the TGF beta family,  
6 BMPs may elicit various types of responses in cells  
7 due to the cell type and/or receptor type expression.  
8 It is reasonable to attempt to investigate the  
9 potential for BMP-2 to stimulate transformed cells.  
10 Some pre-clinical testing was conducted to address  
11 this issue previously by the sponsor. Now I will  
12 review the information contained within the sponsor's  
13 application that is relevant to the topic. Then I'll  
14 go over the additional studies or actually, I'll kind  
15 of briefly go over that since Dr. Riedel has pretty  
16 adequately discussed that already, the studies that  
17 were recommended by us.

18 First of all, I'll go over the  
19 pharmakinetic information pretty quickly. The  
20 experimental observations indicated that the systemic  
21 availability of rhBMP-2 is low. The prediction is  
22 based upon pre-clinical evaluations and assuming a one

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1 milligram per kilogram dose suggested systemic  
2 exposure to rhBMP-2 would be in the low nanogram per  
3 NL range. The experiments indicate that the clearance  
4 of rhBMP-2 from the systemic circulation is rapid and  
5 that the residence time and tissues involved and  
6 clearance is brief. However, individuals implanted  
7 with the device will likely have some low exposure to  
8 rhBMP-2 outside the implant site.

9 To address -- to more directly address  
10 concerns regarding carcinogenicity or for lack of a  
11 better term, tumorigenicity or promotion or  
12 stimulation of transformed cells, the sponsor  
13 conducted the Ames mutagenicity assay in which they  
14 found that the results with that were negative. In  
15 addition, they evaluated the product in a one-year  
16 chronic toxicity study in the rat and they have  
17 evaluated the product's ability to influence the  
18 proliferation or growth of a limited number of tumor  
19 cell lines and primary tumor cell isolates.

20 No carcinogenic effects were observed in  
21 the one-year rat femoral onlay study. In in vitro  
22 tumor cell growth experiments, BMP-2 was observed to

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1 inhibit two prostate carcinoma tumor cell lines, one  
2 breast tumor cell line, one tongue cell line and one  
3 lung tumor cell line and not to effect the growth of  
4 four osteocarcinoma lines. In assessing BMPs activity  
5 against primary tumor cell isolates, Soda, et al,  
6 found that of 65 available specimens, 16 were  
7 inhibited. No tumors were observed to be stimulated.  
8 In neither in vitro cell study did the investigators  
9 evaluate the cells for BMP receptor expression.

10 We cannot state that these studies  
11 demonstrate a lack of stimulatory effects of BMP-2 on  
12 tumor cells or tumor cell lines expressing BMP-2  
13 receptors. Traditionally, the two-year rats  
14 carcinogenicity study isn't recommended for evaluation  
15 of implanted devices. We don't believe this assay  
16 would adequately assess for the potential of rhBMP-2  
17 to stimulate transformed cells. In consultation with  
18 the sponsor we devised a series of experiments that  
19 Dr. Riedel has already gone over.

20 FDA believes that the studies can be done  
21 as a post-market commitment. You will be asked to  
22 comment on the concern of the ability of rhBMP-2 to

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1 stimulate transformed cells and whether you believe  
2 additional studies are necessary.

3 Now I'll go over FDA's question regarding  
4 the potential for an immune response to rhBMP-2 to  
5 cause adverse effects. I'll briefly discuss the  
6 information contained in the application regarding  
7 anti-rhBMP-2 immune response findings and then I'll  
8 present research literature regarding BMP-2 knockout  
9 mice.

10 I'll mention what post-market commitments  
11 the sponsor and FDA have discussed with respect to  
12 revisions of the Elisa used to detect anti-rhBMP-2  
13 antibodies. Finally, I'll tell you what we'd like you  
14 to think about in preparation for our questions at the  
15 end.

16 Enzyme link immune absorbants and assays  
17 were established to measure anti-rhBMP-2 anti-collagen  
18 type 1 antibodies in animals and patients implanted  
19 with the device. Anti-rhBMP-2 and collagen type I  
20 antibodies were screened on rats, dogs and rhesus  
21 monkeys pre-clinically. In the femur onlay rat  
22 models, serum samples were obtained pre-operatively at

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1 four weeks, 26 weeks and 52 weeks. No rats  
2 demonstrated a positive anti-rhBMP-2 or anti-collagen  
3 type I response.

4 In at 28-day daily IV injection beagle  
5 dogs' toxicity study, three of eight animals receiving  
6 a high does of rhBMP-2 were determined to have a  
7 positive immune response. No animals exhibited an  
8 anti-collagen immune response. In non-human primate  
9 studies the antibody responses to rhBMP-2 were  
10 evaluated pre-operatively at four, eight, 12 and 16  
11 weeks post-operatively. Antibodies to rhBMP-2 were  
12 detected in 35 percent, 7 of 20 of the animals treated  
13 with the device. The antibody responses were  
14 transient of a low titer.

15 No control animals exhibited an anti-BMP-2  
16 response. Eight percent of the animals exhibited an  
17 anti-bovine collagen type I response. These studies  
18 suggest that immune responses to implanted rhBMP-2 can  
19 be expected. The type of responding antibody was not  
20 determined in these studies. In addition, we don't  
21 know if the antibodies cross react with endogenous  
22 BMP.

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1           In addition, the antibody response was  
2           undefined as to whether it was of a neutralizing  
3           character. For clarification, a neutralizing antibody  
4           would effectively prevent the BMP-2 from inducing  
5           signal transduction in responding cells. The sponsor  
6           plans to revise the Elisa to better characterize the  
7           immune response elicited by implantation of rhBMP-2 as  
8           a post-market commitment.

9           In the clinical study the immunologic  
10          findings of which Dr. Buch will further discuss, two  
11          of 277 patients implanted with the cage contained  
12          rhBMP-2 exhibited a positive immune response. One  
13          control patient exhibited a positive immune response  
14          to rhBMP-2. The incidents of antibody formation  
15          observed in this limited clinical study was very low  
16          and did not correlate with adverse clinical findings.  
17          In other clinical applications of rhBMP-2 and in the  
18          pre-clinical evaluations done in non-human primate  
19          models, the incidents of the immune response to rhBMP-  
20          2 was higher.

21                 FDA's concern about immune responses to  
22          rhBMP-2 regard to two issues; throatigenecity (ph) and

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1 restimulation of -- and the potential for  
2 restimulation of an immune response in the women  
3 during pregnancy. This concern is driven chiefly by  
4 experimental observations obtained from research  
5 literature regarding BMP-2 deficient mice. Again, I  
6 want to stress that these concerns were not raised by  
7 observations of adverse effects in the pre-clinical or  
8 clinical evaluations done by the sponsor.

9 Also it should be stated that pre-clinical  
10 evaluations were not specifically designed to evaluate  
11 these issues. The sponsor conducted teratology (ph)  
12 and fertility pre-clinical evaluations of rhBMP-2 but  
13 these studies were designed to assess if exogenously  
14 added rhBMP-2 itself would have deleterious effects on  
15 the development of fetuses or if it adversely effected  
16 performance parameters of reproduction.

17 These studies did not investigate whether  
18 the deletion of rhBMP-2 due to antigen-specific  
19 antibodies would cause embryonic morbidity. In  
20 addition experiments were not done to investigation a  
21 fetal expression of BMP-2 in pregnant females immune  
22 responsive to rhBMP-2 could cause toxicity in the

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1 mother. It is important to be cognizant of research  
2 and literature regarding the role of that cytokine  
3 plays in normal bone physiology as well as in  
4 embryogenesis in order to anticipate potential safety  
5 issues.

6 The reason why we pose these questions is  
7 based upon experiments conducted in mice deficient for  
8 BMP-2 or BMP-2 knockout mice. In these mice  
9 investigators noted that a deficiency of BMP-2 was  
10 embryonically lethal. The embryos were noted to have  
11 failed to close the pro-amniotic canal which cause the  
12 malformation of the amniotic cavity and chorionic  
13 tissue. BMP-2 deficient embryos also exhibited a  
14 defect in cardiac development manifested by the  
15 abnormal development of the heart and the exocoelomic  
16 (ph) cavity. Homozygous deletion of BMP family  
17 members has resulted in other embryonic lethal events  
18 as well. For example, as shown in this slide, BMP-7  
19 and BMP-2 deficient mouse embryos, BMP-7 deficient  
20 mice had defects in the development of eyes and  
21 kidneys.

22 BMPs obviously, play significant critical

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1 roles during embryonic development. If antibodies  
2 rhBMP-2 were to cross the placental barrier, they  
3 theoretically could adverse effect embryogenesis.  
4 This diagram captures the essence of the issue. A  
5 woman of child bearing potential is treated with  
6 rhBMP-2 to fuse vertebrae. The implantation of the  
7 cytokine elicits an immune response. During a  
8 pregnancy, fetal expression of BMP-2 restimulates the  
9 anti-rhBMP-2 immune response would have potentially  
10 adverse effects for the embryo as well as the mother.

11 We would like you to discuss this issue  
12 and look forward to your recommendations.  
13 Specifically, what type of animal models do you  
14 believe would sufficiently address the question of  
15 whether maternal antibodies to rhBMP-2 can cross the  
16 placental barrier and cause deleterious effects on the  
17 developing fetus, also what type of animal models  
18 would you recommend to answer the question regarding  
19 fetal expression of BMP-2 and its potential for  
20 adversely effecting maternal or embryonic development  
21 in women who have anti-rhBMP-2 antibodies.

22 We would like you also to consider the use

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1 of a registry for women of child bearing potential in  
2 order to monitor for these potential effects. Thank  
3 you.

4 DR. BUCH: Good afternoon. My name is  
5 Barbara Buch and I'm the FDA's clinical reviewer for  
6 this PMA. I'd like to thank my colleagues for their  
7 assistance with this review, especially Dr. Martin  
8 Yahiro. As the sponsor has already presented a  
9 detailed account of the results regarding safety and  
10 effectiveness of the clinical trial, I will not repeat  
11 that but I would like to start by highlighting some of  
12 the key points relating to the effectiveness and the  
13 safety of this device based on the data that was  
14 presented by the sponsor in PMA. Then I will briefly  
15 review some additional considerations in this and  
16 supporting studies in the PMA regarding the  
17 interpretation of radiographic data specifically.

18 Given all this information, I will then as  
19 you, as the panel, to focus on the radiographic  
20 interpretation issues which will lead you into a  
21 discussion of the radiographic panel question.  
22 Overall, this clinical trial was well conducted. I'd

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1 like to point out that Bayesian statistical analysis  
2 were used and there was a high patient follow-up and  
3 data accountability. In addition, there was  
4 meticulous adverse event reporting. As previously  
5 been discussed many times, there were two arms of the  
6 randomized portion and one non-randomized laparoscopic  
7 clinical trial. I'd like to also point out that the  
8 follow-up rates, again, are very high and that in the  
9 laparoscopic group the follow-up rate does not take  
10 into account those patients who are not yet evaluated  
11 for that 24-month evaluation.

12 Dr. Mathews has already explained in  
13 detail these clinical end points that were evaluated  
14 to determine overall patient success for the  
15 determination of safety and effectiveness of this  
16 combination device. For the randomized clinical  
17 trial, as I've said, the accountability of patients  
18 and the data at 24 months was greater than 85 --  
19 greater than 87 percent. This included the antibody  
20 testing for anti-rhBMP antibodies and for anti-bovine  
21 collagen antibodies.

22 In the randomized group there was very

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1 little difference in the co-variates between groups  
2 pre-operatively. This included a strong correlation  
3 of the pre-operative SF-36 obtained in the Oswestry  
4 evaluation scores. I'd like to briefly highlight some  
5 of the clinical results. In the randomized portion of  
6 the trial, the investigational group had less blood  
7 loss and less overall operative time than the control  
8 group. This is in part attributable to the lack of  
9 bone graft harvest as has been mentioned.

10 The laparoscopic group, as expected, had  
11 a shorter hospital stay when compared to the  
12 randomized treatment groups and also had a shorter  
13 operative time. I'm sorry, the operative time was  
14 equivalent. Regarding antibody testing, as been  
15 explained previously, the patients were tested for the  
16 presence of antibodies to rhBMP bovine type I collagen  
17 and then to human type I collagen. In each of the  
18 three treatment groups, including the laparoscopic,  
19 there was only one patient that had an authentic  
20 positive response to rhBMP antibodies for a total of  
21 three in the entire clinical trial.

22 The overall study outcome was a success

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1 for the control patient that was positive and failures  
2 for the patients in the investigational and  
3 laparoscopic treatment groups. However, because of  
4 the low rate of occurrence, the significance of this  
5 finding cannot be determined. There is also a  
6 relative low rate of authentic positive elevated  
7 antibody responses to bovine collagen in each of the  
8 three treatment groups. Of these greater than 60  
9 percent of the patients in the randomized groups were  
10 overall success. No patient in any of the treatment  
11 groups has a positive response to type I human  
12 collagen.

13 What's important to know is that analysis  
14 was completed comparing clinical outcomes with  
15 antibody responses. There were no correlations of any  
16 of the rhBMP and bovine antibody results with the  
17 overall outcome individual end point success or  
18 failure or the occurrence of adverse events. One  
19 other interesting final result is that in the  
20 randomized treatment groups both sets of patients  
21 returned to work in an average of approximately 64  
22 days following surgery and not unexpectedly the

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1 patients in the laparoscopic arm returned to work  
2 faster than those in the open procedure groups.

3 This clinical trial has demonstrated that  
4 the outcomes for patients treated with the  
5 investigational device were as effective as those in  
6 the control treatment group. As this table shows, for  
7 the results of the primary effectiveness end points,  
8 the investigational treatment group were equivalent to  
9 the control. The same can be said about the majority  
10 of the secondary end points.

11 When looking at the adverse events in  
12 general, the incident of any adverse event in either  
13 of the randomized treatment arms was high. This is,  
14 in part, due to the detailed reporting of the adverse  
15 events and the nature of the surgical procedures.  
16 Specifically, there was one death in a patient in the  
17 control group who had a history of cardiac disease.  
18 The most significant finding was the incidence of  
19 graft site related adverse events aside from pain that  
20 occurred only in the control treatment group and were  
21 absent in the investigational treatment group.

22 These included fractures, nerve injuries,

1 infection and hematoma. Donor site pain was high  
2 immediately post-operatively but as we've seen  
3 significantly resolved by six months to a year.  
4 Finally, important to note is that there were six  
5 pregnancies in women in this clinical trial. Of the  
6 five pregnancy in the two investigational device  
7 treatment groups, that is the laparoscopic and the  
8 open investigational group, there were two early  
9 trimester miscarriages, both in the laparoscopic group  
10 and three healthy births.

11 In the overall analysis of adverse events  
12 in randomized treatment groups, there were 12  
13 categories which -- in which both groups had a greater  
14 than five percent occurrence rate. Of those the  
15 investigational treatment group had a slightly  
16 numerically higher rate of non-device related events  
17 including back and leg pain, GI symptoms, retrograde  
18 ejaculation, spinal events, incidents of trauma, one  
19 vertebral fracture and urogenital events.

20 Of these only the urogenital event rate  
21 was statistically significant as a difference compared  
22 to the control. Approximately half of those

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1 urogenital events involved post-operative urinary  
2 retention. This is not an unexpected event following  
3 spinal surgery. All these events resolved prior to  
4 discharge from the hospital.

5 Other events in this category included  
6 kidney stones, bladder and rectal symptoms and  
7 erectile dysfunction. These events occurred at least  
8 six weeks post-operatively, a period unrelated to  
9 surgical procedure. Retrograde ejaculation was  
10 documented in five investigational and one control  
11 patient but this difference was not considered  
12 statistically significant. And as would be expected  
13 and has been mentioned many times, the incidents of  
14 graft related adverse events were statistically and  
15 numerically worse in the control group.

16 In reviewing all of three treatment  
17 groups, retrograde ejaculation was higher in both  
18 investigational groups but only statistically  
19 different in the laparoscopic treatment group. This  
20 is, again, attributed to the surgical approach. There  
21 were no directly linked immune related adverse events.  
22 There were five possible or potential events that may

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1 be considered immune related and none of these  
2 patients had authentic positive responses to either  
3 anti-rhBMP antibodies or anti-bovine collagen type I  
4 antibodies.

5           There were two cases of cancer diagnosed  
6 during the clinical trial. One case of pancreatic  
7 cancer was diagnosed in a patient in the  
8 investigational treatment group and a case of breast  
9 cancer was found in a control group patient. There  
10 were no cases of osteogenic cancers reported. The  
11 overall occurrence of device related events, as we  
12 have seen, was similar between the investigational  
13 control and laparoscopic groups. What I'd like to  
14 point out is that this includes malpositioning of the  
15 device, migration, loosening and subsidence in  
16 addition to non-unions. When non-unions are removed  
17 from this scenario the incidents is low, falls to less  
18 than one percent which is expected for the caged  
19 devices.

20           When compared to the control group, the  
21 laparoscopic group had a higher occurrence rate of  
22 migration, malpositioning and related anatomic

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1 difficulties as well as has been discussed retrograde  
2 ejaculation. These occurrence rates probably relate  
3 to the procedural approach and are consistent with  
4 other spinal literature. The occurrence of second  
5 surgeries is similar in both randomized groups.  
6 Although the rate of removals was higher in the  
7 investigational group, the rate of supplemental  
8 fixations was slightly higher in the control groups.  
9 The relative rates of occurrence, however, are very  
10 similar with eight percent in the investigational  
11 group, 10 percent in the control group, and seven and  
12 a half percent in the laparoscopic group.

13 Based on the clinical data provided in  
14 this trial, patients receiving the investigational  
15 device achieved equivalent fusion and clinical scores  
16 compared to the patients receiving autograft control  
17 while eliminating the possibility and necessity of  
18 bone graft donor site and its attendant morbidity.  
19 Again, they were mostly equivalent adverse event  
20 profiles and occurrences.

21 Now, I'd like to turn your attention to  
22 the question of radiographic interpretation. This

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1 question arises because this clinical trial was the  
2 first to use both x-rays and thin sliced CT scans with  
3 reconstructions to determine fusion which is an  
4 important primary end point. The sponsor has provided  
5 the results of an x-ray versus CT validation study as  
6 part of the IDE and Dr. Irony will discuss this in her  
7 presentation. All the radiographic results of this  
8 clinical trial, both plain radiographs and CT scans  
9 were presented in order to assess fusion.

10 One other of our concerns is whether or  
11 not we can interpret the radiographs of patients  
12 treated with this combination device in the same way  
13 as we do the radiographs of those treated with  
14 autograft given that the fusion sites may calcify at  
15 different rates and the progressive rate diffusion may  
16 be different. To this end, I will review the current  
17 definition of fusion in this trial, show you some  
18 examples of radiographs from this trial and discuss  
19 some issues and interpretation within this trial and  
20 other studies presented in the PMA.

21 Plain films were reviewed for the presence  
22 or absence of translational motion and angulation.

1 They were then reviewed for the presences of bridging  
2 trabecular bone. If there was trabecular bone present  
3 and no motion on fluction extension films, the patient  
4 was considered to be fused. If there was no bridging  
5 bone apparent on the plain films, the CT scans were  
6 assessed for bridging bone. If there was bridging  
7 bone on CT, no motion on plain films, no lucencies,  
8 the patient was determined to be fused. The sponsor  
9 utilized both plain radiographs and CT scans to  
10 determine the presence of bridging trabecular bone in  
11 the assessment of fusion.

12 There were no instances where there was  
13 bridging bone on plain films that was not seen on CT  
14 scan. However, there were many instances of false  
15 negative plain films, that is cases where the CT scan  
16 showed no bridging bone when the plain film did not.  
17 I'm sorry, there were no cases -- there were many  
18 instances of false negative plain films, that is cases  
19 where the CT scan showed bridging bone and the plain  
20 radiograph did not.

21 This phenomena could potentially inflate  
22 the success rate in the open investigational group.

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1 As seen on this slide, the table compares the  
2 determination of bridging bone by x-ray and CT scan at  
3 various time points. At six and 12 months, the  
4 proportion of disagreement between the x-rays and the  
5 CT scans was high. This problem was minimized at 24  
6 months which was the end point of the clinical trial.  
7 You will also notice that as the study progressed from  
8 six months to 24 in all three groups, there's an  
9 actual decrease in the number and rate of patients  
10 with bridging bone detected.

11 At 24 months, however, only 8.3 percent of  
12 the patients who were considered failures by plain x-  
13 ray became successes by CT. In the control group,  
14 approximately five percent of the patients who were  
15 failure by plain radiographs, became successes by CT.  
16 I'd like to direct your attention now to the next  
17 series of CT scans which are examples of patients in  
18 the clinical trial.

19 The slices are taken through the center of  
20 the fusion cage and while I realize the determination  
21 of bridging bone and fusion are naturally determined  
22 by multiple serial axial to sagittal and

1 reconstruction views, these views are an attempt to  
2 provide you with some representative examples of the  
3 patients in the trial which can supplement those  
4 presented by the sponsor. When reviewing these scans,  
5 consider, if possible, the progression of fusion and  
6 differing densities of the material within and around  
7 the cages at different time points.

8 The first series are patients considered  
9 successful fusions in the trial. The second set  
10 represent patients who were considered failures. I'm  
11 going to ask you if you were able to determine which  
12 side represented the investigational device and which  
13 represented the control. On the left side of the  
14 slide the cuts represent patients who were in the  
15 investigational group and on the right represent the  
16 control.

17 Now let's look at what information we've  
18 learned from prior animal studies and human studies  
19 that looked at radiographic results compared to  
20 surgical findings. These studies that looked at  
21 animal and human subjects implanted with spinal  
22 devices using autografts -- autograft only and then

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1 were taken back to surgery. Fusion was determined at  
2 the time of surgery by manipulation and histologic  
3 analysis and then compared to pre-operative x-ray and  
4 CT fusion status analysis.

5 A summary of these studies showed the CT  
6 scan correlated in most cases to the findings at  
7 surgery and that the CT scans specifically had higher  
8 sensitivity and specificity for determining fusion  
9 status compared to the plain radiographs. In the case  
10 where BMP was used in surgical fusion in animal  
11 subjects, a similar analysis was done at second look  
12 surgery to determine fusion and then compared to pre-  
13 operative x-ray and CT radiographic fusion analysis.

14 In summary the CT scans again highly  
15 correlated with the surgical findings and histological  
16 analysis. In addition, it appeared that the density  
17 and rate of progression of repair or remodeling  
18 differed somewhat in comparison to what's known about  
19 autograft and allograft. In this clinical trial there  
20 was an extremely high fusion rate in all treatment  
21 groups when using both x-ray and CT to make the  
22 determination of fusion.

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1           When considering the data from other  
2 studies regarding the radiographic interpretation of  
3 fusion, you should bear in mind a few key points.  
4 First, in the x-ray and CT validation study that was  
5 done by the sponsor, autograft was the basis for the  
6 conclusion used to consider this method for  
7 determining fusion in this PMA.

8           Second, we may not be able to extrapolate  
9 the information from animal trials to potential human  
10 responses. And finally, we need to recognize that  
11 potentially the rate and extent of radiographic  
12 changes between autograft and rhBMP may differ. With  
13 all of this in mind, you'll be asked to comment on the  
14 interpretation of radiographic data in this clinical  
15 trial. Please keep in mind the following additional  
16 issues when commenting on the determination of  
17 successful fusions in patients implanted with this  
18 combination device.

19           This includes the presence and absorption  
20 rate of the collagen sponge, the identification of  
21 progression of bone repair processes in the presence  
22 of rhBMP and the ability of bone formed at various

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1 time points to accommodate applied loads. And  
2 finally, I'd like you to consider the implications of  
3 all of these factors on the interpretation of  
4 radiographic fusion and physician training in the  
5 future. Thank you for your attention.

6 DR. IRONY: My name is Telba Irony and I'm  
7 going to comment on the statistical issues relevant to  
8 your consideration for the questions presented by the  
9 FDA. I have discussed two statistical issues. I will  
10 briefly report about the analysis of safety and  
11 effectiveness in this submission and these analysis  
12 were made through Bayesian methods. And second, I  
13 will talk about the statistical comparison of the use  
14 of x-rays and CT scans in assessing spinal fusions.

15 First, with respect to the Bayesian  
16 methods that were used here, as was said before, we  
17 have two main studies. One was an open study -- open  
18 surgery study which was a multi-center study  
19 prospective and randomized. There were like 143  
20 investigational devices and 136 control devices. The  
21 second study was a laparoscopic study which was non-  
22 randomized and in this statistical comparison we made

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1 a comparison with the same control as we did in the  
2 open surgery study.

3 Well, Bayesian methods were used and I  
4 will very briefly explain the methodology that was  
5 used in this submission. First, non-informative prior  
6 distributions were used and I'm just stressing that  
7 because usually when Bayesian methods are used, in  
8 many cases they use prior information meaning  
9 information from other studies. That was not the case  
10 here. We computed posterior probabilities instead of  
11 p-values and predictions of results for 24 months were  
12 made from some cases in which the patients had only  
13 some data; in the cases of the patients for which the  
14 24 month values of some end points were missing or  
15 some patients that were lost to follow-up and patients  
16 that were not yet due for their 24-month visit.

17 Such conditions improved the  
18 accountability at 24 months was already high  
19 especially for the open study and as a consequence it  
20 enhanced the accountability and improved the precision  
21 of the estimates at 24 months. Just to give you a  
22 brief idea of what was done here, let's think that for

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1 each endpoint,  $P_0$  will be the chance of success for  
2 that point, endpoint in the control group and  $P_1$  will  
3 be the chance of success for the endpoint in the  
4 treatment group. So if you think about the difference  
5 between zero minus  $P_1$ , you will conclude that if  $P_0$   
6 minus  $P_1$  is large, that will mean that the control is  
7 better than the treatment and if  $P_0$  minus  $P_1$  is  
8 negative, meaning small, the control will be  
9 considered worse than the treatment.

10 So we are going to look for a large  
11 probability that the difference is small enough and  
12 that will provide us evidence that the treatment was  
13 not inferior than the control and then will declare  
14 equivalent. So we are going to look at this  
15 probabilities. Small enough will depend on the  
16 endpoint. For each endpoint, we had a minimal  
17 clinically significant difference and high probability  
18 or large probability was in this case 95 percent. So  
19 here are the results for effectiveness endpoints for  
20 the open surgery control group -- open surgery  
21 compared to the control group.

22 That's the table. For instance, for

1 fusion, the chance of success in the treatment group  
2 and that chance is already corrected for the loss to  
3 follow up and for patients that for instance didn't  
4 come at 24 months was 92.8 percent and for the control  
5 group was 88.1 percent. The probability of  
6 equivalence, in other words, the probability that this  
7 difference was small enough was basically 100 percent.  
8 And you can see for all of the effected endpoints, the  
9 probability of equivalence was considerably high.

10 There were two endpoints which was back  
11 pain and the MCS. I put a little red star there to  
12 say that that probability was high but was not 95  
13 percent. Now, for the laparoscopic group we have a  
14 similar table. The values are different and basically  
15 for all endpoints the probability of equivalence was  
16 larger than 95 percent. And for this group there was  
17 a higher -- the group started late, so there were more  
18 patients that had not yet reached 24 months by the end  
19 of the study, so predictions was -- were made for more  
20 or less 25 percent of the patients.

21 Now the second issue I'm going to assess  
22 which is the statistical comparison for the use of x-

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1 ray and CT scans in determining fusion. First I'm  
2 going to talk about a validation study that was done  
3 independently on the submission and second, I'm going  
4 to talk about the scenario in the current submission  
5 and how it compares to the validation study.

6 Our problem was the false positive rates.  
7 We don't want to have false positive rates because  
8 that will inflate the results on fusion and  
9 consequently on overall success which was the primary  
10 endpoint of this submission. So in the validation  
11 study, it was done, I will stress, independently on  
12 the study in this PMA. There was a surgical  
13 exploration of 53 spinal fusion methods in humans in  
14 order to assess sensitivity and specificity of both x-  
15 rays and CT scans for determining fusion.

16 So before the surgical exploration, which  
17 was the gold standard; they opened the patient, they  
18 could see if the patient was effectively fused or not,  
19 the fusion status was determined by both x-rays and CT  
20 scans and the relevant parameters evaluated in the  
21 study with respect to this PMA are the sensitivity  
22 which is the probability of testing positive, in other

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1 words, determining fusion when in fact there was  
2 fusion, the specificity which was the probability of  
3 testing negative, determine there was no fusion when  
4 there was no fusion and a false positive rate, the  
5 probability of saying that there was fusion when in  
6 fact, there was no fusion.

7           These are the results of the study. These  
8 are point estimates. And for instance, for x-rays,  
9 the sensitivity was 79, about 79 percent, specificity  
10 86 percent, so the false positive rate was about 14  
11 percent. For the CT scans both sensitivity and  
12 specificity were higher resulting in the lower false  
13 positive rates. In that study there was a third  
14 method to determine fusion, which was a combination of  
15 x-ray and CT scan and in that case, the patient was  
16 determined fusion -- fused only if both x-ray and CT  
17 scan determined fusion. That's a very conservative  
18 method.

19           The conclusion for this validation study  
20 is that sensitivity and specificity is higher for CT  
21 scans and for x-rays. False positive rate is lower  
22 for CT scans and the smallest false positive rate is

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1 from the combined x-ray/CT scan method. That's very  
2 conservative and was not used in this submission.

3 Now, the validation study characteristics  
4 were different than the ones in the current PMA and  
5 that's an important point for consideration for the  
6 people that are trying to answer the questions that  
7 FDA has posed. First, the patients in this study did  
8 not have cages, they did not have spinal fusion cages.  
9 The inclusion criteria in this study was different.  
10 The patients in this study were patients with  
11 continued or worsening pain following instrumented  
12 lumbar fusion for instability or degenerative disc  
13 disease requiring surgery.

14 Given that, we will expect that we'll have  
15 a higher prevalence of known fusions in this study but  
16 however, the distribution was even, where 24 patients  
17 that were fused and 29 patients that were not fused.  
18 Second, the time period of the exams were  
19 approximately a year after surgery. The x-rays  
20 examined were flexion extension. There was no  
21 presence of BMP in the study and the method of  
22 performing CT scans was different than the one in the

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1 present PMA.

2 Now, what happened in the current  
3 submission? I will briefly explain how fusion was  
4 determined. It was actually based in several  
5 evaluations. First, it was based on evidence of  
6 bridging bone and the determination was first made by  
7 x-ray. If bridging bone was not detected, then CT  
8 scan was used and if bridging bone was detected by at  
9 least one method, either x-ray or CT scan, then the  
10 evidence of bridging bone was considered present.  
11 After evaluating bridging bone, these other  
12 evaluations were made based on x-ray; segmental  
13 stability, and lucent line criteria and in addition if  
14 there was a second surgery due to pseudoarthrosis,  
15 that will be a failure and the patient was not  
16 considered fused.

17 Now, as a consequence, the actual  
18 comparison that we are making is in the methods of  
19 detecting bridging bone. The other factors are the  
20 same in both methods of evaluation. The adopted way  
21 of detecting bridging bone is not conservative because  
22 it's sufficient to have evidence of bridging bone with

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1 one of the methods. And finally, in the submission  
2 there was no case in which the presence of bridging  
3 bone was detected by x-ray and was not detected by a  
4 CT scan.

5 So I'm going to present a table in which  
6 I will show the disagreement between the x-rays and CT  
7 scans in the examination of bridging bone. But before  
8 I do that, I will note some important considerations.  
9 First, again, in all disagreement cases the CT scans  
10 indicate that fusion and x-rays did not agree. There  
11 is much less disagreement at 24 months than at 12  
12 months and the relevant point for this submission is  
13 actually 24 months. So this is the table that shows  
14 the disagreement. For instance, at 12 months there  
15 was disagreement in 52 patients out of 130. In other  
16 words, 40 percent of the patients there was  
17 disagreement between the determination through CT  
18 scans and x-ray.

19 In the control group, that disagreement  
20 was also high and the same with the laparoscopic  
21 group. When we go down to 24 months, the disagreement  
22 is much smaller. It's about seven percent for the

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1 open group, five percent for the control group and  
2 there was no disagreement for the laparoscopic group.  
3 Now, what is the effect of this disagreement in the  
4 success rates of fusion? At 12 months, for instance,  
5 an open group that will be determined by x-ray to have  
6 only 57.3 percent of success whereas if it was  
7 determined by CT scans the success rate will increase  
8 to 96.9 percent.

9 The same behavior was seen in the control  
10 group; by x-ray the success rate will be about 30  
11 percent and by CT scan will be about 92 percent and  
12 the same with the laparoscopic group. However, at 24  
13 months which, again, I will insist is our final and  
14 primary endpoint, this disagreement is much smaller.  
15 You cannot -- I put in red just to say that in a few  
16 cases actually the success rates decreased but they  
17 decreases slightly.

18 Now, what's the impact of that in the  
19 overall success. Of course, there will be a large  
20 impact as well. The impact will be more pronounced at  
21 12 months with x-rays. For instance in the open  
22 group, the success rate will be about 32 percent and

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1 with CT scans will raise to 59.7 percent. Again, at  
2 24 months, primary endpoint this difference basically  
3 disappears, it was just reduced to a much smaller  
4 difference.

5 As a conclusion, the determination of  
6 bridging bone has impact on the determination of  
7 overall success and the impact is much more pronounced  
8 at 12 months than at 24 months. The validation study  
9 was performed in patients at approximately 12 months  
10 after surgery and in the study both the sensitivity  
11 and specificity of CT scans were higher than for the  
12 x-rays, but the characteristics of the study were  
13 different than the ones in the PMA and should be taken  
14 into account by the panel members. And that concludes  
15 my presentation.

16 CHAIRPERSON FINNEGAN: Thank you. Aric,  
17 we're going to actually ask you to do yours after  
18 lunch so that we can have the panel looking at  
19 questions right away. We're going to have three  
20 short, five to 10 minute presentations from our three  
21 guest presenters and the first one is going to be Dr.  
22 Rocky Tuan who is a -- who has expertise in the BMPs

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1 and their biological effect.

2 DR. TUAN: So the purpose of my  
3 presentation is to give you an overview of the biology  
4 both in vitro and in vivo, of BMP as a group of  
5 molecules. My talk will be divided into four topics.  
6 The first one has to do with the protein itself. The  
7 second part has to do with its molecular mechanism  
8 action. The third part has to do with its biological  
9 activity both developmental and also in post-natal  
10 pharmacological applications and then finally some  
11 discussion on issues related to potential biological  
12 complications related to the usage of BMP.

13 As already has been described and detailed  
14 by previous speakers, the BMP or bone morphogenic  
15 protein of bone morphogenic activity was actually  
16 first discovered quite awhile ago. In fact, more than  
17 100 years ago the work of Nicholas Sen at Rush Medical  
18 College who used bone grafts to treat osteomyelitis  
19 was in fact, the first indication ever of bone  
20 inductive activity coming out from bone itself. The  
21 pioneering study of Dr. Marshall Urist, of course, was  
22 instrumental in identifying, discovering activity from

1 the demineralized bone matrix. Later on the work of  
2 Hari Reddi and Dr. Huggins in the early '70's with the  
3 subcutaneous implantation of demineralized bone matrix  
4 substantiated all of these earlier findings.

5 Later on, Urist, Sampath, Reddi and  
6 several other groups isolated in at least a certain  
7 degree of purity, these bone morphogenic molecules.  
8 Partial sequences were obtained and then these were  
9 then used to generate nucleotide probes to screen  
10 libraries and subsequently these BMPs were cloned.  
11 And at this point there are at least 20 BMPs and they  
12 belong to the larger family of transforming growth  
13 factor beta super family which was originally isolated  
14 from tumor cell extracts and called transforming  
15 growth factor beta for that reason.

16 The only exception is BMP-1 which is  
17 actually an enzyme. It's a procollagen C peptidase  
18 actually, so it doesn't belong in the same group  
19 although it's called BMP-1. There are at least four  
20 sub-families of the BMPs. There's a BMP-2,4, BMP-3,  
21 the OP1 BMP-7 and then finally the cartilage derived  
22 morphogenic protein which are also called growth and

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1 differentiation factors. These are -- and there are  
2 others that have not been neatly fallen into specific  
3 sub-categories.

4 The structure of BMP as already has been  
5 described by other speakers. It's a dimer, some time  
6 homodimer, sometimes heterodimer. They are  
7 synthesized originally as larger precursor forms which  
8 are then photolytically processed into carboxyl and  
9 into yield a mature product. It contains canonical 7  
10 cysteine residues, one of which is involved in a very  
11 critical disulfide knot (ph) structure important for  
12 its activity.

13 Okay, the second part now, the molecular  
14 mechanism action; BMPs because they are in the family  
15 of TGF beta super-family, they are actually signalling  
16 molecules, that's the best way to describe them. They  
17 interact with cell surface receptors. There are at  
18 least two receptors, each of which, of course, also  
19 has cousins and relatives. These are the BMP receptor  
20 1 and BMP receptor 2, both of which are also enzymes.  
21 They are kineses.

22 Upon binding of BMP to the BMP receptor 2,

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1 BMP receptor 1 is then phosphorylated. This then  
2 activates a whole series of signaling events. This  
3 receptor complexed and interacts with a family of  
4 molecules known as SMAD or S-M-A-D. MAD stands for  
5 Mothers Against Decapentoplegic, which is actually a  
6 fly protein and which is also a member of the BMP  
7 super-family. Again, I just want to also reiterate  
8 that the BMPs have been found across all species so  
9 far.

10 So at any rate, the SMAD, these are the  
11 signaling partners, SMADs 1, 5 and 8 interact in a  
12 sequential manner. Later on they then interact with  
13 a common partner called SMAD 4, which then removes the  
14 entire complex into the nucleus of the cell to  
15 activate specific genes, so that's basically how this  
16 whole thing works. There are also anti-SMADs.  
17 They're also called SMADs. They's called SMAD 6 and 7.  
18 So these are the inhibitory SMADs. Now, I want to  
19 emphasize one point in this description of the  
20 molecular mechanism of action is that this signaling  
21 pathway does not work in isolation.

22 Nature being the way it is, there is

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1 tremendous cross-talk between one signaling pathway  
2 and other signaling pathways. Recent data from many  
3 laboratories have shown that this particular -- from  
4 the outside of the cells to the surface receptor and  
5 then to the nucleus, this particular pathway, this  
6 access, actually interacts with other axes, such as  
7 the extracellular matrix and receptor complex  
8 signaling mechanism via intergrins and fibronectin and  
9 collagen, et cetera, as well as most recently the  
10 wind-signaling pathway. Again, that's another distant  
11 relative of some fly protein. Again, the function  
12 there is to stimulate cell growth, proliferation,  
13 differentiation, morphogenesis, et cetera. So when we  
14 consider BMP family as a family of signaling molecule,  
15 we have to consider what they also do with other  
16 signaling pathways.

17 All right, the third topic is activity,  
18 developmental as well as post-natal. One thing I want  
19 to emphasize again is that BMP action is highly cell  
20 specific. There we should get it out of our mind that  
21 there is one cell that is -- all cells react to BMP  
22 the same way. That is absolutely not true. BMP --

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1 the same BMP can do different things to different  
2 cells depending on its own repertoire of receptors and  
3 also all the signaling molecules inside the cell.

4 Now, during development as Dr. Hudson  
5 already pointed out earlier, BMP is absolutely crucial  
6 for survival and development of the fetus. The  
7 evidence is ample at this point. If you have a  
8 knockout, i.e. deletion of BMP genes, you will get  
9 embryo lethality. If you also are missing, again by  
10 transgenic methodology, the receptors for BMP, you  
11 also get embryo lethality. So now, remember these  
12 things happen way before there is any bone or  
13 cartilage or anything like that.

14 So where BMP works is actually depending  
15 on the developmental stage of the animal. For  
16 example, during very early development, during  
17 gastrulation, BMP works be defining the polarity of  
18 the animal, particularly the dorsal-ventral polarity,  
19 who's on top, who's on the bottom, and again, nothing  
20 to do with bone or cartilage at that point.

21 And a very crucial example would be the  
22 specification of the formation -- of the development,

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1 the differentiations of the paraxial mesoderm. In  
2 fact, those are the cells that ultimately give rise to  
3 the spine. So before you even have a spine, the cells  
4 that are precursors to the spine already are  
5 responsive to BMP. Whether it's in the same manner or  
6 not, we do not know at this point. Nevertheless, if  
7 there is a perturbation in the distribution of BMP,  
8 the dorsal aspect and the ventral aspect would get all  
9 mixed up.

10 In the development of a limb, which of  
11 course has bones and cartilage, et cetera, again BMP  
12 is very, very crucial. It is important for the  
13 initial differentiation event of forming cartilage as  
14 well as the death of cells in the interdigital area.  
15 So it can be a positive factor in the sense that it  
16 makes cells, becomes something else or it can make  
17 cells undergo apoptosis and die so that there will be  
18 a space between the fingers.

19 And also member of the BMP family, TGF-5,  
20 is absolutely crucial for joint development. Without  
21 that, there would be a decrease in the number of  
22 joints. There would be a fusion of joints, mainly the

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1 joint never will actually form in the first place. So  
2 that's developmental.

3 In terms of post-natal, we have already  
4 seen many pieces of data on the results of  
5 pharamocological application or therapeutic  
6 application of BMP to a post-natal animal, the  
7 historical findings of osteochondroinductive activity,  
8 of course, is obvious. Fracture repair, critical size  
9 defect, feeling, spine fusion, we saw many pieces of  
10 data and also recently in terms of osteointegration  
11 and that is how bone cells interact with an implant  
12 bio-material. In this case it may be relevant to the  
13 topic at hand, namely that there is a piece of alloy  
14 that is part of this device.

15 Now, how the presence of BMP may influence  
16 the interaction between the neighboring cells and the  
17 metal alloy is something for us to think about.

18 Finally, potential biological  
19 complications; one thing that needs to be considered  
20 is the distribution of the BMP that has been placed  
21 into a particular site and also retention of this  
22 material once it has distributed to other places. We

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1 notice the low systemic level. However, exactly where  
2 the BMP finally ends up is something that perhaps to  
3 think about.

4 Tumor induction in terms of either  
5 inhibitory or stimulatory in terms of cell  
6 proliferation for transformed or not yet transformed  
7 cells, hematological perturbation has been shown for  
8 the grandfather of the TGF beta super-family, TGF  
9 beta-1. The presence of TGF beta-1 can cause  
10 hematological perturbations.

11 Teratological effects, which will be  
12 discussed later, for example, whether the BMP can  
13 cross the placenta, the window of time in terms of its  
14 action, whether the effect can be transgenerational is  
15 also something worthy of consideration and finally  
16 immunoreaction which has also been discussed, so I  
17 think I'll stop here.

18 CHAIRPERSON FINNEGAN: Thank you very  
19 much, Dr. Tuan. Now, Dr. Miller is going to talk to  
20 us generically about animal models and the use of  
21 registries for teratogenicity. While he's setting up,  
22 the really bad news is we do not need to have a closed

1 session, so we will go to lunch once Dr. Kostuik has  
2 finished his presentation. We do need to start back  
3 immediately at 2:00 o'clock, so I would ask you to  
4 make it a short lunch. Consider it a way to get over  
5 your Christmas indulgences.

6 DR. MILLER: Good afternoon. I'll try to  
7 make it brief. You have a handout so some of the  
8 slides have been eliminated in the interim to shorten  
9 it a bit. I've been asked to look at some principles  
10 and concepts. The developmental toxicology animal  
11 testing is how it is done. The evaluation of biotech  
12 products which really introduces a whole new question  
13 into the reproductive and developmental area and then  
14 post-marketing pregnancy registries and I'll try to do  
15 that all within 10 minutes.

16 I am offering a course at the FDA next  
17 month that takes four hours to do this, so I'm putting  
18 it in perspective. Different molecules will produce  
19 a different spectrum of malformations depending upon  
20 the mechanisms of action as one sees here with  
21 Accutane, with valporic acid in terms of spina bifida  
22 and methyl mercury down below. We know that the

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1 pregnant female is a pharmacologic orphan. We don't  
2 study products in them by choice necessarily and that  
3 we really are treating two different organisms and  
4 that's actually one of our questions.

5 Dose is the problem, threshold concept is  
6 critical to the area of developmental toxicology and  
7 usually we say where is that threshold there is a  
8 toxic effect? Well, in many instances when we're  
9 looking at it there are doses that won't produce that  
10 toxicity and maybe that's what we should be looking at  
11 as well. Along those lines, dose, length of exposure  
12 and time during gestation are our critical areas of  
13 evaluation and this will certainly become more  
14 important when one is talking about different  
15 surgeries and what time they may be occurring in a  
16 woman if she is pregnant.

17 There are certainly sensitive windows  
18 along these lines and I've borrowed this from Keith  
19 Moore, where you see in red here many different organ  
20 systems that are sensitive from the brain down to  
21 limbs and other organs. If we move just a little  
22 earlier, the whole pre-implantation, implantation area

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1 is one also of equal concern. I added this just at  
2 the last moment. I had removed it. However, when we  
3 are thinking of mechanisms of action, the National  
4 Academy of Sciences just completed their work in the  
5 past year and published a volume called Risk  
6 Assessment of Developmental Toxicology, which I  
7 recommend to you and have been using the 17 different  
8 signal transduction pathways to look across species to  
9 see the commonality for agents and I do have an  
10 asterisk up there; one for transforming growth factor,  
11 because obviously, that is the family cluster in which  
12 BMPs are found.

13 So if these are some of our concepts, what  
14 are the animal testing that we must undertake and  
15 follow guidelines on? And there are three areas, one  
16 being fertility and early embryonic development,  
17 usually performed in the rodent, the rat; embryonic  
18 and fetal development, sort of the teratogenic period,  
19 that is done in two species; one the rat, the other  
20 the rabbit or some other species that is a non-rodent.

21 And then some pre/post-natal developmental  
22 studies to look at behavioral and functional changes.

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1 Along those lines, studies are conducted according to  
2 these guidelines and these are sort of the minimum  
3 requirements that we really need to think about.  
4 Treatment via the likely human route with obviously  
5 some exceptions but we would like to perhaps more  
6 closely mimic that.

7 Results should permit identification of a  
8 NOAEL and a LOAEL and also look at a maternally toxic  
9 dose. Maybe the compound one is looking at doesn't  
10 get to a toxic dose that one can demonstrate in the  
11 mother but at least you've tried to go there.  
12 Extrapolation from the most sensitive species unless  
13 there is evidence that the species is inappropriate  
14 might, in fact, be reason to look at another species  
15 based upon drug metabolism, formation of reactive  
16 metabolites, and then obviously, we need to have  
17 clarity of a thought about detection versus  
18 characterization.

19 If these are our primary roles, then we're  
20 looking at the identification of hazard and we're  
21 looking at the identification of risk. And along  
22 these lines, hazard really is an animal studies

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1 agenda, especially with a new agent because we don't  
2 have human case reports to rely upon in many instances  
3 and if we generated that, the dose response model from  
4 animal studies is what we would need to utilize in  
5 trying to identify risk. And probably the most  
6 important phenomena we need to consider here is  
7 biological plausibility.

8 And biological plausibility really  
9 encompasses all of what we know about pharmacology and  
10 about actions in pregnancy and is that, in fact,  
11 reasonable what you are seeing. So here in terms of  
12 the risk assessment model we're talking  
13 toxicokinetics, toxicodynamics and outcome and the  
14 toxicokinetics becomes an extremely important  
15 component here to try to extrapolate among species.

16 Range finding studies are important as  
17 well as doing the definitive study as listed below  
18 here and in that one would certainly stop at delivery,  
19 actually before around 21 days to do a Caesarean  
20 section to evaluate the animals and in other studies  
21 doing the follow-up post-natally to see survival and  
22 what may, in fact, be happening in terms of behavior.

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1 In the rabbit, one usually starts with the non-  
2 pregnant dose ranging study and then does a pregnant  
3 one to see if there is enhances sensitivity and then  
4 going on to embryo fetal developmental studies,  
5 exposures between seven and 25 days to look for those  
6 types of problems that may be associated with the  
7 agent under study.

8 So selective reproductive toxicity can be  
9 detected in range finding studies and if there aren't  
10 any, usually one would perform according to the ICH  
11 guidelines and do sort of the minimum requirements.  
12 However, if you have found toxicity, you would  
13 certainly want to characterize it better by doing the  
14 dose response relationships looking at the critical  
15 periods and looking at the adverse effects in terms of  
16 both structural and functional but also emphasizing  
17 again, this toxicokinetics in terms of the critical  
18 periods and determining whether the agents are formed  
19 and delivered in fact, to the conceptus.

20 In vitro models can be used to better  
21 understand the toxicity itself. So in an  
22 identification of risk, we have a decision tree and

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1 these you need to keep in mind. Is the species  
2 appropriate for risk assessment? Are there  
3 differences in pharmacokinetics and dynamics among  
4 species especially trying to extrapolate to human  
5 risk? Are there differences in reproductive  
6 physiology or timing of development which should be  
7 taken into account? What is the likelihood humans  
8 will be exposed and treated under the conditions one  
9 has used in these animal studies for critical periods  
10 and characteristics of the patient population?

11 And finally, conclusions about the  
12 potential of the agent to produce reproductive  
13 toxicity, is that similar to other agents and in this  
14 case you sort of have a unique agent and you may not  
15 be able to look across therapeutic classes. One of  
16 the main questions here is though early in pregnancy  
17 and I show here a Doppler where you can see the heart  
18 in red here in the early embryo and you can also see  
19 the blood flow in the mother.

20 Along these lines, this is the time we  
21 really want to know what is going on inside. Are we,  
22 in fact, having our compound arrive at the site?

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1 Well, here in a more schematic diagram we are looking  
2 at the early embryo and we can see the exocoelomic  
3 cavity and the amniotic fluid cavity. Now, these, in  
4 fact, can be sampled very early on and Eric Jauniaux  
5 over in London has done such. And I want to share  
6 just a bit of data with you to help put some of your  
7 deliberations in perspective.

8 Now, neither you nor I can read this from  
9 this distance but what it indicates is that mother  
10 villous tissue, decidua and embryo all are producing  
11 different products. And, in fact, if we sample them,  
12 can we find some of those products there? And Eric  
13 has done a very nice job of looking at this and I have  
14 circled two in particular, IgG and IgA. And if you  
15 look at the maternal serum, you will find that there  
16 is substantial IgG there and also certainly  
17 substantial IgA.

18 If we though, look at the celomic fluid,  
19 we find very little IgA and non-detectible in amniotic  
20 fluid but still the IgG tends to get across. And one  
21 of the reasons for this is, in fact, that the placenta  
22 does have receptors that will allow for that to occur.

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1 In this particular study you can see also that HCG is  
2 produced and tremendous amounts are ending up in the  
3 conceptus.

4 So one can say do IgGs get to the early  
5 embryo and the answer is, yes. In terms of our  
6 evaluation of biotech products, we're really on the  
7 horizon here of unique agents to try to evaluate and  
8 how do we try to assess that? Well, we have many new  
9 proteins. Now cytokines are not new but Fab fragments  
10 which are used clinically such as RheoPro have, in  
11 fact, been unique agents. Do they cross into the  
12 conceptus, anti-sense (ph) compounds?

13 The issue here is the difficulty in  
14 testing in rodents and lagamorphs because if it's a  
15 human protein you might get a heterologous response.  
16 Also extrapolations from human are often difficult to  
17 do and the biological plausibility issue comes forward  
18 with SARs and pharmacokinetics and pharmacologic  
19 action. Well, what can we do to look at this and I'd  
20 like to leave two thoughts with you along those lines.  
21 One is again, returning to the non-human primate  
22 model, and in the non-human primate model there are

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1 some studies that have been undertaken with  
2 recombinant cytokines, G-CSF and stem cell factor and  
3 they have looked at these in terms of whether they  
4 transit the placenta and enter into the fetus.

5 And to abbreviate which was a very  
6 extensive study, is that when they administered it to  
7 the mother and these were recombinant cytokines, they  
8 found insignificant transfer even though they had huge  
9 concentrations of materials in the maternal  
10 circulation. They also did not find any fetal effect.  
11 However, when they directly administered it to the  
12 fetus, they found rapid rises in fetal neutrophil  
13 counts. So you can see that in terms of some agents,  
14 they may or may not be transiting and having fetal  
15 impact.

16 So the non-human primate model may be a  
17 good one to explore in the reproductive area as well.  
18 Another possibility is looking at human placental  
19 profusions where you isolate a lobule and you have a  
20 maternal circulation and a fetal circulation and the  
21 maternal circulation you can add your agents to and  
22 see if they cross into the fetal side. If they do,

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1 you can quantitate how much one has seen. I just give  
2 you a list of examples here of a few that might be of  
3 interest to you and here is G-CSF again and you find  
4 very little really transferring across in four or five  
5 hours in the Gregor study published a couple of years  
6 ago.

7 Interleukin-8 was not detected when it was  
8 given to the maternal side. Epidermal growth factor  
9 had a very, very small amount of the maternal dose  
10 appear in the fetal side, as also with recombinant  
11 erythropoietin where they really did not find any  
12 significant levels on the fetal side. And the same  
13 with the RheoPro which is an FAB fragment. So there  
14 are examples. Now, how do you explain this particular  
15 issue and one is the placenta is a wonderful machine  
16 for breaking down proteins and if you aren't bound to  
17 a receptor mediated process, such as IgG being bound,  
18 the rest of them may, in fact, be catabolized and  
19 reutilized as basic amino acids to support the  
20 placenta as well as the embryo fetus.

21 So many of these are being broken down and  
22 recycles. So if these are going on, then if we make

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1 a decision that a compound has survived all of the  
2 pre-clinical analysis, what do we do in terms of post-  
3 marketing evaluations. And in fact, this has been  
4 reasonably undertaken in about the last 10 years  
5 mainly because of Accutane. And that has been the  
6 most rigorous registry by the Boston group headed by  
7 Alan Mitchell but along those lines, these are some of  
8 the issues that one needs to think of whether you're  
9 doing an in-house one using the university center or  
10 using the Organization of Teratology Information  
11 Services.

12 But along these lines, pregnancy  
13 registries are epidemiologic studies and therefore,  
14 you have to think about what is an appropriate control  
15 group when you are initiating those? Prospective  
16 identification of exposed pregnancies based upon  
17 voluntary contact from patients or health care  
18 providers, i.e., the referral bias that can often come  
19 in; follow-up of exposed pregnancies to obtain  
20 complete information because often times,  
21 unfortunately, at the FDA as well as at many  
22 pharmaceutical companies, that information is not

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1 completely collected.

2           When should pregnancy registries be  
3 conducted? And perhaps the best time is when a new  
4 molecule entity is being introduced such as live virus  
5 vaccines or an entity like this one, BMP, expectations  
6 of high use in pregnant women or of women of child  
7 bearing age, agents necessary for conditions  
8 associated with high morbidity or mortality that  
9 cannot be discontinued as a recognition of pregnancy  
10 and an agent's suspected adverse effects during  
11 pregnancy based on SAR, pharmacology and laboratory  
12 findings and agents known to be harmful during  
13 pregnancy which obviously was an issue with Accutane  
14 when it was first marketed.

15           So what design of the pregnancy  
16 registries; one, you need a preparation of written  
17 protocol, you need to explore consent issues, you need  
18 to have incentives to promote voluntary reporting and  
19 have a preparation of information documents which is  
20 a means to communicate with the public and also have  
21 a major advertising campaign. And with these, the  
22 initiation at the time of marketing for new products

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1 is probably the optimal time.

2 Window of opportunity for collecting  
3 reports is really within the first five years; quickly  
4 identifying any potential risks and not likely to be  
5 used for agents on the market for an extended period  
6 of time due to diminution of voluntary reporting. So  
7 with that sort of background, the next part that  
8 obviously needs to be done is to provide annual  
9 reports, publish occasions of interim results and  
10 really get the care providers involved.

11 So I hope we've reviewed that in as quick  
12 an amount of time as I can possibly do.

13 CHAIRPERSON FINNEGAN: We thank you both  
14 for the quality of information and the time. Thank  
15 you. Dr. Kostuik? Dr. Kostuik is going to give us  
16 generics on different ways to image the spine.

17 DR. KOSTUIK: Thank you, Dr. Finnegan. My  
18 name is John Kostuik. I'm the director of spinal  
19 surgery at Johns Hopkins and as I was preparing this  
20 talk in the last few hours, since I was only notified  
21 that I would be asked to do this yesterday, I realize  
22 that I have been a spinal surgeon for 35 years. That,

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1 in itself, is frightening since it constitutes  
2 approximately 40 percent of the time since spinal  
3 fusion was first introduced to mankind so I am getting  
4 old.

5 What is the problem in assessing a fusion?  
6 It's a difficult proposition. It is far more  
7 difficult today than it was when I was an embryonic  
8 spinal surgeon because of the advent of rigid internal  
9 fixation. This is particularly true in posterior  
10 approaches to the spine. There is no doubt today that  
11 the implants used are much better than they were even  
12 seven to 10 years ago. It has been relatively easy to  
13 assess fusion from an anterior interbody approach up  
14 until the development of metallic interbody cages.

15 It has been stated that expiration of the  
16 fusion mass is the gold standard. One, of course,  
17 would be very reluctant to explore a fusion mass on  
18 the anterior side of the spine because of scarring and  
19 potential risk to vascular structures could result in  
20 serious problems. But even on the posterior side of  
21 the spine, it is not a very valid technique because a  
22 bone graft regardless of how it may be stimulated, may

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1 fuse to itself but not fuse to the underlying host and  
2 therefore, you have a pseudoarthrosis which is very,  
3 very difficult to ascertain in any form of  
4 radiological investigation, including three  
5 dimensional CT scanning.

6 When should one do plain x-rays following  
7 a spinal fusion? I think that they should be done, of  
8 course, immediately post-operatively, probably at  
9 about 10 days after that. Those are for medical-legal  
10 reasons and not pertinent, I think to this group; then  
11 I think probably at about eight weeks, four months,  
12 six months, nine months, one year, 18 months, two  
13 years, after that depending upon the problem, for  
14 instance deformity cases, on should follow those for  
15 life.

16 Now, it has been stated also that flexion/  
17 extension x-rays are valid. They are not valid since  
18 the introduction of rigid forms or internal fixation.  
19 If you have gross motion on flexion/extension, that is  
20 fine but generally that is not seen particularly with  
21 modern implants. Therefore, I rarely ever recommend  
22 their use. I do recommend, however, at least four

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1 views, including oblique views, which are frequently  
2 not done but which can be of great value in looking at  
3 the spine from other angles.

4           There are many, many false positives with  
5 flexion/extension x-rays which brings us next to the  
6 question of CT scanning. This has been controversial  
7 as well. There is no doubt that I think that the CT  
8 scans as presented here today are of more value with  
9 the sponsor's product than it would be with autograft  
10 since there is no intercage density at the beginning.  
11 However, it isn't the beginning that we are interested  
12 in. It is the end point that we are interested in and  
13 we do not know or at least I don't think there is  
14 sufficient data to tell us when we see significant  
15 enough ossication or it has been called bridging  
16 within the cage. Moreover, the bridging we see is  
17 within the cage only.

18           There has been studies done, including  
19 some of our own work, to show that if you take a cage  
20 and fill it with bone and take a CT scan, the first  
21 day post-operative, it looks like it's fused. So I  
22 think CT scanning has a lot of potential error and

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1       although I do admit that it may be more valuable with  
2       this product.

3                       What about the type of CT scans? There's  
4       no doubt that the modern new thin scans are much  
5       better. There are -- there is software available that  
6       allows you to subtract the metal artifact. However,  
7       it is still inaccurate and recently has been thrown  
8       out in a court of law where it was presented as a  
9       means of assessment in a particular patient where a  
10      legal suit arose. Probably one of the most difficult  
11      radiologically to tell whether or not you have a  
12      fusion is the question of radiolucency or loosening.  
13      Particularly loosening I think is obvious.  
14      Radiolucency around a device screw cage can be a bit  
15      more subtle. It is my opinion that any lucency means  
16      non-union if there is still the presence of pain which  
17      may be different than the original pain the patient  
18      presented with.

19                      If there is a lucency and pain then I  
20      think investigation probably should lean towards  
21      injections of dye to see if it flows freely or semi-  
22      freely and, perhaps, the addition of local anesthetic

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1 for pain relief. Bone scans are very little value,  
2 radioactive bone scans are very little value in  
3 assessing fusion mass since most fusions will remain  
4 warm or hot until two years approximately two years  
5 from the time of fusion. Hot after that probably  
6 indicates a pseudoarthrosis at least unless proven  
7 otherwise.

8 The real way, I think with anterior to  
9 body fusions with metallic devices to tell whether you  
10 have a solid fusion is the presence of an anterior  
11 sentinel graft, that is anterior to the cage. Now,  
12 the big question comes up is how thick should that  
13 anterior bridge be and that is not known  
14 scientifically. I have certainly had the personal  
15 experience on many occasions to remove a few  
16 millimeters of solid looking anterior bone definitely  
17 fused to the vertebral bodies to find a significant  
18 underlying pseudoarthrosis.

19 So I think we do need to know the answer  
20 to how thick should an anterior bridge be? Should it  
21 be eight millimeters, five millimeters, 10 centimeters  
22 -- 10 millimeters rather. I don't know. A question

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1 also which has not been announced and I'm perhaps  
2 unclear here is, what about more than one level of  
3 fusion, if the devices are to be placed at more than  
4 one level because it is far more common to do a two-  
5 level fusion than it is to do a one level fusion and  
6 then when do you decide when you have a  
7 pseudoarthrosis.

8 That is about all I have to say. Thank  
9 you very much.

10 CHAIRPERSON FINNEGAN: Thank you so much.  
11 All right, we will reconvene at 2:00 o'clock.

12 (Whereupon, at 1:38 p.m., a luncheon  
13 recess was taken.)

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## A-F-T-E-R-N-O-O-N S-E-S-S-I-O-N

(2:13 p.m.)

CHAIRPERSON FINNEGAN: Ladies and gentlemen, I do think we are ready to begin if you would take your seats. Dr. Reddi, we'd be waiting for you. We are now going to have the panel reviewers give their presentations. The panel reviewers are three. Dr. Hari Reddi is going to give his review of the pre-clinical. Dr. Kirkpatrick is going to give his review of the clinical and Dr. Larntz is going to give his review of the statistics.

DR. REDDI: Madam Chairman, I would like to do you a favor and finish my comments in five minutes. I'll give you an extra five minutes.

CHAIRPERSON FINNEGAN: Well, your comments are very valuable, so you actually get as much time as you'd like.

DR. REDDI: I just want to help out the Chairperson. First, as far as the biological problem is concerned, we are going into a stage where how can we improve on nature, that is bone itself. So the autograph has three main ingredients; the cells, the

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1 matrix, and the signals. It turns out these are the  
2 same three ingredients which are needed in manmade  
3 approaches for tissue replacement, what is generally  
4 referred to as tissue engineering.

5 Now, I want to make some comments  
6 concerning this isolation of BMPs and some of the  
7 questions which were posed by FDA and what comments I  
8 can make in relation in general, not specifically.  
9 First, the BMPs during evolution they have been found  
10 not just in mammals but in other organisms. Let me  
11 tell you what I mean by that. First, there are  
12 several ways to get out the signals during  
13 development. One can isolate it from a tissue like  
14 bone. One can look at other organisms and find out if  
15 they are found in other tissues.

16 In the case of BMPs, it happens to be a  
17 rather unconventional method in which signals were  
18 isolated from bone which is really one of the  
19 ingredients in the graft itself, so bone morphogenic  
20 proteins are natural substance. Dr. Tuan mentioned  
21 the history for about 100 years Nicholas Sen. I want  
22 to take it back further that the idea that normal

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1 substances present in human body could be used as  
2 therapeutic agents was first propounded by none other  
3 than our old friend Hippocrates. He said 23 centuries  
4 ago the best therapeutics are therapeutics mined from  
5 the human body.

6 Next. These signals, although isolated  
7 from bone, it turns out in this case was later  
8 described in other organisms. This addresses the  
9 issue of possible immunity. Of course, I can see one  
10 should keep in mind but I want to make a point that  
11 because it has been conserved in evolution, the insect  
12 BMPs could be equally effective and safe in humans.  
13 The other point which I want to make upon which  
14 considerable effort has been directed mainly because  
15 of some misunderstanding about the transforming growth  
16 factor, it terrifies people because it is something  
17 called transforming growth factor and if one reads the  
18 literature, it's only the name and the name is a  
19 misnomer.

20 Although it's considered as involved in  
21 cancer research, it is really due to an in vitro  
22 artifact that this particular factor was called

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1 transforming growth factor. In effect, all these  
2 proteins are very important to normal physiology. So  
3 the point which I want to make is, one needs to be  
4 careful but not to worry too much about the  
5 teratogenicity which, of course, will come up. I'm  
6 making general comments, not specifically for a  
7 particular BMP. I'm talking about signaling  
8 molecules. These are normal constituents to the human  
9 body and the word here is moderation.

10 And the point which I want to make in  
11 response to certain tests is again, one needs to  
12 really look at the physiology. This is normally  
13 present. I want to add one other point. BMPs are not  
14 just in bone. It turns out this particular family of  
15 molecules are involved long before bone formed during  
16 the pattern formation. That is, for example, your  
17 right hand and left hand are the same, yet the DNA is  
18 the same but the right hand is a mirror image of the  
19 left hand which is involved in a subject called  
20 pattern formation.

21 Simply put for a lay person, if you want  
22 to build a building, you need to have architecture.

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1 This is usually referred to in the parlance of  
2 developmental biology as pattern formation. The point  
3 which I want to make is long before bone and cartilage  
4 appeared, BMPs have arose in defining where particular  
5 tissue forms including that your heart is placed on  
6 the left side so that is very important, the pattern  
7 formation having that it is involved in the initial  
8 differentiation of tissues such as cartilage in the  
9 lumbar. For example in the developing spine it is  
10 involved in the early stages.

11 So in effect, what we are looking at in  
12 terms of repairing is really a recapitulation.  
13 Finally, these same molecules play a very important  
14 role in the maintenance of tissues and finally in the  
15 regeneration and repair. So in summary then, in  
16 conclusion, I want to point out that BMPs are normal  
17 natural substances, normally found in the human body  
18 and it is not surprising they may have therapeutic  
19 implications.

20 CHAIRPERSON FINNEGAN: Thank you very  
21 much. Dr. Kirkpatrick.

22 DR. KIRKPATRICK: Thank you. I was

1 beginning to fear that not only did I need to have  
2 prompting for what I was going to say but I was going  
3 to prove the orthopedic surgeon still is not  
4 technology proficient but fortunately with the aid of  
5 our gentleman there.

6 I'm going to provide an overview from a  
7 clinician's standpoint of the clinical results that we  
8 heard about today. The device basically we know  
9 pretty well by this time. It's a combination product  
10 with a titanium fusion cage, recombinant human BMP-2  
11 and an absorbable collagen sponge. The study groups,  
12 from my standpoint, appear to be reasonably similar.  
13 There was an open arm with a surgical placement of the  
14 device for the control, fairly evenly divided and  
15 randomized.

16 The laparoscopic arm was basically a non-  
17 randomized group but compared again to the controls  
18 that were done. There was -- it was multi-center,  
19 which is one of the things that we always like to hear  
20 and there were roughly 135 patients in each group  
21 meaning the numbers were reasonable from my standpoint  
22 but, of course, the statistician will add to that and

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1 blinding wasn't possible, obviously, because of the  
2 graft site implications.

3           The indications for the surgeries were  
4 degenerative disc disease at L4 to S1, single level  
5 disease, Oswestry scores of greater than 135.  
6 Spondylolisthesis had to be grade 1 or less. For  
7 those of you that don't recall, that means just a  
8 little bit of subluxation but not more than 25 percent  
9 of the size of the vertebral body and then failure of  
10 non-operative treatment for four months, although I  
11 heard it was six months. So maybe they could make  
12 sure that the paperwork -- just confirm whether the  
13 paperwork is right or what you said was right would be  
14 appreciated.

15           I do want to remind the panel that many of  
16 us have been away from spine surgery for a little  
17 while and maybe don't do spine surgery. Degenerative  
18 disc disease as an indication in itself, is a fairly  
19 controversial subject. Degenerative disc disease is  
20 thought to be a source of low back pain.  
21 Unfortunately we cannot attribute it specifically as  
22 the source of low back pain. And so when we look at

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1 clinical results in here, 70 percent range, we wonder  
2 if that means that they're really doing better for  
3 back pain. So from a panel consideration issue I  
4 think we need to have the clinical understanding that  
5 most of the patients that have degenerative disc  
6 disease and are having fusions for degenerative disc  
7 disease, it is for back pain and not for the disease  
8 that they're getting fused.

9 Many people have degenerative disc disease  
10 without having evidence of discomfort or clinical  
11 limitations or functional limitations. And in fact,  
12 one of our panel -- I mean, not our panel experts but  
13 one of the applicant's experts, in fact, has published  
14 well on asymptomatic degenerative disc disease. So we  
15 can't equate fusing degenerative disc disease with  
16 eliminating pain which may be a consideration that we  
17 have to raise later with our discussions.

18 At any rate, the other indications are all  
19 appropriate and for their device it may have been the  
20 only reasonable one that they could get us a defined  
21 population for. Sorry, I went the wrong way. They  
22 excluded appropriate things, prior fusion at the

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1 level, significant co-morbidities, inorganic behavior,  
2 that's people that are trying to fake out the doctor  
3 about their pain, for those of you that aren't  
4 familiar with what inorganic behavior would be,  
5 substance abuse and then a few others that made a lot  
6 of sense as well.

7 The patient populations were very similar  
8 in the three groups and so beyond just stating that  
9 once again, I don't think we need to belabor that  
10 point. The primary outcomes, radiographic fusion, Dr.  
11 Kostuik pointed out exactly why I put it in quotes.  
12 I don't think we need to go on with that. The  
13 Oswestry scales, the neurologic function and the  
14 overall success were the primary outcomes. Secondary  
15 outcomes, of course, were the back pain, leg pain, the  
16 PCS and MCS of the SF-36 and then they also had  
17 another issue of this type early on to see about  
18 subsidence, I believe was the main target of that.

19 Basically, they found either equivalent or  
20 superior results. I would attribute the Oswestry  
21 superior rating there as being simply because they  
22 didn't have to take the bone graft is in my mind one

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1 of the bigger things as well as the limitation of the  
2 surgical exposure. Surgical exposures do lead to some  
3 patient symptoms and some problems down the road and  
4 I think that's the main reason that we're seeing a  
5 difference there. I don't think it's attributable to  
6 the device itself.

7 As far as the secondary outcomes that they  
8 were looking at, again, we didn't find a great deal of  
9 benefit there or difference there between all the  
10 groups, but you do notice that there was really in the  
11 open procedure for back pain we're getting back into  
12 that clinical problem, I think, where even the  
13 morbidity of the exposure may be enough of a problem  
14 to give them a bad result from a back pain standpoint.

15 And then, of course, as you see the PCS on  
16 the SF-36 was superior. Antibodies, I really didn't  
17 find anything in the data to attribute a problem with  
18 the antibodies either from the BMP or the bovine  
19 collagen antibodies. I will be asking the applicants  
20 if they wouldn't mind taking the question now and  
21 writing it down so that I can have an answer later.  
22 I'm just curious as to why -- how would you explain

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1 the fact that you would get bovine collagen antibodies  
2 in the control group when they did not apparently get  
3 exposed to the bovine collagen? And I'm sure you have  
4 an answer prepared for that. I'd just like to hear  
5 your explanation.

6 Let's see, so in summary, the device in my  
7 review of the data appears as safe as a cage with  
8 autograft for a single level fusion in degenerative  
9 disc disease. It appears to be as efficacious as well  
10 again with the quantification of the fusion data and  
11 I really have to reserve the comment on some of the  
12 embryological effects and that sort of thing for our  
13 other experts on the panel.

14 Discussion issues again, will be a  
15 radiographic evaluation of the cage fusion from my  
16 standpoint, the immune response, the tumorigenicity  
17 and the time course of the BMP-2 presence and just to  
18 reiterate again, the quality of the films that we were  
19 provided on our CD roms, failure or success, I have no  
20 idea how to tell this as a clinician, which one is the  
21 failure and which one is the success.

22 I'd be interested to know if the audience

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1 could pick those out. Similarly with the CT scans,  
2 I'm not convinced that they could tell me which of  
3 these were study or control and so from a radiographic  
4 standpoint, we have those questions and I thank you  
5 for your time.

6 CHAIRPERSON FINNEGAN: Thank you very  
7 much. Dr. Larntz.

8 DR. LARNTZ: I'll just sit here if that's  
9 all right. I've got a few comments, actually not very  
10 many. First, let me say I don't know if anyone said  
11 it but compliments to the company and the FDA for  
12 their presentations. I thought they were very good  
13 presentations and very clear and well, I'll just say  
14 that, that's true.

15 Compliments to the company for their  
16 randomized open study. The device clearly meets the  
17 criteria set up in the protocol. As a statistician I  
18 should just stop there and maybe you should say please  
19 do. Not only in inferiority or equivalence or  
20 whatever you call it, the device clearly establishes  
21 that with respect to the primary endpoints and  
22 actually comes close to this from the secondary

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1 endpoints. I mean, that's pretty good. Some of us  
2 have been involved in studies where that's not always  
3 true. So I think it's a very clear case that as far  
4 as the protocol criteria is concerned, the device  
5 meets the specifications.

6 Again, compliments. The documentation,  
7 has anyone seen what we have up here? The  
8 documentation is actually quite extensive, but it  
9 actually gives me good confidence in what was done and  
10 even down to providing some interesting programs which  
11 gave me great confidence in how the calculations were  
12 carried out. I appreciate that.

13 Okay, enough of that. Now, one issue that  
14 seems to be coming up are CT scans and x-ray. I'm a  
15 statistician. I don't know anything about those  
16 things. I don't know anything about lots of things but  
17 I do know it's important to take measurements in a  
18 blinded fashion and to have adjudication and  
19 remeasurement and a process that allows multiple looks  
20 at these x-rays or CT scans. It appears to me that  
21 the company did that. It appears to me that with  
22 respect to some issues, with respect to that, it

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1 doesn't matter much in the sense that the -- all of  
2 the conclusions wouldn't change whether you use the x-  
3 rays or the CT scans.

4 So I feel very comfortable that with  
5 respect to the clinical aspect, we can talk about what  
6 fusion is or is not, I'm not going to deal with that.  
7 That's not a statistical issue but I don't think  
8 there's an issue with respect to the data or the  
9 conclusions with respect to that issue. So I would  
10 like to say that the study conclusions don't depend on  
11 that issue. How is that, don't depend on whether CT  
12 scans or plain films are used.

13 A terribly small point and this is only  
14 because the documentation, there are some missing  
15 data. It's not all perfect. The world sometimes  
16 doesn't collect all the data and there are some  
17 methods given in the documentation which no one talked  
18 about today which is fine, called intent to treat and  
19 I'm just going to say for the record, that particular  
20 method of dealing with missing data is not  
21 appropriate. We need to do some kind of sensitivity  
22 analysis, that is some kind of analysis that says, if

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1 the control group did better than the treatment group  
2 by a certain amount, would it change our conclusions.  
3 There wasn't, as far as I could tell, and it's a  
4 question, if any sensitivity analysis of that sort was  
5 done, I didn't see that and I think we saw a lot of  
6 what was done.

7 But I don't think it would change the  
8 conclusions much in this case because again, I think,  
9 as I said, the criteria set up and protocol, were met  
10 and met fairly convincingly. Another question which  
11 is I don't know how much analysis was done of  
12 covariates to find out if there are sub-groups of the  
13 patients that do better on one -- on the device, not  
14 comparatively but are there sub-groups of patients for  
15 whom this procedure is better indicated, "the overall  
16 success rate", quote, unquote, I realize it's a very  
17 stringent criteria, but they're not very high, so are  
18 there ways to pick out sub-groups that have higher  
19 overall success rates for instance, and I don't know  
20 the answer to that.

21 Again, a small minor point, this is not  
22 necessarily for the company, maybe for the FDA, a

1 number of these measures are scales. The Oswestry, is  
2 that how you say it, is a scale, back pain are scales  
3 and they're analyzed as success/failures because of  
4 some arbitrary criteria and actually the company  
5 mentioned -- I was actually pleased. The company  
6 mentioned that they might have some slight difference  
7 on back pain because they actually have a higher  
8 average but their success proportion was lower.

9 And I think that when we have scales like  
10 that we lose information when we go to arbitrary cut  
11 points. That's a comment, it's actually a comment I  
12 made before and it probably -- if you're on this panel  
13 again with another study, it will be a comment I'll  
14 make again because it seems there seems to be this  
15 drive to call it success or failure rather than trying  
16 to measure the size of the effect and the amount of  
17 change, and I'd prefer to see the continuous variables  
18 analyzed as continuous variables and there was, of  
19 course, some of that analysis done in the reports.  
20 Okay. So that's the open randomized study.

21 Now, the laparoscopic study is not a  
22 randomized study. It's an extra arm, right? It was

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