even a bone graft, secondary bacteria and infection tend to cause loss of product but not loss of the sponge. So there hasn't been any systemic or gastrointestinal disturbances associated with this product.

CHAIRMAN BURTON: One follow up to that, Dr. Marx. It might not lead to particularly large loss of the product, or the sponge. Given the fact that it's placed on the sponge in a liquid state, is there any leaching out or other dilutional factor that might reduce it? Because, again, we saw from the studies that it is dosage-dependent. So let's say that early on you had -- or less than adequate closure. Would there be the potential that you would lower -- in essence, have lowered the dosage, thus lowering the effectiveness of it?

DR. MARX: That's essentially an excellent question, because the binding to the sponge for the type of the protocol -- 15 minutes -- 93 percent of the protein is bound

to the sponge. And so even if you wring out the sponge, if you will, the protein stays within the sponge, bound chemically to the ACF sponge. It is only released upon biologic activity within the wound, so you wouldn't dilute the product if that were to occur.

CHAIRMAN BURTON: Did that answer your questions, Dr. O'Brien?

DR. O'BRIEN: Yes. Thank you.

CHAIRMAN BURTON: Does anyone else have comment or questions on -- in regard to question 1? Dr. Patters.

DR. PATTERS: Yes. I wonder if anyone from the sponsor would like to address the antibodies to bovine collagen that we're seeing in patients who didn't receive the bovine collagen.

DR. CILLO: My name is Yolonda Cillo. I'm an orthopedic surgeon. I'm Medical Director for Biologics at Medtronic, an employee of Medtronic, and my role in this has been safety issues.

And you're correct, in the study there were patients who had antibodies to bovine collagen. The thought is that some of them may have had prior exposure, particularly talking like in the control group. Is that what you mean? In the control group there were some, and most likely some of them had prior exposure to bovine collagen, because with autograft there would be no other explanation. Does that answer your question?

DR. PATTERS: Yes. That was not one of your acceptance and rejection criteria -- previous exposure to collagen sponge?

DR. CILLO: I'm going to ask the clinicians on that.

DR. COCHRAN: It wasn't a part of the inclusion or exclusion criteria, but most people don't have too much exposure to collagen sponge. We think it was actually more related to bovine products that are on the market in a number of different types of products. And so they inadvertently have this

apparently in our systems. We probably have more of it than we realize, obviously.

DR. PATTERS: Something to do with steak consumption or something like that?

(Laughter.)

DR. COCHRAN: Well, we are from Texas now, you know.

(Laughter.)

CHAIRMAN BURTON: Yes. Dr. Cochran, my question would be: was there anything tracking I guess -- because the other representative brought this up -- and the fact that had these patients had other previous grafting procedures, let's say that they had some other bovine collagen product, not a collagen sponge, but there are a number of them on the market --

DR. COCHRAN: Right.

CHAIRMAN BURTON: -- that they may have -- I mean, was there anything that either looked at -- not so much as an inclusion or exclusion criteria, but whether that was --

that even -- would that have been noted anywhere?

DR. COCHRAN: Not to my knowledge maybe. But we did a -- you know, a normal history on the patients as they came in from a medical and dental point of view, but nothing that we asked for specifically I think if they had bovine collagen.

CHAIRMAN BURTON: Thank you. I see your hand up. Dr. Marx, did you want to make a comment or --

DR. MARX: Just to amplify on that. In the preoperative screening for the sinus augmentation study, which I am most familiar with, the history included questions of previous surgeries and exposures to bovine products, but many patients receive bovine products that they're unaware of at the time of even their surgery. And so I think those were just unaware to the patient, did not come out in the histories.

CHAIRMAN BURTON: Thank you.

Are there any other comments or discussion? Yes, Dr. Fleming.

DR. FLEMING: One practical clinical question that I have is in the case of an endodontically-treated tooth, which is removed, is the idea that the stuff is inserted -- the product is inserted immediately after removal? My question -- the basis of it is that many of these endodontically-treated teeth probably contain pathogens.

So if they are moved and the material is inserted immediately afterward, then I'm concerned that you have a potential for degradation of the graft, as a result of placing it in an endodontically-treated tooth extraction site.

Dr. Cochran.

DR. COCHRAN: I can make a comment. Some of our patients had some sort of periapical infection or something like that when we took the teeth out, but we were real

careful, as always, when you take out a tooth that has an infection that you clean that out real well prior to putting in whatever you're going to put in -- in this case, the sponge or the sponge plus BMP. And so we never saw any residual effects of that at all.

I want to also make a comment that earlier I think there was a comment about maybe exposure to a nerve in the mandible. This sponge is placed in the extraction sockets, and it's really not placed lower than that, so you're not going to really have exposure to nerve tissue as well.

And remember the sponge -- and another comment was about dehiscences. Remember that a collagen sponge or the collagen protein itself is really suitable for epithelial migration, and, in fact, most of the membranes that we use in periodontics, the collagen membranes are the ones we prefer, because the epithelium really covers that very nicely.

So even in the sinus augmentation procedures, if there was a small tear in the membrane, which we weren't aware of, the collagen sponge is an excellent carrier because it supports that and helps that tissue growth back.

CHAIRMAN BURTON: Let me ask one continuation. I can certainly understand that in terms of both the sinus and the collagen membrane issue. But, again, if it was in the mandible, there are going to be, if you use it in the bicuspid or molar area, there are going to be -- not so much that you're packing it down that much, but you certainly would have a, you know, real potential of actually having nerve coming.

We know that certainly bicuspid and -- some bicuspid and molar roots can have contact with the inferior bower nerve. I mean, that's -- you know, we know that both radiographically and clinically.

Now, there should be a thin of bone

maybe, whatever. But, again, you would have the potential of having that in contact with that. So I guess -- that came up earlier. I guess that's one of the things about having nothing in the mandible is that nobody really knows whether that might be an issue or not.

DR. COCHRAN: Yes. As a clinician, one of the things we learn -- because I was involved in all these studies since the early '90s, and one of the things we learned is we didn't pack the material in. This is not something like a bone graft material. It's osseoconductive, that you're going to, you know, press down in the socket.

So when we put the sponge in, we just put enough sponge in to fill the void of the extraction socket. So it's really never -- I don't think ever, certainly in our studies, did we ever have enough in there that we expressed it in the apical area where it would be in contact with any tissue that we shouldn't be.

CHAIRMAN BURTON: Thank you.

Dr. Triplett.

DR. TRIPLETT: I'm Gil Triplett, an oral maxillofacial surgeon.

CHAIRMAN BURTON: Yes, go ahead.

DR. TRIPLETT: I have a question. In the orthopedic studies, was there -- what was the -- how close in proximity was the material placed to some of the spinal nerves?

DR. CHIN: Well, in the orthopedic studies, obviously, in the spine you're going to be in various spinal segments based on indications close to the nerve roots that coming out of the -- you know, the spinal cord. So you're going to be collocated, and there has not been any issues that we're aware of.

Does that answer your question? Thank you.

DR. TRIPLETT: That was the point I was going to make.

(Laughter.)

CHAIRMAN BURTON: Are there any other comments or discussion on question 1?

(No response.)

Hearing none, I'm going to try to go ahead. It would appear -- and please correct me -- that on question 1 that the panel conclusion is that the preclinical data and adverse events show that it is safe and -- for both of the indications as listed.

Okay. That being completed, we'll move on to question 2. I won't take the time to read completely back through this, but we're going to turn to this, and this is basically looking at the statistical analysis that was provided from the FDA statistical presentation.

Discuss what you feel may be the clinical implications of the results presented in the PMA for this. And based on the data in the PMA, discuss whether the reduction in morbidity associated with infused outweighs the potential reduction in effectiveness,

because, again, looking at this there was a -- in the analysis was whether or not the infused may be up to 20 percent less effective than an autograft.

And, again, based upon that, how do you feel -- what are the clinical implications of that? Yes, Dr. O'Brien.

DR. O'BRIEN: Looking at the data, it appears that the autograft might be superior, but the whole point of this product appears to be offering an alternative to the autograft. If, for example, a surgeon is removing a wisdom tooth at the same time as implanting implants, then obtaining an autograft is very easy.

Most oral surgeons have devices that will take the extracted tooth and grind it to produce material for an autograft, but that's an unusual situation. Obtaining an autograft from other parts of the body besides the teeth is a difficult clinical challenge, so it appears to offer an alternative to that.

CHAIRMAN BURTON: Dr. Amar.

DR. AMAR: When we compare autograft with a material like this, given the limitations of the source of the autograft and the morbidity associated with that, I would have hoped to see some of the data compared to other allograft materials such as DFDBA. And I take it that if it performed less than the ultimate gold standard, which is the autograft, it would perform pretty well against the DFDBA.

And given the fact that with the autograft we have limitation of getting the material to graft this material in several sites, etcetera, I think it provides a safe and efficacious alternative.

CHAIRMAN BURTON: Yes.

DR. DIAMOND: Being the industry guy, I'm sort of approaching this from a little different perspective. But, you know, to pick up on what Dr. Amar has said, I think it makes a very important point when he brings

up the other graft materials.

True, autograft is the standard, but, you know, what are we truly comparing? You're comparing autograft or DFDBA or some synthetic allograft material, alloplast material. These provide structure. It's a solid material that we hope gets incorporated into the existing bone or ultimately replaced by bone, but it's solid -- essentially, a load-bearing material.

This is a very different kind of product, because a collagen sponge is not designed, really, for any kind of load-bearing. It's designed as a carrier for BMP that will induce native bone growth, so I think we need to look at it within that particular context. We're not comparing -- you know, comparing it to a graft material that's going to provide structural support. We're looking at a material that will induce the formation of that structure.

And as far as the morbidities,

clearly, anything that will reduce the morbidities of second surgical sites is -- you know, is highly desirable.

CHAIRMAN BURTON: Dr. Gunter.

DR. GUNTER: I would like to make two points. The first one is to remind the panel that the definition of "success" in the protocol, in the sinus augmentation protocol, was a very rigorous one. So even the patients that failed actually went on to receive a prosthetic implant. So keep that in mind when you're considering this question.

The other is since I'm not in this profession, I can't really comment clinically on how to weigh the risks versus the benefits. But maybe perhaps I could comment as a potential patient. You know, I think that if I was presented with the choice I would take a potentially lower success rate as something that I'd be willing to undergo with the option of not having to have an autograft obtained.

And another way to look at that is,

you know, it's a reasonable option to give a patient. You know, patients are entitled to make choices in health care, and this gives them an option in their care that they didn't have previously. So another point I'd just like you to consider when deliberating on this one.

CHAIRMAN BURTON: Dr. Li.

DR. LI: By the data presented, not only the 6-month but also 24-month, apparently if we accept the 73 percent success rate is acceptable, then apparently it is effective, although the percentage is lower than the autograft.

In addition, by considering the potential unknown tremor and pain sustained by the autograft procedure, the infused does have the distinctive benefit.

However, I do have a question or somewhat a little concern. I already mentioned this, so I would like to ask Dr. Zhang the question again. For the autograft,

and it was stable, it had to be stable for 24 months in terms of the success rate, but for the infused group, in the pivotal study it decreased slightly and probably now significantly, but it was fairly consistently over the 24-month period.

I don't know whether you have done the adjusted studies to grant a license for the 12-, 18-, and 24-month or not. If you do or do not -- you either did or did not. Do you have any possible predictions of the statistical method, whether that trend will continue, or will be -- kind of taper off?

Because if you look at it in that trend, it was -- there was a further three percent decrease, and that means if that continues at a same rate, then after 48 months that would probably drop below the 73 percent success rate.

So I understand the data was not adjusted. I don't know whether -- from statistical point of view whether you can

explain a little bit further on that concern.

DR. ZHANG: As a statistician, I can only make inferences about the data we have. So that means we -- I can only, you know, make inferences about the success rates up until 24 months, not beyond, because -- simply because we don't have data on that.

Now, within 24 months, yes, there was a -- there appear to be, you know, a declining success rate over time. But much of that was due to the fact that patients dropped out or, you know, got lost to follow up over time, especially if they had the prosthesis successfully placed, and, you know, didn't have a problem with it.

So recognizing that, it may not be all that surprising to see a declining success rate, you know, if we consider those losses to follow up as failures.

It's not clear -- well, until we understand -- we can better understand the mechanism for patient dropout and loss to

follow up, it's not clear how that should be adjusted for statistically.

CHAIRMAN BURTON: Yes.

DR. DIAMOND: Actually, expanding on what -- Dr. Li's comment, I had a question for the sponsor. I know the difficulty sometimes in trying to determine what a success criteria is. When looking at literature, it can be all over the place, and that can be clear for any kind of medical treatment.

Was there any calculation or attempt to make a calculation based on what the expected failure rate might be over time? Knowing from the clinical side that a certain percentage of implants will fail over time naturally. Is that something that was considered and factored into the -- could be, you know, factored into the equation?

DR. HAWKINS: I'm Douglas Hawkins. I'm a professor of statistics, University of Minnesota. I have no financial interest in

this product. I'm a consultant to Medtronic, who have paid for my attendance here.

I'd like to just come back to the previous question with a clarification. There was -- after the prosthesis placement, a single failure in the infused group -- and that occurred between 18 and 24 months -- all of the other patients were successful right through to 24. And this entire apparent decline in the success rate is a result of the loss of patients who were still successful up to the time of their withdrawal.

I'll have to defer for the followup question.

CHAIRMAN BURTON: Can you please turn the mike off, because it alters the system when you've got it on. Just hit the little button on the front of it. There you go. Thank you.

Does anyone else have any comments or questions? Yes, Dr. Patters.

DR. PATTERS: Well, to specifically

address points 1 and 2 there, it seems to me that point number 1 can be adequately dealt with through proper labeling. And it's clinical judgment as to whether one wants to take a treatment that may have a slightly lower probability of success if, indeed, it has considerably less morbidity. And that's just a matter of clinical judgment, but appropriate labeling to explain that to the clinicians should deal with -- should be able to deal with that issue.

The second issue in my mind, it's been my experience that oftentimes patients, matter of fact more times than not, will tell you that the morbidity at the donor site of an autograft is far worse than the morbidity at the recipient site, where the actual surgery is being performed. And, therefore, it seems to me that clearly with regard to sinus augmentation the benefits far outweigh the risks.

CHAIRMAN BURTON: Thank you, Dr.

Patters. Any other comments or questions?

(No response.)

Hearing none, we'll move on. I'm going to try to summarize question 2, and I think, actually, that Dr. Patters did an excellent job of completing that. I think in regard to point 1, it appears that it meets the statistical components for the PMA in terms of success.

And on the second question, it would appear that, again, that there is a differential from an autograft, but that probably is within the risk-benefit ratio, an acceptable risk-benefit ratio for the procedures versus the potential decrease in success.

Is there any other discussion, or does that seem to adequately summarize it for everyone?

(No response.)

Okay. Let's move on, then, to question 3. Again, given the data that was

submitted for ridge augmentation at tooth extraction sites, we want to discuss whether there is sufficient valid scientific evidence for this indication to arrive at a clinically meaningful conclusion respect to its effectiveness.

And again, one, is the data submitted rigorous enough to support this indication for use? And, two, given the data provided, please discuss whether it's possible to evaluate the risk-benefit for this indication. So I'd like to open the floor to question 3.

Dr. Patters.

DR. PATTERS: Thank you. My concern is the proposed indications for use with regard to augmentation of ridges at extraction sites. And if, indeed, an autograft is not the standard of care, then why would the indication for use be that this is an acceptable replacement for an autograft?

So I'm having problems with the way

the indications have been stated, and I could see that they need some type revision. Quite clearly, there does appear to be a benefit. I'm very impressed with the scans that show increase in bone height as well as bone width. But I'd have to look at them primarily as well-controlled case reports rather than a pivotal study. But I do have a problem with the indications for use and lumping this use with the use for sinus augmentation.

CHAIRMAN BURTON: Other comments? Dr. Diamond.

DR. DIAMOND: First of all, I think the comment on the study design, historically most studies I've been involved in where we've done extraction studies have involved posterior, you know, extraction where you have -- we have a nice cone that can certainly hold the graft material.

I think that the actual challenge was probably greater, given the fact that you had limited base of bone to work off of, and

the challenge, you know, of the material to actually have to grow bone into that particular area.

And, actually, sort of the question in terms of, you know, the criteria for success, a lot of times even going into synthetics we often -- and I know the 14K process is different from the PMA process, and there's certainly a much higher degree of rigor that has to be applied to the PMA process.

But for synthetic -- to establish some kind of clinical performance data for synthetics is often based on a series of case studies. And routinely, usually using posterior extraction sockets, it grows bone and you're really preserving the ridge height rather than augmenting it. Or at least that's the challenge, the direction to go in.

I think that there are, really, you know, two questions here. One, does it grow bone? And is that bone strong enough or

sufficiently developed enough to be able to be implanted? And then, the second question is: is that implantation of bone strong enough to withstand the forces, especially, you know, given it's an anterior maxilla, where it's subject to a lot of -- not just direct vertical forces but lateral forces, too, which I've seen, you know, cause a lot of implants to fail.

If you look at the success criteria for how much -- how many -- what percentage of the grafted sites were able to be implanted, it's 86 percent compared to 59 for the sponge, and 47 percent which I guess would be the non-treatment group. I think that, you know, it looks to me that it does grow bone.

So does it -- is it efficacious? I mean, to me, it would seem so. Rigorous with regard to statistics -- clearly, you know, that's a different question.

CHAIRMAN BURTON: Dr. Lin, do you have any questions or issues you'd like to

bring out in this as well?

DR. LIN: No.

CHAIRMAN BURTON: Thank you. We'd like to try to get -- and particularly getting into this one being a little bit more open, we'd like to try to get some other comments from some of the other panel members, if possible, at least just give us your views of this, so we can get a little better consensus if possible.

Dr. Zuniga.

DR. ZUNIGA: Well, I'll bring up again one of my concerns regarding the application and extraction sockets, and that includes the mandible. I think in the sponsor's study in the maxilla there may be some indications, although we can talk about, again, scientific rigidity. However, I think the mandible might be different.

And so the no treatment extraction socket in the mandible may do just as well as the device treatment in the mandible. So I

think that information is lacking in considering the overall verbiage of the indication -- would merit that group of studies, and you can't take the maxilla and apply it to the mandible, in other words.

CHAIRMAN BURTON: Yes. Dr. Amar.

DR. AMAR: Yes. I was alluding to that. I would tend to support Dr. Patters when he commented about the labeling, and that was in my initial comment, making that -- a comparison with the autograft may not be exactly the appropriate way. But if we would compare it against an allograft such as a freeze-dried demineralized bone graft, efficacy would come up, and I would tend to support something like that.

CHAIRMAN BURTON: Does anyone else care to make a comment? Dr. Chin, yes.

DR. CHIN: Can we have a moment to come to the podium?

CHAIRMAN BURTON: Yes. Dr. Marx.

DR. MARX: My charge here is to

kind of bring things to a clinical reality, and many of you already have done that. I was not a participant in the extraction socket data or that study, but I was part of the planning. Essentially, kind of what I'm hearing from you all is that it's a reminder to us that the infused product is not here as a replacement for autogenous bone but as an alternative to that.

And that the point I would like to make is that the extraction socket defect was not amenable to a pivotal study, because there was no standard of care for an autogenous bone graft. First of all, IRBs would not approve autogenous bone graft for an extraction socket where the given is that nothing is placed.

And so it would challenge that the placebo would be the control. There is essentially no positive control that you can use in the extraction socket data. And so what was used as an unfilled socket that heals with no ability to place a dental implant.

Now, I think the point that Dr. Patters brought up about labeling is probably correct. You, therefore, can't compare it to an autograft. But at the end of the day, the BMP, the infused, produces predictable bone. It produces bone equal to that bone that we saw in the sinus augmentation, which we felt at the time of planning was a more challenging defect, because bone doesn't normally exist in the sinus cavity and doesn't regenerate.

And so we felt we could honestly extrapolate the bone formation de novo in a maxillary sinus augmentation to an extraction socket, particularly this extraction socket.

What is unique about the extraction socket is it is not an extraction socket. No doubt extraction sockets will regenerate bone on their own, or roughly we'd graft every one of them.

But this extraction socket was a classic buccal wall defect, and when you lose that buccal wall it becomes a unique defect,

which is a true critical-sized defect, that bone will not regenerate in that particular socket defect, and that if you can regenerate bone -- and I think we have an X-ray or something to show, I think Dr. Cochran showed it very nicely -- that this will not hear on its own, that the outcome is to have a minimum amount of bone that you could not place an implant at all, yet the infuse is able to regenerate bone here de novo similar to what we saw in the sinus augmentation.

So at the end of the day, the histology is the same, the CT scans are the same, and that the issue from a patient perspective is a choice between having no ability to have a dental implant placed and an ability to have a dental implant placed if something like infused is indeed used.

And so I hope some of these comments clarify why I think the extraction socket, although I wasn't a participant, really has a strong scientific evidence that

meets the criteria I saw in your valid scientific evidence that I wrote down as 21 CFR and a couple other numbers that I long since have forgotten.

But I think it meets that criteria, reasonable assurance that it's effective in developing bone that is clinically a benefit for patients.

Now, to amplify on that, I'd like to introduce Dr. Myron Nevins, who was actually a participant in the extraction socket data. I think he could reinforce some of those points as well.

CHAIRMAN BURTON: Can we just actually -- there's going to be an open comment section later. I'm trying to bring another person in now. I think we'll -- there will be a period for that later, and I think we'd be happy to have you introduce it at that time.

Dr. Patters.

DR. PATTERS: Yes. Dr. Marx, if

you could remain.

(Laughter.)

I do appreciate your comments, and I was not questioning the validity of the data that this is effective. However, and I appreciate you see my concerns regarding the labeling.

I'd like you to respond to Dr. Zuniga's concerns that if you've only tested this in the maxilla that you really can't make labeling claims about how it will perform in the mandible.

DR. MARX: I'm not too sure I can comment that -- to that, because, indeed, it wasn't studied. Dr. Zuniga is initially right. But look at the practicality of it. I'm not too sure you can do a randomized prospective clinical trial for every one of 32 tooth positions in each jaw. There's a practicality that becomes unreasonable to test the canine position versus the molar position versus the third molar versus the incisor in

the aesthetic zone.

And so, you know, for the dentists on the panel, I think we have no doubt 32 teeth. Is an extraction socket reasonable? And why it was chosen to be the buccal wall defect as the most difficult one to regenerate bone. We hope it suffices for extraction sockets in either bone which have a similar embryology. They're both intramembranous bone under the influence of the neurocrest or embryology. That at least was a scientific basis for that.

DR. PATTERS: Would you have any problem, then, if the labeling would state that it has not been tested in mandibular buccal wall socket defects?

DR. MARX: That may be an answer better answered by the sponsor. But my personal -- I would not have any difficulty with that labeling. Yes.

CHAIRMAN BURTON: And let me actually -- just a second, Doctor. Let me

finish with Dr. Marx before he gets to sit down.

(Laughter.)

Thank you. I guess my concern has been along with this. I mean, I think those of us who have been in the implant business for 15, 20 years know the fact that implants -- and we know historically -- don't exactly perform the same way in the mandible and the maxilla or anterior maxilla.

There has always been different, shall we say, success percentages, at least floated around for a long time in terms of -- and the truth was, most people thought the mandible was higher than the maxilla. And probably the most challenging, and I think you are very correct, was the maxilla.

But given that, the question which is sort of unanswered with this -- and if we look at the statistics is the truth is in the mandible you might actually find out that, yes, it's efficacious, but the truth is is

that doing nothing is efficacious.

As we saw, statistically, the dosing studies showed the fact that -- statistically when we analyzed it that when they used -- when you used the sponge alone, which, again, should not be active, versus the other, that it was actually almost statistically insignificant in terms of whether it was really effective or not.

Carrying that out one more step, you may -- you could come along and say, you know, in the mandible you might actually find out that they're identical. And so, yes, you'd have something which is safe. It's efficacious. But the question is it may not be any more efficacious than doing nothing.

So, again, trying to give an indication based upon just the maxilla that then by conjecture goes over and says that it's efficacious and necessary in the mandible, might be a bit of a stretch.

Do you want to respond to that?

DR. MARX: I think we have somebody more appropriate to respond to that.

(Laughter.)

CHAIRMAN BURTON: Dr. Cochran.

DR. COCHRAN: I'd like to comment on two aspects of that. One is I think you're getting a little confused between an intact socket versus one that has missing walls within the component. And we chose the one that was challenging by having the missing walls.

In the mandible, I think your point is correct that if you have existing surrounding walls you're going to probably get pretty good fill. But my concern is when you have an extraction socket where the -- during the procedure you lose that buccal plate, which happens a lot of times in the mandible as well, so you're creating a situation which, in fact, is a defect site and not an intact site.

Secondly, your comments about the

implants in the maxilla versus the mandible -- I think those comments were probably appropriate a number of years ago when we were using machine-surfaced implants, and we were really talking about the quality of the bone that those implants were placed in, because when machine-surfaced implants are placed in the posterior maxilla they clearly had significant problems there.

Today, I don't think anybody sells machine-type implants anymore, and most all the implant companies sell implants with some sort of micro-textured surface on them. And I think that issue has really gone away.

CHAIRMAN BURTON: Thank you.

Any other comments or observations? Yes.

DR. DIAMOND: A question. You know, Dr. Zuniga made a very important point that probably in the mandible, given its structure, you probably will not be able to -- it's probably not a good clinical model,

because the -- it probably is much more stable for implants, and that's the challenge.

I guess my question is, you know, to the panel is that -- is it appropriate to view the data as a clinical model? And often clinical models are not exactly totally reflective of the actual clinical case, but something which, you know, the system is stressed maybe a little bit more so than you would normally see in a clinical situation. And can that be -- you know, can we impute a particular performance or would some kind of post-marketing, you know, series of case studies be appropriate? So I'm just throwing this out to the panel.

CHAIRMAN BURTON: Yes. Dr. Janosky.

DR. JANOSKY: I would like to take the conversation back to the question. And the question was regarding valid scientific evidence. And if I think through the data that were presented, and I think through study

designs and what is acceptable to FDA as well as what the sponsor had presented, I'm left with looking at the indication as the companionship with the study design that was utilized.

So if I think about the indication that the sponsor is presenting, does the study design get at that indication? And we have a couple of approaches. One is the approach regarding your comparison, and the other approach is reaching a criteria.

And if I look at reaching a criteria and I'm still not sure about the 73 percent and sort of the appropriateness and what that actually is telling us, I think a criterion has been met. Why a comparison is there and the importance of a comparison is taking us in a different direction.

So now let me evaluate whether that criterion was met and whether it was met in a valid scientific way based on the information presented by FDA -- what is acceptable or not

acceptable.

And that's where I'm having difficulty, because if I think about the research designs that were done, and the research design that was done for this particular study, all of the issues that we would hope to see have not been met, or seem to be very weak in terms of being met -- namely, heterogeneity of patient base, heterogeneity of provider or physician clinician, understanding of outcomes, and the significance of those outcomes.

So in terms of these two -- this question 3, and A and B, I actually would say that, no, that the data submitted is not rigorous enough to support the indication for use. And given the data provided, the question says, "Please discuss whether it is possible to evaluate the risk and benefits for the indication." It seems to suggest to me that something is there. Is it strong enough for the criterion? The answer -- my summation

is no.

CHAIRMAN BURTON: Thank you. Are there other comments from the other panel members in regard to that?

Seeing none -- I'm sorry. Yes, Dr. Gunter.

DR. GUNTER: Just a couple of comments regarding this question. And I'm glad Janine brought us back to the question, because I was having trouble following all the discussion.

But, you know, when I look at the data overall from the extraction site study and go back to the FDA definition of "efficacy" and "valid scientific evidence," I do think that those definitions have been met in this case. And one reason I state that is that I think, quite clearly, this material stimulates the formation of new bone.

And, you know, I'm a pathologist, and when I look in the microscope and see bone I can't tell where it's coming from. I can't

tell if it's from -- if it's trabecular bone. I can't tell where it's coming from. So the fact that it does stimulate what appears to be what both the FDA and the sponsor have said is apparently normal bone.

But that makes a big impression on me, and so I believe that the data from the sinus augmentation study would show that that normal bone supports functional prosthesis can be extrapolated to the study. And I would urge the panel to think about it in that way.

DR. JANOSKY: Actually, can I respond to that, or at least --

CHAIRMAN BURTON: Oh, yes. Yes, Dr. Janosky, please.

DR. JANOSKY: Okay. What has gotten me hung up is that if you read the definition for "effectiveness," there's a very clear statement within that definition for "effectiveness." And it says "significant portion of the target population." And that's the issue in which I'm very uncertain, given

the study design, given the number of patients enrolled, given the findings of those, whether a significant portion of the target population had been, 1) treated, and 2) shows a positive result.

I do agree that there are positive results. The issue is: has it been a significant portion of the target population? And I think that's some of the issues that you had raised in your summation of the review of the PMA, and perhaps that might be a reasonable discussion for a while.

Clearly, Dr. Burton, that would be your decision. But at what point do we consider what type of studies, the size of the studies, the extent of the studies? And size is not the only determinant. We could have a very small study that is directed in the patient population that we want to go to and still use it for effectiveness.

CHAIRMAN BURTON: Dr. Amar.

DR. AMAR: I think to alleviate a

little bit your concerns it's a product that is already in the market for other uses, and I would take a venture to say from the sponsor that the polymorphism, the human polymorphism is present when they use it in spinal fusion. And they have provided sufficient efficacy over there.

So I think that that leap can be made when it comes to spinal fusion into the dental application. Where I'm having problems is on the labeling again. And, again, I will come back to the labeling issue. Is it labeled sufficient in regard to replacement of autograft as opposed to just allograft?

And when we come again on the extraction site, is it just indicated on the maxillary teeth and not in the mandible? Or at least having some kind of indication to the dentist.

CHAIRMAN BURTON: Dr. Diamond, you started to have a comment?

DR. DIAMOND: Yes, to what Dr. Amar

said when -- you know, judging -- taking the efficacy in orthopedics, along with the data that was presented today, I think we can, you know, make the assumption that it would work in other bony -- on other bony sockets. I think we can -- that's not a tremendous leap of faith here, I think, given the total body of evidence.

If that's a wording issue, you know, then that's a different situation, and that -- I don't know whether we're charged with discussing wording, but -- of science.

CHAIRMAN BURTON: Sort of secondarily. Dr. Zuniga, would you care to comment in here as well? Because, you know, your review of this sort of sparked a little bit of this in terms of -- we sort of got in -- are sort of getting two sides here, and I guess that I'd just like to get a couple more opinions from some of the other people on the panel to try to fill this in, so we can try to get towards some kind of a consensus.

DR. ZUNIGA: I'll try. The concern about the actual study in the extraction is -- again, as discussed before, was use a placebo. That's one issue. I think the no treatment group is probably not appropriate, but it did point out that the -- if you do not treat the extraction socket, you have a natural loss of bone that would not -- probably not support an implant.

And, therefore, future implantation would require either another device, product device for that, or autograft. So the placement of the device at the time of extraction may obviate that in 86 percent of the cases, based on the rigorous comments. So there is a positive reason for looking at this.

I think, however, the fact that it was -- that group was not blinded, I don't think it's a fair statistical comparator. A probable appropriate statistical comparator would be a true blinded sponge with no

product, etcetera, and I would include both the mandible and maxilla, even though there is some discussion that you could apply one to the other.

I'm not sure we can just generally make that -- the mandible may act, in fact, different than the maxilla in terms of regeneration. And, again, the importance of the criteria, the sponsor indicated that -- the placement of implants.

CHAIRMAN BURTON: Dr. Patters.

DR. PATTERS: Yes. In response to Dr. Diamond, I wasn't quite sure when you said, "Well, if this is a matter of wording," is that like a matter of semantics? Because all my years on this panel has taught me that labeling is everything. It's not just wording. I mean, it is critically important.

DR. DIAMOND: Just to respond, no, I didn't say it's -- I didn't mean to imply that it was trivial. But if the -- it is very important. I think that I guess parsing out,

you know, does infuse -- you know, is it efficacious with regard to growing bone? Which is, I think, the overall intent.

And if that's -- you know, if we will sort of agree and accept that, and if the issue is in terms of whether, as a replacement for autograft is the issue, then that's -- you know, it's certainly a discussion that needs to happen, and something that needs to be addressed.

But is it doing what it intends to do? Or is it stated appropriately in the labeling? You know, that's what I was trying to get to. But, clearly, labeling -- it has to be labeled appropriately. There's no question about that.

CHAIRMAN BURTON: Dr. Patters.

DR. PATTERS: I'd like the opportunity to address Dr. Cochran again, if I could.

CHAIRMAN BURTON: Certainly. Dr. Cochran.

DR. PATTERS: Dr. Cochran, I think we all agree that there is not an adequate positive control for extraction sockets. But clinically, given the existing products on the market, and given what the clinician has available, if you're faced with an extraction in the maxilla that is going to have a buccal defect, what do you do as a clinician, given what you have available? Don't you use some type of grafting procedure?

Because you know that if you do nothing you're going to have to find another way to augment it in the future. You are not going to be able to use -- to do the implant.

DR. COCHRAN: It's a good point that you make, and I'll certainly give you my opinion on that. And, clearly, as a clinician, when we take out a tooth and we're losing buccal plate like that, we have to do something, in my opinion, for the benefit of the patient.

Whether the patient thinks they're

going to get an implant next week, or, you know, a year from now, you don't want to exclude that possibility. So the benefit for the patient is to do something.

Generally, we have solutions that I think are not ideal for what we can do for our patients. Generally, we used to use EPTFE membranes and let a blood clot fill in that area. But the EPTFE membranes about 50 percent of the time got exposed and became infected, and gave us a less than adequate result, and there is data to support that.

If you go to these other types of materials that are osteoconductive materials just to fill the space, as was pointed out a little bit earlier, you end up with material that's residual in the extraction socket area, and that is not ideal for placing implants in that area.

Some of the osteoconductive materials stay in there for years at a time, and that's certainly not ideal in my -- in my

view for placing implants. I would like to have native bone that's there without residual material, and this gives us that option.

One other comment I would like to make is that the -- some of the discussion is centered on the design of this trial. But if you think about this design, if you're thinking about, okay, well, let's design another trial, this was a randomized, prospective, blinded human clinical trial, an RCT about as high a level evidence as you can design. And that's what we were trying to do.

Clearly, you knew when the patient wasn't treated with anything, as has been pointed out, which was a good point. But in the other case of the sponge versus the non-sponge, we had no idea, because that was prepared in a room outside of where the clinician was working.

DR. PATTERS: So can I conclude, then, that it is your conclusion that there is nothing presently on the market that is

suitable to help you regenerate a socket defect with a buccal -- in the maxilla that's missing a buccal wall?

DR. COCHRAN: Yes.

CHAIRMAN BURTON: Before you sit down, I guess one other sort of extension of what Dr. Patters was asking about was, how do you -- how would you like to -- I don't want to say explain, but how would you relate back to Dr. Zhang's statistical analysis that showed that when you didn't go with no treatment versus the BMP, but you went to the placebo versus that, that you suddenly got down to an effect which was actually not statistically significant between the two groups in terms of efficacy.

I mean, that would lead you to believe that literally almost any material -- I mean, you put a collagen sponge in, which is not either particularly osteoconductive or inductive. At least given the sample size, could have been just as effective in a larger

size sample. I mean, so how do you then address the concept of efficacy given that statistical outcome?

DR. COCHRAN: Well, I'm not sure that I agree with the way the statistical analysis was performed in that case. I have to go back to the data that I presented this morning. And when I look at the data on the height of the extraction defects, whether you put in the BMP sponge versus the sponge alone, there was a significant difference, very significant difference.

Also, if you looked at the width of the bone fill in areas where there was not existing at one-quarter and one-half there were statistically significant advantages to having the BMP versus the collagen alone.

Also, if you go back and look at that data very carefully, patients that received the .75 milligrams per mil received more of a benefit than the collagen alone, but not as good as the 1.5. So there was dose-

response relationship which scientifically is a pretty strong relationship for the protein.

CHAIRMAN BURTON: Any other questions or comments?

(No response.)

Thank you, Dr. Cochran.

Dr. Lin.

DR. LIN: I just would like to remind the panel about our PMA regulations. I think in order for the panel to recommend the approval of any PMA events, I think one thing you need to consider, what is sort of valid scientific evidence. And, right now, I think the question in front of the panel is, which of those parasites, would that constitute a barrier to scientific evidence? And I'd just like you to take that into consideration.

CHAIRMAN BURTON: Dr. Janosky.

DR. JANOSKY: That actually was the issue that I was raising, is that given that study design, the size of the study design, the heterogeneity of the subjects, etcetera,

etcetera, my conclusion would be no, more work would need to be done.

CHAIRMAN BURTON: Any other comments to that? Yes, Dr. Li.

DR. LI: I also would be cautious to use -- directly use the spinal augmentation and sinus augmentation effect of this data to the extraction socket, because it is known that BMP effect can be different, depending on the circumstances of the defect, including the size and the shape of the defect.

So we do need some direct evidence on the socket augmentation itself, and I have no doubt it is a fact -- effective that BMP will -- does promote the bone growth. But on the other hand, the direct evidence for the socket augmentation is needed.

CHAIRMAN BURTON: Why don't we try to sum up, since we've got pretty disparate comments around here.

On question -- can we bounce back to 3 again, please? Dr. Chin. Yes, go ahead.

DR. CHIN: I would like to get clarification on the comment that was just made, the implication that it is known. There's a difference in response of use of BMP in different areas, I believe is the indication you were making. Could you make sure -- clarify that for me, please? It's known that there is a difference is what I heard.

DR. LI: Well, what I meant was sometimes the response to the BMP effect could be different at the different -- under the different circumstances, including the physical shape of the defect itself. There have been publications, for example, by Dr. Reddi of U.C. Davis.

DR. CHIN: Okay. So you're referring to the shape of the defect depending on the defect that it's repairing?

DR. LI: No. All I was saying is you -- it is known that could be the response, the fact of the BMP, to promote the repair of

the bone defect could be different at different places under different circumstances.

CHAIRMAN BURTON: Dr. Janosky.

DR. JANOSKY: Dr. Burton, can I ask Dr. Li a question, please, related to that?

CHAIRMAN BURTON: Yes, that would be fine.

DR. JANOSKY: One of the issues that we have been talking about is the max versus the mand. In light of what you just said, would you please comment on that difference, given that the study was only done in one and not the other?

DR. LI: That why I said for the evidence on the mandibular, however, we do need the results on the mandibular socket augmentation.

CHAIRMAN BURTON: Yes. And who are you? I'm sorry.

(Laughter.)

A new face has appeared at the

podium.

DR. WOZNEY: Yes. I'm John Wozney. I'm a scientist and Assistant Vice President at Wyeth. And I directed most of the preclinical pharmacology work supporting this PMA.

I'd just like to make a couple of comments. We've done a huge amount of preclinical pharmacology work with this particular device in a wide variety of anatomic locations. And I would have to say that bone inductive effect is essentially identical everywhere that we placed it.

And, certainly, if you form bone in a very large defect site such as the sinus, forming bone in a smaller site as an extraction socket is relatively easy.

CHAIRMAN BURTON: Thank you.

Any other comments?

(No response.)

I'll try to summarize this. We obviously have some -- obviously, some

differences which may be more appropriate when we get to both the summation and -- the overall summation and to the panel voting -- may be more in line comment-wise with some of that.

But the answers -- or the summations to question 3, part 1, is the data submitted rigorous enough to support this indication? It would appear at least from what I'm hearing from part of the panel at least that there is some question whether some of the extrapolations off the existing studies and the solo study for ridge socket preservation, ridge augmentation, may not have been met for part 1.

And then, based upon that, it's certainly that there's a -- there is a risk-benefit ratio, and even in this particular indication it certainly is safe. The question is whether whatever risk may be present is benefitted in the fact that at least it's unclear, based to a degree on the existing

clinical study, the dose studies, whether or not it is -- we know that it appears certainly to be effective.

The question is whether whatever risk is present is actually necessary, given the fact we're not clear whether that's necessary at all at this time.

Given that, like I said, we'll move on to -- okay, do you have any other comments, Dr. Lin?

(No response.)

Okay. Thank you.

We'll move on to question 4. Please discuss whether sufficient, valid scientific evidence has been provided to demonstrate the safety and effectiveness of infused bone graft for the following indications requested by the sponsor -- 1) sinus augmentation, 2) extraction socket augmentation. This is, in a way, sort of a continuation of 3, but let's move forward with question 4.

Point 1 on sinus augmentation -- again, we want discussion on whether there's valid scientific evidence for both its safety and effectiveness for the indication.

Yes, Dr. Amar.

DR. AMAR: Could you reiterate, of the comments that we have, we have said and expressed all around -- when it comes to safety, I think that it's -- at least in my opinion, there is sufficient data to support safety of this compound. When it comes to efficacy, I think that sinus augmentation would go for that, but the extraction socket augmentation falls somewhat short of it. And that's my recommendation.

CHAIRMAN BURTON: Other comments? Dr. Janosky.

DR. JANOSKY: Mine is very similar. I think safety for both. For effectiveness, definitely for sinus augmentation; for socket augmentation, no.

CHAIRMAN BURTON: Dr. Patters.

DR. PATTERS: I generally concur. Certainly, yes for one, and some question about two. But I would hate to not have this product available for this indication, if the indication were very, very specific for the treatment of buccal wall defects in extraction sites in the maxilla, and with disclaimers that the product has not been tested in molars. Is that correct? It has not been tested in molar extraction sites? It has not been tested in the mandible, etcetera.

Because as Dr. Cochran pointed out, and I think his point is excellent, there is no alternative that is suitable to the clinician. And if one does not put anything in such extraction sites, we're going to have to find another way to augment that bone if, indeed, an implant is the treatment of choice.

So I think this is all a matter of labeling, and I would recommend to FDA that they very carefully negotiate some very, very specific labeling and indications for number

2.

CHAIRMAN BURTON: Yes, Dr. Amar.

DR. AMAR: If I follow your argument, then the labeling would become maxilla interior with buccal only missing. That's pretty specific.

DR. PATTERS: That's all they tested.

DR. AMAR: That's what it comes down to. And if it's the case, I have no problem with the labeling. But the range of patients that are going to be benefitting from this is pretty limited, rather than asking for more data.

DR. PATTERS: Well, my question then, if you could clarify what you just said, Dr. Amar. Is it you're saying that -- not to have more exclusive labeling language, but to go ahead and request further data in other anatomical sites as -- I mean, what are you recommending, then, if you don't have exclusionary language?

DR. AMAR: I'm just following the -- his argument by saying we would recommend a specific labeling. And if we recommend a specific labeling, it becomes maxillary buccal, not mandibular, and only anterior teeth, probably not even a canine, because a canine is in the angle and you would argue that it's not being tested.

So the indications towards usage for such a compound becomes very limited rather than waiting for more data and expanding it to a larger number of treatment sites.

CHAIRMAN BURTON: Dr. Cochran, a point of clarification for me. My understanding was that this was tested from like -- I mean, other than molar sites in a maxilla, is that correct? So bicuspids, etcetera.

DR. COCHRAN: We did a lot of bicuspids.

CHAIRMAN BURTON: Okay. So it's

basically molar teeth.

DR. COCHRAN: Molar wasn't examined in this trial --

CHAIRMAN BURTON: Okay.

DR. COCHRAN: -- in the mandible.

DR. AMAR: Was not.

DR. COCHRAN: Was not.

DR. AMAR: Was not.

DR. COCHRAN: But the premolars were.

DR. AMAR: Premolars were.

CHAIRMAN BURTON: Other comments? Yes, Dr. Patters.

DR. PATTERS: Well, let me respond to Dr. Amar by saying that I think giving very specific labeling indications would allow the company to conduct further trials. And FDA can correct me if I'm wrong, but it would allow them the 510(k) process to seek other indications if they have the data for them. Does it not? If it's approved for very limited indications, and then --

DR. GUNTER: It's a supplement to change it.

DR. PATTERS: It's a supplement in the PMA to change it? Okay, thanks.

CHAIRMAN BURTON: Dr. Fleming.

DR. FLEMING: Well, as the consumer rep, I tend to agree with Dr. Patters that we are limiting the use of this material in socket site extraction sites to the point that there would be a number of patients that could benefit that would not have it available to them.

So in my opinion, given the fact that this material has been used in spinal applications in a very sensitive part of the body, I cannot imagine it would not be successful in a broader range of applications than the maxilla and the mandible. The fact that it hasn't been tested probably is going to require some additional labeling requirements.

So I'm in agreement with Dr.

Patters that I think that it's very useful. I think it probably could be used in the mandible, frankly, but since it hasn't been tested, then we've got to decide what the data supports and what it does not.

CHAIRMAN BURTON: Dr. Zuniga.

DR. ZUNIGA: I'm a little bit concerned about the direction we're going. I think the question is valid scientific evidence. And if the study -- Pavlov study had been done, we wouldn't be -- we'd be finished and there wouldn't be any question about labeling or other issues.

And so I'd -- I think that we -- there's not enough evidence to support the second. I wish we could bring it to a labeling. I think they do have a labeling issue. I think it's a varied treatment effect. It's effective. I would love to be able to offer it for our patients, but not for the maxillary anterior buccal space fracture. So that's my concern.

CHAIRMAN BURTON: What's your recommendation, Dr. Zuniga? I'm trying to pull people out a little bit here, but try to give us a little more concrete things to work with. But what's your recommendation? So yes on one, but on two you're saying that you don't feel that there is valid scientific evidence to support efficacy in those indications, correct? Okay.

Dr. Lin, do you have any comments?

DR. LIN: Well, I just wanted to also, again, remind the panel members that the sponsor request is -- on PMP be approved for these two indications. The second indication, there is no sort of hint of what's to come, so it's very broad indications.

So when you decide whether to make a recommendation to FDA, first, have those two indications and have enough scientific advice and scientific evidence for FDA to approve these two indications. And that's what I would like to remind again.

CHAIRMAN BURTON: Dr. Janosky.

DR. JANOSKY: Dr. Lin, can I get further clarification, please? Is it possible for us to separate these and recommend the ratio be positive for some -- for one but not the other? Or are they definitely linked and we -- and it's one decision?

DR. LIN: That's probably -- after you make a recommendation, we can work with the sponsor. But the sponsor right now in this PMA, particular subject PMA, they request that these two indications be approved -- and not the data to provide to FDA or provide to the panel.

CHAIRMAN BURTON: In answer, Dr. Janosky, when we get a little closer to being completed, once we finish these questions and go to the actual summation and votes, that will become -- there is some explanatory material that explains it. There has been some rule changes in what we're allowed to do from some other previous panel hearings, so we

will explain that at that time.

Is there any other discussion on this one? I think we've really sort of completed that at this point in time.

Given the fact that it's currently 2:30, we are going to take a 15-minute break at this point. We will start promptly at 2:45 with the second open session.

Thank you.

(Whereupon, the proceedings in the foregoing matter went off the record at 2:29 p.m. and went back on the record at 2:44 p.m.)

DR. BURTON: Please take your seats. Thank you, let's get started again. We are going to convene now the second of the open public hearing portions. If there are any individuals wishing to address the panel, please raise your hands and identify yourself. You are reminded that the same identification process is the closure requirement and the time limit of 10 minutes will be -- as announced in the first public hearing will be

applied to this session as well. So we'll move forward. I saw Dr. Assael raise his hand there, recognizing him. Dr. Assael.

DR. ASSAEL: Leon Assael, from Portland, Oregon. I'm an oral and maxillofacial surgeon. I'm speaking for myself only, but I'm here also with my expenses paid by Medtronic. I was not involved with the product development or any of the research and have actually just become involved this week with this process.

My comment is as follows. If you're going to look at a clinical problem, one of the best ways to look at it is to look at the most vexing, the most difficult and the most challenging aspect of that problem and if your idea works with that most vexing and most difficult part of the clinical problem you're looking at, you can extrapolate that it's going to work in a more simple state.

When analysis of InFuse was done with tibial plateau fractures, for example, it

was done because -- open fractures because that's a very vexing problem with a high infection rate, high non-union. And as an oral and maxillofacial surgeon I could say that looking at the maxilla and mandible in toto, and the need for dental implants, clearly the most vexing and difficult and problematic area is the atrophic posterior maxilla. And the second most vexing and troubling area is the anterior maxilla in the aesthetic zone when there's been a loss of a wall, especially the facial wall. So in terms of study design, it seems to me that -- and in terms of the design of site, it seems to me that to try to limit the site doesn't make a lot of sense in that regard concerning the most difficult sites and the most difficult problems were selected.

In terms of the biostatistics, that's certainly another issue and study design but I wanted to address that issue of anatomic site since it's come up. Thank you.

DR. BURTON: Thank you, Dr. Assael. Are there any other individuals that would like to speak during this open public session? Yes, please come forward.

DR. YAHIRO: Good afternoon, my name is Martin Yahiro. I'm an orthopedic surgeon. I'm the Global Director of Clinical Regulatory and Medical Affairs for Medtronic and I've been asked to read some letters into the record. I'll just read the body of the letters.

"Dear Mr. Ryan: I am a private practitioner and a principal investigator for the BMP-2 sinus augmentation implant five-year study. My personal observation is that this protein works and is the only osteoinductive material type on the market. We implore you to give us the opportunity to use BMP and reduce our need for the use of cadaver bone, secondary site autographs and allographs. The use of BMP out of the bottle would greatly enhance our armamentarium." This is signed

Michael R. Wiland, DDS.

The second letter, "Dear Sir: I am a practicing oral and maxillofacial surgeon and also a board member of the American Association of Oral and Maxillofacial Surgeons as the immediate past president. Although our association does not have a current official position statement on BMP 2, I would like to express my opinion about bone morphogenetic proteins or BMPs. Being familiar with the research in this area, I can say with great certainty that BMP has been one of the most heavily researched areas in all of oral and maxillofacial surgery. Since the late Dr. Marshall Urist first discovered these proteins over 30 years ago, an unprecedented amount of publications and research efforts have been dedicated to studying these proteins.

For all practical purposes, all of these studies have demonstrated to the research and medical community that safe and new alternative methods are available to the

current autograft, allograft and xenograft. This product would be an important step in reducing surgical morbidity and the costs of conventional grafting. I strongly urge this panel to approve these desperately needed proteins for oral and maxillofacial surgery. It is truly time to approve these proteins for the use in the oral cavity. I have been part of the original research team and I have seen the incredible difference they make in the restoration of lost bony complex in the maxilla and mandible.

Finally, I should like to point out that I have no financial interest in this product or the companies that have developed this protein." Signed J.M. Malmquist, DMD, Immediate Past President, American Association of Oral and Maxillofacial Surgeons.

And finally a third letter, "Dear Dr. Ryan: My name is Dr. Keith Kreuger. I was part of the pilot study with RH BMP 2, ACSLT and sinus grafting. Through detailed

research, the effectiveness of this protein was proven. The patient benefit from this protein was tremendous. The use of this protein would revolutionize the current concepts of patient care for bone grafting in oral and maxillofacial surgery. I'm submitting to you my strongest recommendation for full approval of the rhBMP-2/ACS by FDA. Please feel free to call me for further information." Respectfully submitted, Dr. Keith E. Kreuger, DMD, Diplomat, American Board of Oral and Maxillofacial Surgery.

DR. BURTON: Are there any other speakers for the open public section here? Seeing none, we will conclude at this point the open public hearing section. Before we proceed with the panel's recommendations, I would like to invite both the FDA and the sponsor to make brief closing statements. The first one will be made by the FDA. Dr. Runner? Thank you very much, Dr. Runner.

DR. RUNNER: You're welcome. I

think at this point, FDA has made all the comments it wishes to make and we really have not further comments at the present time.

DR. BURTON: Thank you very much. Dr. Chin, are you or another person going to represent the sponsor, please?

DR. CHIN: Sorry, we'd like to have a couple surgeons speak and then I will wrap up at the very end if that is appropriate with you.

DR. BURTON: That would be fine. We're trying to keep it down to seven, eight minutes in there.

DR. CHIN: Sure.

DR. BURTON: Thank you.

DR. NIVENS: My name is Myron Nevins. I'm a periodontist. I'm an Associate Professor of Periodontics at Harvard School of Dental Medicine. I have no financial interest in the product under review. I am a consultant for Medtronic which is covering my expenses attending this meeting. That said,

I'd like to speak to you as a clinician and educator. I have now practiced beyond 40 years and I've encountered a significant number of the issues that we're discussing. I also have been a participant in the -- in five of these six studies that we're discussing.

In the study of the extraction sockets, we selected the maxilla because of prominent roots and thin buccal plates and felt this was a significant problem for our patient base. Most patients are interested in what the aesthetic result will be in addition to the reliability or success of a product. The inclusion criteria included 50 percent loss of the buccal plate. With this bace maintenance for whatever material is going to be selected becomes an issue.

In addition just to consider another area that we're discussing, another significant area is the classical knife-like ridge in the mandibular posterior, so when we assume that maybe the maxilla will just heal

by itself, going back to my father's generation of dentists, they've had difficulty constructing removal partial dentures when the mandibular posterior teeth are missing because the buccal plate is lost to extraction. This is a classic finding in dentistry.

That said, I'd like to look at how you consider valid scientific evidence and as we get to the second line, I don't want to read this because it will take too much time, but partially controlled studies, studies and objective trials without matching controls, well-documented case histories conducted by qualified experts and reports of significant human experience with a marketed device. I think that we have a panel of very well qualified experts with significant years of experience both in clinical practice and patient care and in terms of educating future generations of specialists in oral and maxillofacial surgery, and in periodontics.

And I think that if you don't want

to accept what we did as a well-controlled randomized trial, that was double-blinded, you can at least consider it as one of the other issues that you have here. But as a clinician, it's very necessary to bring to your attention that these benefits are mandatory for patient care. You can talk about the use of autogenous bone for extraction wounds because in truth most -- extraction is probably the most common procedure in dentistry. And unfortunately many of these extractions occur before we get to see a patient.

But on those issues, where we see significant recession of the buccal plate before we remove the tooth, an experienced clinician knows that we have to have tools to work with. And in this instance, we're asking you to approve a tool that is of a significant benefit to the patient with, according to your own conversation, a minimal risk or no safety risk. You can't say -- nothing is no safety

risk but certainly a minimal risk. So the risk-benefit ratio is one that has already been decided. What you have to decide is if you were the patient and you had this problem, or a loved one had this problem, how you would like to be treated and that's the issue that we have.

Autogenous bone is not the standard of care for this. The standard of care should be what is the safe and efficacious way to treat our patients that present with these issues, and these issues present on an everyday basis in a clinical practice or at an educational institution. Thank you.

DR. BURTON: Thank you very much, Dr. Nevins. Dr. Marx.

DR. MARX: I think I've probably said too much already but I'll say one final closing remark. I think after hearing the panel's discussion, that I'm concerned that we may be losing the forest for the trees concept. In pointing out, I want to echo what

Dr. Nevins had just pointed out and that if you look at the extraction socket data, yes, the N of 21 is not as ideal as a sinus augmentation study. It probably seemed less compared to such a rigorous study as a science augmentation study, but it was a randomized blinded, clinically controlled study of an N of 80. It seems to have met the valid criteria that has been brought forth. At the very least it's a partially controlled study or at least documented case histories of at least 21 patients by qualified experts.

It is not, as is cited here, an isolated case report. It's not random experience. It's controlled experience and I think if we take a couple giant steps backward, you can see that it's met the assurance of efficacy and met the assurance of safety and that's particular indication as well.

DR. BURTON: Dr. Chin.

DR. CHIN: Thank you. I, first of

all, would like to make a comment about a clarification of a comment that was made earlier today just about 30 minutes ago. If I understood the comment correctly, the implication was the sinus and the augmentation -- sinus augmentation, extraction socket augmentation indications were pooled together at our request, the sponsor's request. That was not the case. During much discussions, you know, we did pool many indications out but at the very end, prior to you receiving your package, we did not ask for these indications to be lumped together for one vote. And I think that was the implication of the comment that was made earlier.

So now I would like to conclude our sessions. I'd like to borrow from Dr. Zuniga's summary, which was very eloquently giving an explanation of the clinical program that we provided. He did an excellent job in reviewing and summarizing our data. I'd like to reinforce and address some of his

statements with some comments. We believe that we've provided a reasonable assurance of safety and effectiveness of InFuse bone graft for the proposed indications.

InFuse is already the subject of two approved PMAs in orthopedics. The product before you today is the identical product which is under consideration for these important indications. Let me take this opportunity to address some few points that have been raised during the meeting. First, the question was raised about reducing the number of indications from five to two. I want to assure the panel that we did not remove these indications for untoward safety or effectiveness observation.

Frankly, we believe these indications are consistent with an oral maxillofacial indication and have a desire to ultimately pursue them. The removal of these indications resulted from discussions with FDA regarding the limitations of the data due to

their nature, for instance, retrospective case studies, and the amount of the information to support PMA approval for this indication.

Another point that has been discussed today is the justification for the extraction socket indication. This indication is justifiable as you just heard from Dr. Marx and Dr. Nevins. The clinical data that are available are prospective in nature and based on randomized treatment allocations. The results show that high quality bone that would support the long-term placement of dental implants. A statistician may argue that the sample size is small. It is small but as Dr. Zuniga pointed out, these patients were distributed across seven different clinical sites, not just one or two.

However, the differences between the InFuse and control treatments were nonetheless impressive and consistent with the information available from the larger augmentation study. We also believe that the

sinus augmentation results can be extrapolated to this indication and that the available extraction histological, and density information as well as the functional loading data confirmed this.

Dr. Patters said that the data seemed to represent a case study. Well, based on the FDA regulation as shown on the slide that was up, the case studies do fall under the rubric of valid scientific evidence which can support a PMA.

Also we heed the comments about proper labeling for the indication for use and are willing to work with the FDA to address the panel's comments regarding labeling. The use of InFuse in an extraction socket is an important indication for dental surgeons and their patients as well-stated by Dr. Patters and we strongly desire to make that available to the patients and the surgeons.

Finally, InFuse bone graft is safe. There is an already established safety

profile for this product. The clinical data further contributed to this. In terms of effectiveness, it is just another location in the body where InFuse bone graft has been shown to make high quality bone. For this indication InFuse bone graft predictably makes bone that predictably supports functional loading of implants over term, over long term. As Dr. Zuniga highlighted it really boils down to the risk-benefit ratio. For these two indications, the risks are few, well-established and clinically acceptable. The benefits from the use of InFuse bone graft are that quality functional bone is formed. In procedures where the standard of care is the use of bone graft, InFuse precludes bone harvesting and the morbidity and pain associated with it.

In procedures where the standard of care is not filling the cavity, the data strongly suggests a treatment effect of InFuse bond graft and that it performs better than

the standard treatment. Therefore, we believe the benefits more than offset the risks associated with the product.

In conclusion, we have met the standard of PMA approval for these indications, meaning that we have provided a reasonable assurance of safety and effectiveness. We want to thank the panel and review team for the time and efforts during this submission process.

DR. BURTON: Thank you very much, Dr. Chin. We will now proceed to the panel's recommendation concerning the PMA and the Executive Secretary will now provide some background information prior to our deliberations.

MR. RYAN: Thank you, Chairman Burton. The Medical Device Amendments to the to the Federal Food, Drug and Cosmetic Act as amended by the Safe Medical Devices Act of 1990, allows the FDA to obtain a recommendation from an expert advisory panel

on designated medical device Pre-market Approval Applications or PMAs that are filed with the agency. The PMA must stand on its own merits and your recommendation must be supported by safety and effectiveness data in the application or by applicable publicly available information.

I'll now read the definition of safety from the CFR as was presented before. "There is reasonable assurance that a device is safe when it can be determined based upon valid scientific evidence that the probable benefits to health from use of the device for its intended uses and conditions of use when accompanied by adequate directions and warnings against unsafe use outweigh any probable risks."

The definition of effectiveness: "There is a reasonable assurance that a device is effective when it can be determined based upon valid scientific evidence that a significant portion of the target population

the use of the device for its intended uses and conditions of use when accompanied by adequate directions for use and warnings against unsafe use will provide clinically significant results".

And once again, the definition for scientific evidence, "Valid scientific evidence includes evidence from well controlled investigations, partially controlled studies, studies and objective trials without matched controls, well-documented case histories conducted by qualified experts and reports of significant human experience with the marketed device from which it can fairly and responsibly be concluded by qualified experts that there is a reasonable assurance of the safety and effectiveness of the device under its conditions of use".

Isolated case reports, random experience, reports lacking sufficient details to permit scientific evaluation and

unsubstantiated opinions are not regarded as valid scientific evidence to show safety or effectiveness. Your recommendation options for the vote are as follows: approvable, that's a third, no conditions attached, approvable with conditions, the panel may recommend that the PMA be found approvable to specified conditions such as physician or patient education, labeling changes or further analysis of existing data. Prior to voting all of the conditions should be discussed by the panel.

Not approvable, the panel may recommend that the PMA is not approvable if the data do not provide a reasonable assurance that the device is safe or if a reasonable assurance has not been given that the device is effective under the conditions of use prescribed, recommended or suggested in the proposed labeling. If the vote is for not approvable, the panel should indicate what steps a sponsor might take to make the device

approvable. And now I'll transfer it back to Chairman Burton.

DR. BURTON: Excuse me, as we proceed with this, I'd like to go around and try to get some comments prior to making our motion, so could some of the panel members please make any comments that they would like to have? Dr. Patters.

DR. PATTERS: Yes, I'd like to ask Mr. Ryan a question. Is this an all or none vote on both indications or can we say that one indication is approvable but the other is not approval?

MR. RYAN: You have to make your vote based on the Indication Statement as read in the PMA. You cannot separate the indications and vote differently for each indication.

DR. BURTON: A clarification, my understanding is that it's actually -- there is -- in the past, some meetings have been voted based upon individual indications. My

understanding now is that we make one vote for the two indications as -- I don't want to say as a pair but as an indication basically with two parts to that. Dr. Betz, do you want to make a comment?

DR. BETZ: No, sir, just trying to put it up on the screen.

DR. BURTON: Thank you. Yes, Dr. Gunter?

DR. GUNTER: Thanks for that clarification. Just to push it a little more, my understanding is that we could -- I can't vote but that the panel could vote on a condition of changing part of the Indication Statement; is that correct?

DR. BURTON: I guess I can address that as well. My understanding of this is the fact that if you consider these to be two indications. If one indication, and again, was acceptable in your estimation and one was not, then the indications as a pair are not -- and such you would have a vote not to approve.

However, there is a comment period once that is done and each person has to make a comment along with their vote. And if the recommendation from the panel back to FDA was the fact that there was an indication that one indication was acceptable, then they, in discussions with the sponsor, can approve the -- can approve the product for that indication and then enter into further discussions with the sponsor regarding the other indication which was felt not to be acceptable.

So in some past situations, we could actually separately vote those. In those particular case, you vote one way or the other but with your vote you can indicate if you feel one is and one is not. Then that becomes a staff issue, an FDA staff issue to work with the sponsor to allow approval for the first indication and the other. So I don't want to say if you vote no, you can -- it's sort of being in a strange way sort of conditional. This is a change from some of

the past meetings. Dr. Diamond.

DR. DIAMOND: Yes, as a further clarification, based on what Dr. Gunter has said, for example, if there was an issue, let's say with one indication, it could conceivably be voted as approvable with conditions specifically directed to the indication where there was some question, correct?

DR. BURTON: I don't know if it might be better, Dr. -- I still have not been quite clear on that. I'm not sure that when we say "indications" is really not -- what's allowable within indications is what is not particularly clear. Dr. Lin, if you'd care to clarify that.

DR. LIN: As I said before, in this PMA the sponsor request for approval of these two indications with the data they submit to support these two indications. So now I think your responsibility to decide whether the data submitted in this PMA would suffice to approve

these two indications. If one of the indication -- the data support one of the indication and not rigorous enough or not sufficient to support that, then that would up to the panel's recommendation either to disapprove or approval with recommendation and what will be that recommendation then the agency would work with the sponsor.

DR. BURTON: Dr. Amar?

DR. AMAR: Would it be possible to propose approval with recommendation that the sponsor needs to work closely with the FDA for labeling?

DR. LIN: I think you have to propose, that Michael Ryan has point out, approve or approve with condition or disapprove. You have to vote that first and after that you can come out with some recommendation to FDA as to how FDA should develop.

DR. BURTON: Dr. Janosky?

DR. JANOSKY: Am I correct, if we

would choose to place a vote for approvable with conditions, one of the conditions can be a labeling change or label recommendation?

DR. BURTON: Yes, I don't believe that we can recommend -- Susan, give me clarification on that -- we cannot recommend post-marketing studies as part of that though, is that correct?

DR. RUNNER: Yes, you can also change labeling.

DR. BURTON: Okay, so the recommendations could be for both labeling and/or potential post-marketing studies for clarification as part of that. Dr. Patters?

DR. PATTERS: As has been my experience, when you seek clarification from FDA, you are further confused after they speak.

(Laughter)

I hope you didn't take offense at that. It seems that there's a point that you have to stop. You can't say this is

approvable and the condition is that one of the indications is unacceptable. I mean, it seems to me there's a point you can't say it's approvable with a condition that we approve only half of it. So, I mean, there must be some limit as to what your conditions can be and from what I understood from Mr. Ryan, this is essentially an up or down vote on the indications as has been presented in the PMA with the data that has been presented with the PMA and to say that our conditions are that half of it's okay but half of it's not seems to be overstepping our authority. Is that correct or not correct?

MR. RYAN: It is correct that you cannot make a condition to change the indications for use. That's correct.

DR. BURTON: My interpretation -- we're all trying to -- in our minds I can see everybody sort of jockeying around trying to figure out what the real limitations are. My understanding is that, again, we have a single

vote to either approve or disapprove. They are one vote. If the -- if you feel, however, that one of the indications is approvable and one is not in your mind, you would still have to make a vote to disapprove. However, once that portion is done, then we get to the discussion phase to explain that. We then can provide in our report or information back to the FDA the recommendation that the first indication was acceptable but that the second was felt -- which is -- obviously, I'm distilling down what people have been saying, was not acceptable due to the fact that they didn't feel that there was enough -- that there was not a safety issue and we can address that, but that there was an efficacy and an applicability issue to the second one which should be addressed in the discussions between the agency and the sponsor.

That then, gives the agency, is my understanding, the ability then to approve the product for the first indication and then to

enter into discussions with the sponsor to address that secondary issue in that.

DR. PATTERS: Dr. Burton, did I understand then that the only way we can reach that conclusion is to vote non-approvable?

DR. BURTON: That's my interpretation of what I have been given. Yes, Dr. Chin?

DR. CHIN: Okay, I join Dr. Patters in saying when I hear from the FDA, I am confused, but Dr. Runner did just say, you can vote on approvable with condition that follows Dr. Amar's comment. Now, I am very confused and I -- the sponsor is very confused because we were led to believe that you know, we were not told and we did not ask for one indication combining those two as you are saying, Dr. Lin.

Now, we really need some clarification and we agree with Dr. Runner.

DR. BURTON: Yes, please.

DR. YUSTEIN: Ron Yustein, Deputy

Director, Office of Device Evaluation. What Mr. Ryan said is correct and I know that the company does not agree, but this is correct. You are voting today on what is in the application. You are voting on one application. You are voting on the two indications, that one application includes two indications which they have listed. You cannot change the indications as a condition of approval. When we say labeling changes, if there are warnings you want added, if there are contraindications you think need to be added, if there's instructions for use that need to be changed, those are the kind of labeling things you can request as a condition of approval.

If you do vote for not approvable and I'm not saying that you should but if you do, and it's your consensus report to the FDA that one of the indications was approval but the second wasn't, the sponsor can come in with an amendment to their PMA, withdrawing

that second indication and we can go into discussion with them about approving that first one. That's why we look at not just the vote but what you say during how you vote. So that is the way we're going. That is the office policy and that's how I'd like you to proceed. Does that make it any clearer?

DR. PATTERS? (Nods head)

DR. YUSTEIN: Okay, thank you.

DR. BURTON: Thank you for the clarification. Do any of the panel members -- would anyone on the panel like further clarification of the last input to that in terms of what -- the guidelines that we're operating under at this point? Okay.

I guess what we're understanding is we can't change the indications. Those are what were submitted and that is what we are considering are the indications as presented. Keeping in mind that we must vote on the device as submitted including its indications for use, the formulation design, would anyone

like to make a motion for any of the three options as were presented by Mr. Ryan? Now, let me -- I'm sorry, I need to stop. We need a recommendation from the industry representative and the consumer rep?

Let me point out that in the panel there are six voting members, plus myself. I do not vote unless there is a tie. So there will be six votes and I do not vote unless there is a tie. The industry, yes, sir. No, actually Dr. Li -- no, he is a voting member, given some of the parameters that have been given out.

The industry representatives and the consumer representatives are non-voting members but we do ask for their comments prior to that point.

DR. YUSTEIN: One other comment, clarification. If there is one of the two indications that you don't like, if there is a recommendation that the data would support a different indication, that's something that

you can also give us as part of the end recommendation to us that although -- and I'm just saying a hypothetical here. Although the panel recommended disapproval, we would have thought the second indication would have been approved if they changed it to this. Then when the sponsor comes in with an amendment, they can also change that indication for that and we would look at the data for that particular specific indication. So you can push it a little further. Thank you.

DR. BURTON: Thank you. Okay, would -- Mike, would you care to make comments as the consumer representative?

DR. Fleming: Being a consumer representative, as I mentioned earlier, I tend to be very patient centered and have my concerns surrounding the welfare of my patients and we want to be evidence based and have the science back up what we're doing clinically. It is my estimation that this product meets the requirements for safety and

effectiveness both as a treatment of sinus violations and also for socket management. So in my view, I cannot see, frankly, seeing all the work that's been done, have to be set back and have the needs of our patients set back given the testing that this material has undergone in the past in broader applications in the human body.

I believe that this evidence is supportive of the safety and effectiveness under both of these particular applications.

DR. BURTON: Thank you, Dr. Fleming. Dr. Diamond?

DR. DIAMOND: Yes. You know, a little knowledge can be a terrible thing and having worked on synthetic bone graft materials and albeit, you know, sometimes under 510Ks where the burden of evidence is somewhat less and clearly the evidence presented here would overwhelm that, I have a very good comfort level with regard to the safety and effectiveness of this product. I

think that looking at -- well, based on the evidence of the large defects of the sinus augmentation, clearly it grows bone in large defects as well as anterior maxilla challenged, you know, mechanically challenged upon implant loading, I would agree with Dr. Fleming that the evidence does support approvability.

DR. BURTON: Dr. Gunter?

DR. GUNTER: Yes, thank you for the opportunity to address this. I do agree with both Michael and Mason regarding their conclusions. Just let me add a little more color around that. I think we all agree on the safety of the product. I think we all agree that the sinus augmentation study supports the efficacy of the product. The issue is with the socket extraction. You know, let me respectfully remind the panelists that we're dealing with a product that's been out on the market for a long time, a product that has been shown to generate bone.

Generation of normal bone is the key to how this product works.

I'm not totally familiar with the orthopedic program but I would imagine that it was not tested in every single bone in the human body. I think that probably the FDA reviewers looked at results from certain key difficult to treat bones and extrapolated to other anatomic sites. I suggest that we undergo a similar process -- that you undergo a similar thought process when you think about this one. So I would urge you to support approval of the PMA as it is and that's really, I think, a short statement of how I feel about it. Thank you for your time.

DR. BURTON: Thank you, Dr. Gunter. At this point, I would entertain a motion for any of the three options that are currently available to us, which is approvable, approvable with conditions or non-approvable. Dr. Amar.

DR. AMAR: The motion would be

approvable with recommendation.

DR. BURTON: Could we -- do we have a second to that motion? A second would need to come from a voting member. Dr. Li?

DR. LI: I will second that motion.

DR. BURTON: We have it moved and seconded that it would be approvable with conditions. At this point, I would entertain discussion of the motion. Dr. Patters.

DR. PATTERS: Well, the guidelines that we've been given by FDA, I think, put the panel in a box. And that's unfortunate, because our responsibility is beyond just to FDA but it's to the American public at large in my opinion. My biggest concern is the labeling issue as an indication that this is an alternative to an autograph for localized alveolar ridge augmentation for defects associated with extraction sockets. If there is some way that that can be reworded so that it is not an alternative to an autographed because an autographed is clearly not

indicated in such, and therefore -- then I can support the motion, but I'm not sure from the guidelines we got from Mr. Ryan that we can rewrite that indication and take out alternative to autograph for that particular indication. Therefore, I am in the proverbial box.

DR. BURTON: Dr. Amar.

DR. AMAR: Again, I was under the impression that we could work -- the sponsor could work upon the recommendation of this panel for labeling issues and one of the labeling issues would include that it was not tested in areas, that it was not tested. Am I correct?

DR. BURTON: That's sort of the $64,000.00 question --

MR. AMAR: I mean, we're running in circles here.

DR. BURTON: -- is whether -- Dr. Runner?

DR. RUNNER: The labeling issue of

not being tested in certain places is one issue but changing the wording of the indication is another. So if you're changing the labeling of the indication, that is not a condition that would be acceptable. If you're talking about labeling stating where it was not tested, that's a different issue. That would be acceptable.

DR. BURTON: Yes, Dr. Amar, go ahead.

DR. AMAR: See, that --

DR. RUNNER: Well, you said that you would like to have labeling conditions that indicate that it had not been tested in the mandible. That would be a labeling -- acceptable labeling statement.

DR. AMAR: But we cannot change autograph as opposed to allograph, for example, am I correct?

DR. RUNNER: We cannot change the indication as stated there.

DR. AMAR: Even if the sponsor

works with you. I'm trying to get out the --

DR. RUNNER: If the sponsor worked with us to change the indication, that would require you to have not approved the application as it is stated here.

DR. AMAR: Thank you.

DR. BURTON: Dr. Janosky?

DR. JANOSKY: Dr. Runner, just all the way down to the basis, every one of those words on that slide where it starts with "as" ends with "socket", we cannot make a recommendation that that be changed; is that correct, if we do approvable? That's not a condition.

DR. RUNNER: That is correct.

DR. JANOSKY: Thank you.

DR. BURTON: Dr. Lin.

DR. LIN: If I may also clarify to when it's like earlier point out, in case you recommended non-approval and then you can sort of recommend to the FDA as well, the sponsor, how can sponsor make some certain type of

correction or address certain issue that make the PMA become approvable and that's is when you get to the point, then you can recommend it to FDA how that sponsor can make some kind of a change or some kind of a correction to make the PMA approvable.

DR. BURTON: Are there any other comments? Yes, Dr. Li.

DR. LI: If I understood correctly, again, and I think the indication specifies the

-- as an alternative to autograph, actually as a property because in the study the autograph was the -- was the other method compared. If this wording includes others, I would not feel comfortable because the data did not present the other type of methods.

DR. BURTON: Dr. Diamond?

DR. DIAMOND: So a clarification from Dr. Runner, the panel can recommend it would be approvable by the sponsor providing more data. Would that be an acceptable -- no?

Okay.

DR. BURTON: My -- I don't know whether you want it coming back but my -- let me see if I can distill this out because I think it's going to come down to how I word this. Would it be at this juncture which appear that we -- first of all, we currently have a motion on the floor which has been seconded, which at that point we would have to move the question and either accept it as approvable with conditions and then be in the position of writing the conditions, or we would vote that down with a negative vote.

If it was voted down, then we could entertain a second motion which would be for disapproval, okay, which once that was voted up or down, would then turn both to the committee and then to myself then to give the conditions or I'd say the verbiage that goes with that, that goes to the agency and to the sponsor on how they would remedy that vote. Yes.

DR. YUSTEIN: Chairman Burton, can I ask the sponsor a question? On the proposed indication for use, are you saying infused bone graft as indicated as an alternative to autogenous bone graft for science augmentations separate and it's for use for localized alveolar ridge augmentations?

DR. CHIN: Yes.

DR. YUSTEIN: I think if that's what they're saying, then I think what Dr. Patters said may be applicable. Does that make sense, that perhaps the way -- if you go back to what the FDA slide was, maybe it was just a matter of the logistics of the slide. Okay, that's not what the sponsor is proposing. Go to the sponsor's slide, and so it's an alternative to autogenous bone for sinus augmentation but you're not saying it's an alternative for autogenous bone for the other indication and that's what you were getting at, Dr. Patters, correct?

DR. BURTON: Dr. Patters, yes.

DR. PATTERS: So Dr. Diamond was right all along, it is a matter of wording.

DR. BURTON: Can I get one question actually from Dr. Chin or from the sponsor then? My only I won't say it's concern with what's being said here, but then is there actually -- if I read that slide correctly, it says it's indicated as an alternative for autogenous bone for sinus augmentations and localized alveolar ridge but there actually aren't any indications for localized alveolar ridge augmentations. There actually aren't any indications for this second --

DR. CHIN: It's for defects associated with extracting socket and the study that was conducted with local defects with 50 percent loss for bone grafts.

DR. BURTON: Okay, thank you. Let's proceed with any other further discussion of the motion as it is currently stated which is for approval with conditions. Dr. Patters?

DR. PATTERS: Is FDA going to allow them to add that word and that comma?

DR. YUSTEIN: I don't think that changes the indication. I think it just clarifies it. Does the Division disagree? Okay. Dr. O'Brien?

DR. O'BRIEN: I have a question on the motion in terms of it's not voted in favor of it, that you said that the only other motion would be that it's disapproved.

DR. BURTON: No, at the point at which the current motion is disapproved, then you have no motion on the floor until a new motion. You could make a similar motion with conditions. You could make it for approval, you could make it for disapproval. It's just that currently there is a motion on the floor. That must be addressed first with a vote either for approval or disapproval of it. At the point at which it was disapproved, then you would move forward and request then another motion.

DR. O'BRIEN: Thank you.

DR. BURTON: Is there any further discussion of the motion, which as it stands and I don't know if we can have this read back, was for approval with recommendations, with conditions, pardon me.

Okay, are there any motions for conditions to this, then? Okay, I was just trying to get some clarification on the procedural issues. At this point, prior to proceeding to the vote, we have to ask for recommendations on conditions. And the reason for that is if you voted for approval with conditions and you couldn't reach an agreement on the conditions, then you would go back and invalidate the first vote. So at this point, can we have recommendations for conditions to apply to this motion? Dr. Patters.

DR. PATTERS: Well, I would recommend that the labeling indicate that the product has not been tested for alveolar ridge augmentation for defects associated with

extraction sockets in molars or in the mandible, just as they say it has not been tested in patients with metabolic disorders, it has not been tested in those sites. So I think the label would require them to label that as such. It doesn't mean you can't use it in those sites, it just that it has not been tested in those sites.

DR. BURTON: All right, is there a second of that recommendation for condition? Dr. Li seconded that.

DR. LI: That would be my recommendation, too.

DR. BURTON: Would anyone else care to place any other recommendations for conditions on the primary motion? We'll have to consider any recommendations individually, so we'll have discussion upon Dr. Patters' recommendation for a condition that the labeling language be for exclusion for molars -- that it has not been tested for molar or the mandible. Can I entertain discussion on

that recommendation? Dr. Li?

DR. LI: And I think my condition, this condition, I agree to that and that was my original thinking. Also it's based on largely because at this time there is not any options clinically available and the BMP has substantial evidence to be safe. And it does promote the bone growth. And I think, although the study you presented has limited sample size and there are some weakness, it does show the evidence it could be beneficial to the extraction sockets that you investigated. That's the reason why I recommended that condition. It would be acceptable to me if you only limit that at this time.

DR. BURTON: Is there any other discussion on the recommendation for condition? Hearing none, then are there any further recommendations for an additional condition to be applied to the motion?

DR. YUSTEIN: You have to vote on

that one.

DR. BURTON: Thank you, but that was not what I was just told. Okay, I've got people on both sides and they actually aren't always exactly on the same page. Okay, given that, what we are going to be voting on, let's be clear on this, what we are voting on is the recommendation for a condition that there would be packaging and the indications be or the guidelines for this be that it has not been tested in molars or the mandible. That is what we are voting for it as a recommendation for a condition, okay, for the primary motion. So we will move around the table going from left, I'll start on my left with Dr. Amar and would like each of the six voting members to indicate their vote and I would like some explanation regarding what is supporting their vote regardless of which direction it is. Dr. Amar.

DR. AMAR: I vote in favor and the reasons were that in regard to the most

important aspect of the panel is safety and safety has been proven, efficacy and I've heard the panel members going back and forth and back and forth. It's been efficacious. There are some effect -- there's some issues that the recommendation in any case will and should take care of.

DR. PATTERS: Are we voting?

DR. BURTON: No, we are voting just on the recommendation at this point. You have to vote the recommendation, then we'll -- it's very procedural but I'll back up and give you what the next step is after this. We're voting on the recommendation for -- we're voting on the condition. Okay.

DR. PATTERS: So it's not impossible that someone could vote for the condition but then vote against the motion.

DR. BURTON: Yes. Dr. O'Brien?

DR. O'BRIEN: Yes, I vote for the condition. The scientific evidence part of it, or the validity in general has much to do

with the mechanism or the phenomena that's involved in the question that you're dealing with as well as the data that's involved. And there's a large body of literature supporting this mechanism of bone growth stimulation. This, I would say, offsets the limited but otherwise successful clinical study data that has been presented. You have to have both involved. If this was just the clinical study with somebody's theory of what happens out of the blue, then it wouldn't be acceptable, but there's a large body of evidence that we can see that this mechanism is established as operating under the conditions of the clinical study. So I would have actually voted -- that's the reason I vote for this motion because I think this motion has a good chance of getting through rather than just supporting -- I would have preferred to support a motion of just approval, but I will vote for this motion because I think it will work.

DR. BURTON: Dr. Li?

DR. LI: I vote in favor of this condition. I already have given the reasons why I support this condition.

DR. BURTON: Dr. Zuniga?

DR. ZUNIGA: I vote in favor of this condition because the data did provide evidence for effectiveness and safety but I would encourage the sponsor to not -- to explore other areas as was provided by the panel.

DR. BURTON: Dr. Janosky?

DR. JANOSKY: My understanding, we're just commenting on the condition.

DR. BURTON: This is a vote on the condition, yes.

DR. JANOSKY: Condition, yes, and I agree with the condition, given that the data were not available for those areas.

DR. BURTON: Dr. Patters?

DR. PATTERS: Well, it would surprise people if I didn't support the motion that I made, but I do. Anyway, I can't -- I

don't think it's appropriate that conditions be provided that have not been tested. Therefore, it seems appropriate that here's how it's been tested and therefore, the label should state to the clinician that there is no data available for molars or in the mandibles. I think that's appropriate.

DR. BURTON: Thank you. What I would then summarize the vote that the motion for the condition carried with a six to zero vote and there were no abstentions. That then being the indication, we will reopen the floor. Are there any further conditions that anyone would like to put forth for consideration to modify the primary motion which we'll get to after this point? But are there any other conditions that you would like to apply to the primary motion?

Hearing none, then we will move to the primary motion. It has been moved and seconded that the Medtronics Sofamor Danek's Pre-market Approval Application for InFuse

bone graft was conditionally approvable with one condition as previously just voted upon with the fact that it has not been tested in molars or in the mandible and we will now be voting on the primary motion with the condition that we just approved. And again, we will go around with an individual vote, starting on my left. This is for the primary motion.

DR. AMAR: I made the motion, therefore, I approve it.

DR. BURTON: Dr. O'Brien?

DR. O'BRIEN: Yes, I vote for the motion and think it's the best possible of worlds in this situation, thank you.

DR. BURTON: Dr. Li?

DR. LI: My vote is yes with the condition approved.

DR. BURTON: Dr. Zuniga?

DR. ZUNIGA: My vote is approval for the motion.

DR. BURTON: Thank you.

DR. JANOSKY: Yes, for the motion.

DR. BURTON: Thank you, Dr. Janosky. Dr. Patters?

DR. PATTERS: I vote yes for the motion. I must say it's the first time that all of my concerns were alleviated with a comma and a three-letter word.

DR. BURTON: Thank you very much for that. It has been moved and seconded and that the motion carried with a six to zero vote and there were no abstentions. Now, I'll poll again the panel members and they can have comments at this point from any of the panel members in regard to the vote if they would care to make those at this time prior to moving forward. Are there any comments? I believe everybody has had plenty of comment time. I would like to thank all of you -- yes, Dr. Patters.

DR. PATTERS: I think the sponsor should be encourage to expand their research efforts and to try to gain additional

scientifically valid indications and I personally encourage you.

DR. BURTON: Yes, Dr. Amar.

DR. AMAR: I will strongly support Dr. Patters' recommendation to have some sort of post-market surveillance just to make sure that everything is under control.

DR. BURTON: Yes, thank you. The representatives have the -- both consumer and the industry reps would be happy to get comments from you as well. Thank you. Dr. Gunter.

DR. GUNTER: Well, I certainly appreciate the well-thought out deliberations here and just going back to something that was mentioned very early in the meeting, we heard about other indications that apparently have been discussed. I haven't had an opportunity to look a the data but certainly, I think there may be an unmet medical need with regard to cleft palette. So I just want to encourage the FDA and the sponsor to get together and

talk about approaches to getting those patient populations -- products for those patient populations. Thank you.

DR. BURTON: Are there any other comments? I'd like to make my closing comments. First of all, I'd just like to go ahead and clarify for the record that the motion was just voted for approvable with conditions and it was approved with a six to zero vote with the single condition as prior approval. I'd like to thank all of you in attendance as the Chair of this for a long and somewhat arduous day. I'd like to thank the sponsors for their -- for their efforts and on a personal basis, like I said, I hope they'll bear with us. It's a difficult world on your side and for our side as well working with the FDA which are actually quite easy to deal with. And --

DR. LI: Do you want to reword that a little bit?

DR. BURTON: Yeah, just a little.

But I'd like to thank everybody for their tolerance as the Chair today and I would just like to say to the sponsor on a personal basis that, you know, the issues that we all came down to a simple fact. That the data was so good with the pivotal study and the sinus augmentation and if you look at the ridge augmentation issue, it was a dosing study and just did not have the data, the power and the authenticity that it would have and I think that there was certainly a contrast between those two, led to a lot of the issues that we all had in trying to deal with that.

So try to understand the position. We're looking back at an excellent well-designed study with very complete data versus another one which is certainly the implications are very good, but fortunately the safety of this was never in question. It was really an efficacy issue and I would echo what Dr. Patters said, that we know that there are other indications that were in the

original package, which are probably applicable but just need better information before they're brought forward for approval as an indication and we'd certainly hope that you would move forward in those areas as well, but again, thanks for everyone's cooperation and support today in getting this done. And then for the Executive Secretary.

MR. RYAN: Just a quick message to the panel as we adjourn. You are required to return all of the materials you were sent pertaining to the PMA itself. Materials you have with you can be left at the table. Any others should be sent back to the FDA as soon as possible. Thanks.

DR. BURTON: And my last comment, I'd like to thank all the speakers and members of the panel, for their preparation and participation in this meeting and I would like specifically to thank Dr. Zuniga for leading the discussion portion of this meeting after lunch. And since there appears to be no

further business, this meeting of the Dental Products Panel is adjourned. Thank you all very much and have a safe trip.

(Whereupon, at 3:48 p.m. the above-entitled matter concluded.)