So, in conclusion, I can only say that I see no reason why the FDA should not approve the collagen scaffold for reinforcement and repair of soft tissue injuries of the meniscus.

MR. DICHIARA: I'd like to address one other issue that was brought up by the Panel before, and that was the issue of -- that was brought up by the FDA and was discussed, and that was the issue of the type of collagen and the type of tissue and the biomechanical viability of that tissue. I'd like to have Dr. Vigorita talk to the pathology and the histology that was done on this study.

DR. VIGORITA: Well, with all due respect, I'm not going to try to read tea leaves, but the pathologist does report on what he or she sees, and, of course, there are things that we do not see. And what I saw in this tissue, both in the canine and human model, was fibrocartilage, and I can say that because I've looked at hundreds of thousands of specimens of tissue, and this looks like fibrocartilage.

But let me get to the very important point that Dr. Kessler raised. Is this normal fibrocartilage? Well, what is fibrocartilage? It is glycosaminoglycans, aggrecan moieties. We're all

familiar with that. It's water. And it's collagen. And his question, I think, was directed at the architecture, the three-dimensional architecture of the collagen. I can't see that looking under the microscope. But I would ask the question: Do we really know the relevance of the answer to that? And I believe it was Dr. Kelly in the last hour who said maybe it is a type of fibrocartilage that will be beneficial, which is not normal under our understanding of the three-dimensional structure of normal fibrocartilage.

Now, I did mention in my last comment when I presented the histology that if this was tissue which biomechanically was defective in some way, we might anticipate seeing damage to that tissue even at the one-year mark. And I reported that I did not see the type of damage which I would expect from cartilage damage from Achilles tendon, from an annulus fibrosis, you name it, cystic changes, and bursa-like formation. So I think it was a good, provocative question, the relevance of which may be elusive.

MR. DICHIARA: I'd like to have Dr. Stephen Badylak talk about the meshes and what to expect with these meshes.

DR. BADYLAK: Thank you. I'll also be brief. Been a lot of discussion about what type of cartilage is being -- or what type of tissue even is being laid down in place of the mesh. And if we think of this in the terms of other surgical meshes that have been approved, one's never asked or expected those meshes to turn into exactly the type of tissue. The hernia repair, for example, doesn't turn into a musculotendinous -type tissue when put in a ventral hernia location. The rotator cuff, all the meshes out there, aren't asked to turn into normal rotator cuff.

When we use these meshes, they're meant to reinforce the damage to injured tissue. And the type of tissue that will be deposited there is what the body considers to be appropriate for that particular location. I talked a bit this morning about the microenvironmental influences and the way that the cells respond and the tissues that are formed. The body does know what it needs in these locations. And I, you know, I think it's more appropriate to look at the outcomes studies and see that you've got a tissue there. Whether it's perfect, you know, cartilage, it's got Type 2 collagen in it, or a fibrocartilage, if it's serving as a weight-bearing tissue that keeps

the articular surface of the femoral condyle on a tibial plateau from rubbing on each other, then it's doing its job. That's probably a more adequate measure of effectiveness than suture pull-out strength.

And the bottom line is that I would never expect -- in fact, I would be very surprised if normal meniscal cartilage formed in what is clearly and abnormal joint. These studies are being done on patients that have had two and three surgeries. Their weight-bearing, load-bearing situation is completely different. They've already got damage in this joint. It's not a normal joint. Why would we expect normal cartilage to replace any of these surgical meshes. That, I think, it unrealistic. The question should be is what does form there, like in the other surgical mesh applications, adequate to do the job? Are we doing good? That's all I have. Thank you.

DR. MABREY: Yes, Dr. Kessler?

MR. DICHIARA: Yeah, one other comment is regarding the serious device-related adverse events. You have to be careful in looking at that. In the study, since the control group had no device, there is no comparison, so you can't look at serious

device-related adverse events. What we did look at is we looked at all serious adverse events in the study, and when we looked at those numbers, there is never a statistically significant difference in the rate either on a per patient or a per event rate at any time point or cumulatively in the five years' mean follow-up with those patients, you know? And that's significant.

Also, when they, when Dr. Kessler presented information about the serious -- the non-serious device-related adverse events, you have to remember the definition in this trial of a non-serious adverse event. An adverse event here, a device-related adverse event would mean that it's anything that you thought may be related to the device, but those events would be defined as anything that's not a benefit to the patient. So if the patient reported pain, you would not then -- that would be reported as an adverse event even if pain was expected at that time point.

So you have to look very carefully at those numbers. Thank you very much. I appreciate your attention, and your questions were really good. I hope that you can get the answers that you need. Thank you.

DR. MABREY: Dr. Kessler, you have something to add?

DR. KESSLER: Thank you very much, Chair. So the first thing I'd like to do is I'd like to thank the Sponsor because of the debate and the issues they're bringing to the table because I think that's exactly what we're hoping to get from you is a reflection back and forth of what you hear scientifically about these issues.

Let me talk about the comments about tissue. Excellent comments from Dr. Vigorita and Dr. Badylak, and I think we asked some of the same questions when we were reviewing the 510(k). What we wondered about when we didn't see any evidence of the tissue that we expected to see, oriented in the way that would work like the meniscus, we were wondering why the staining wasn't done to determine whether it was Type 1 or 2 collagen. If indeed, as Dr. Badylak says, you may not care what kind of tissue it is -- it could be disorganized, or something else, then we'd want to see if the body is smart enough and it's producing tissue that's going to work, then we want to see effectiveness.

We look at the data. There is no effectiveness in any of the measures. So if it's

working, it's not working clinically. So if this tissue is replacing and reinforcing in a way that the body wants it to, it's not showing any clinical improvement. Over and over and over, we go back to the clinical data. And we wonder whether the mechanical forces, which both doctors commented on, may or may not be having an effect on this tissue. We've got five or six, depending how you count, explants, which may be the underlying cause having to do with the tissue.

So it just raises those questions. We don't think we have all the answers by any stretch of the imagination. We don't think the Sponsor does either, and we hope that you'll reflect on those issues.

Now, this is very tricky. The Sponsor began and just referred to a recently cleared device for use in the knee. And, unfortunately, I have to say that we're concerned that these statements misstate the indication for which this product was cleared. We emphasize that you are here to provide your expert advice on the scientific issues relevant to this product, that is, the ReGen Collagen Scaffold, and ask you to concentrate on those issues.

I stated earlier today that compliance with

regulatory precedents is FDA's responsibility. We cannot disclose confidential information to you related to other applications in this meeting. The Sponsor has access to what's publicly available. What's in our house, for what we clear these products for and the data on which they're based is not necessarily available. Take Abbott. You would not want me to casually say, "Oh, what they said about your product is wrong. Here's what Abbott really told us," if that's confidential. We cannot do that.

Accordingly, we can express concerns about misstatements or inaccuracies and half-truths, but we must honor our obligation to respect the confidentiality of the information with respect to other applicants. And so, again, go back to the DePuy Restore product. You saw the indication for which we cleared it. It was different than what the Sponsor believed it to be either by clinical use or by other information. But what we cleared for is what we review. So we're responsible for that, and those precedents are what we're responsible for.

I want to thank you for your time. I'm very sorry, sort of, that I can't stay for the rest of the afternoon. If you have further questions of FDA, Mark Melkerson from the Office of Device

Evaluation will help with the answers. And I once again want to thank the Panel, and I really do want to thank the Sponsor as well. Thank you.

DR. MABREY: Does the Sponsor have any last comments, any brief last comments?

MR. DICHIARA: Yes, you know, I want to make clear the BioDuct is not a predicate device. And you have to look at the shoulder mesh, for instance, and the indication for use that was cleared by the FDA and what they think the understanding is or the wording says and what the -- what your interpretation of it is. If you look at the labeling for the shoulder mesh, it certainly does not have the wording that other labeling that's used for suture line reinforcement has. Suture line reinforcement is specifically called out in other predicate devices when the intention of that device is suture line reinforcement. In the shoulder it's clear when you put a patch over an entire area, not just a suture line, and you're saying that it's within the delaminated tissue, and the use of the surgical mesh, you would use it in the shoulder to thicken thinned delaminated tissue, you know? So it's not exactly what their wording is, but they have to be able to look at the device and understand how the device

functions and be able to address those issues.

The BioDuct product is another one. It's cleared as a device for meniscus repair. However, the device has to be used with suture, which is the device that does the meniscus repair. And this device is actually a hollow tube that guides cells to the site of the repair. Now, you can say that, you know, the labeling that they submitted said that this is for suture repair, but when the device looks and behaves and the actual published study talked about it as a conduit for cells, that's a very different thing than the way that the device is used and what FDA may think that they cleared the device for. Thank you very much.

DR. MABREY: I'd like to thank the Sponsor and the FDA for some great presentations and for helping to clarify many of the issues before the Panel today.

At this time, we will focus on the FDA questions. The Executive Secretary will now read the questions to the Panel.

COL KRAGH: Jay, can I ask a question?

DR. MABREY: Yes, Dr. Kragh?

COL KRAGH: I'd like to ask a question. I'm not really sure who would best answer it. And a

Public Citizen person gave a talk and in his writing nearly equated indication with intended use, and the Sponsor specified intended use as being a subset of the written indication. Does that matter? And that seems to affect the flow chart if they are one way or the other. Is that relevant and --

DR. MABREY: Dr. Schultz, can you clarify that for us?

DR. SCHULTZ: I think what we're saying is, you know, there can be a general intended use, and within that intended use, there can be multiple indications. I think it was a little bit different than the way you phrased it. We've obviously cleared a lot of surgical meshes under the intended use of repairing and reinforcing tissue. And the question is -- and each of those has had specific indications whether it's an indication for repairing and inguinal hernia, repairing a ventral hernia, reinforcing a suture line in the lung to prevent air leaks, reinforcing a shoulder repair. So -- but the over -- sort of the overarching question is does it satisfactorily reinforce and repair tissue? That would be the intended use.

And I guess, you know, again, what I think we're all struggling with, and obviously we're sort

of asking for your help, is whether or not this particular indication can fit under that broader umbrella. And, you know, as I think you've probably figured out over the course of the last four or five hours, there is no bright line, and there's no -- there's nothing like -- I think you said, you know, there's a lot of data, there's a lot of questions, and, basically, it's a matter of putting it all together and trying to make our best judgment. And that's why we brought you as orthopedic experts together to try to help us make that best judgment.

DR. MABREY: Thank you. Can we have the first question, please?

DR. JEAN: There is a preface statement to all this. ReGen is requesting clearance of the ReGen Collagen Scaffold for the following indications: For use in surgical procedures for the reinforcement and repair of chronic soft tissue injuries of the meniscus (one to three prior surgeries to the involved meniscus) where weakness exists. In repairing and reinforcing meniscal defects, the patient must have an intact meniscal rim and anterior and posterior horns for attachment of the mesh. In addition, the surgically prepared site for the collagen scaffold must extend at least into the

red/white zone of the meniscus to provide sufficient vascularization. Please note that the acute indication as proposed by the Sponsor is acknowledged, and there will be a question related to this issue.

FDA has not previously cleared a surgical mesh device for this specific indication. In its 510(k) submission, ReGen referenced several legally marketed surgical meshes used in orthopedics, thoracic, and general surgery as predicate devices (these are included in your panel pack).

In order to establish that a device with a new indication is substantially equivalent to a legally marketed predicate device, the 510(k) submission must include appropriate supporting data showing that the manufacturer has considered the consequences and effects the new use might have on the safety and effectiveness of the device. The 510(k) submission also must explain why the new indication does not affect the safety and effectiveness of the device when used as labeled. With respect to this 510(k), then, FDA must determine whether use of the device for the indication described above affects the safety and effectiveness of the device when used as labeled. FDA is

requesting the assistance of this Panel in evaluating the data submitted by ReGen in making this determination.

The first question is: Compare the mechanical properties of the ReGen device and the mechanical properties of the referenced predicate devices as they relate to the ability of the devices to serve as a scaffold for tissue in-growth in the parts of the body for which they are indicated. Please consider the following:

Are the devices able to withstand the mechanical forces present in the joint or other parts of the body for which they are indicated sufficiently to achieve their intended purpose?

What is the impact on joint or other bodily function should the devices fail?

DR. MABREY: We'll just go around the Panel and get your thoughts on this. Dr. Shawen?

LTC SHAWEN: As far as the strict wording of the question, I think that we can say that the device withstands the mechanical forces present. From what I've seen from the relook surgeries, the device isn't failing or falling apart. What I don't know is if it's functioning to the level of a normal meniscus. All I know is that it's not falling apart

in those instances.

As far as what impact on the joint, I think that it probably has, as far as if it just fails or tears, it's not much different than having a torn meniscus again. And from the safety data that they've provided, I can't say that there's been a significant detriment by having the device in place. I'm being technical on my wording here just because I don't know all of these answers, and I don't think that we will know the answers at this time.

DR. MABREY: Dr. Kadrmas?

MAJ KADRMAS: I'd agree with Dr. Shawen. I think they're able to withstand mechanical forces based on the second look, as well as comparison to the predicate devices. They're not being asked to perform at the same level and function as native meniscus, so -- but compared to the predicate devices, I think they're adequate.

Impact on the joint, I think from what I've seen in the data has been pretty minimal should they fail. Oftentimes, we'll repair a questionable meniscal tears just because it's our only option. You know, and the reason we do that, if they fail, they'd just take them out anyway. So I think if this fails, they just end up with the partial

meniscectomy. So I don't see a big impact on the joint or bodily function should it fail.

DR. MABREY: Thank you. Dr. Potter?

DR. POTTER: My sense is that we don't have sufficient data to really comment on the mechanical properties of the scaffold. We have the pull-out data in the canine meniscus, and we've discussed that on both sides. If we look to the interpreted mechanical properties, that is, the rate of progression of arthritis, it seems to -- there was no difference. So it does not seem to -- it does seem to have somewhat of a chondroprotective effective. I would feel more comfortable with the data if it had been more independent in term of the evaluation of cartilage. It's very subjective by the orthopedic surgeon that put the implant in. That being said, the Outerbridge scores did not show any difference, so in that sense, they do -- did meet their purpose.

Impact on joint, again, similar to what was previously stated, I don't see any potential concern. It's not a bio-absorbable type of device. It's not something that incited any kind of immune reaction in their cohorts, so there is nothing to suggest that it would have an adverse effect.

DR. MABREY: Yes?

DR. ENDRES: From the histological and clinical data that's been presented, I do feel that the device seems to serve as an effective scaffold. In terms of tissue in-growth, although I don't think it is likely that the new tissue functions in a normal biomechanical way similar to the normal meniscus, I do think it probably is able to withstand the mechanical forces in the knee, and I think there is a low impact if the device fails.

DR. MABREY: Thank you. Dr. Kelly?

DR. KELLY: I think from the data presented, I think that the substrate is at least substantially equivalent to the predicates. I read the fine print. It's 43 percent of the patients had at least 80 percent of the meniscus removed. So looking at the shear stresses across the joint, I think that it indeed suffices mechanical properties. And in terms of deleterious effects, there were none that I could see were discernible.

DR. MABREY: Dr. Kragh?

COL KRAGH: I take the first bullet, withstand the mechanical forces, as an orthopedist, we think of it as tearing up the meniscus or the implant, and so that data that we know seems to indicate that, yes, it is able to do that.

What's the impact on the joint if it fails? In the big picture, it seems no different than a partial meniscectomy with a certain degree of fuzziness.

DR. MABREY: Thank you. Dr. Propert?

DR. PROPERT: No additional comments.

DR. MABREY: Thank you. Ms. Dalrymple?

MS. DALRYMPLE: I don't have anything to add. Thank you.

DR. MABREY: Great. And Dr. Spindell?

DR. SPINDELL: The only other thing I would add is that part of the question says serves as a scaffold for tissue in-growth, and I think if I look at the data, it looks like it did serve that purpose, that there was tissue in-growth into the scaffold. I think that was shown in the studies.

DR. MABREY: Great. Dr. Schultz, in regards to Question 1, the Panel generally believes that there is evidence of some soft tissue in-growth. However, it is not clear if the device is actually functioning like a meniscus. However, failure of the device appears to be no different from a simple meniscal tear, and, therefore, the device does not appear to carry any additional harm or risk. Is that adequate for the FDA?

DR. SCHULTZ: Thank you.

DR. MABREY: Thank you. Question 2?

DR. JEAN: Discuss any issues related to fostering the growth of tissue by the ReGen device in the knee as compared to issues relating to fostering the growth of tissue by the referenced predicate devices in the parts of the body for which they were indicated. Please consider the following:

Histologic and clinical description of new tissue.

Effectiveness of the devices in achieving their labeled indications.

Risks associated with use of the devices for their labeled indications.

And timeline for tissue in-growth.

DR. MABREY: Dr. Kadrmas, I'll start with you this time.

MAJ KADRMAS: Yeah, I think based on some of the histology we saw and what we saw in our orthopedic packets, I think the implant did foster growth of tissue with the ReGen device. It's similar to other predicate devices. The tissue, like we say, based on the forces it sees in the part of the body it's in, is going to form different types of tissue, different makeup of the tissue, fibrocartilaginous

tissue that's within the body. I did think that fostered that. We saw the in-growth as well as the histology in the biopsy samples.

So in that regard, for it's labeled indications, it served a scaffold for tissue in-growth and -- repair. I think it met those indications.

I think there is minimal risk with the use of the device for the labeled indications. Again, like we talked about with the last question, if it fails, they end up with a simple meniscectomy or partial meniscectomy and are generally no worse off than they would be without the ReGen device.

The timeline for tissue in-growth, we saw the histology of three to six months and the weakness between eight and twelve weeks, which is fairly standard I think. So based on these issues, I think it met its labeled indications.

DR. MABREY: Thank you. Dr. Potter?

DR. POTTER: I think we saw good histologic evidence of lack of inflammatory infiltrate. We have to remember that the histology is limited to a single punch biopsy and it's not a global assessment of the knee.

As I previously stated, I do have concerns

about the assessment of tissue regeneration based on its subjective analysis and to some extent based on bias of the operative surgeon performing a second-look arthroscopy.

I think it's important to recognize that, to a large extent, based on the ability to see some tissue in-growth and a lack of any serious immunologic effect, that they did achieve their labeled indications.

I think as we potentially move forward, it's important to recognize that the loads placed upon the scaffold will vary tremendously based on the patient that it's indicated for. And that's an important point in terms of what are the recommended inclusion/exclusion criteria for use of such a device, based on the contact pressures and its success clinically and also biologically.

DR. MABREY: Thank you.

DR. ENDRES: I think in terms of the device fostering the growth of tissue as compared to the referenced predicate devices, it's very similar. In terms of the histologic and clinical description of the new tissue, it appears to be appropriate. I think it'd be outstanding if the new tissue functioned like the normal meniscus, but I don't

think it's fair to expect that.

In terms of the effectiveness of the device in achieving its labeled indication, I do think it has shown that in terms of the ability to foster new tissue. As I stated earlier, when you compare the effectiveness to the predicate devices, specifically the patches used for rotator cuff surgery, I think the bar is actually very low. There has been no evidence, to my knowledge, that the mesh devices in shoulder surgery have been shown to be particularly effective. So, in that regard, it's at least as equivalent, if not better.

I think, again, the risks of the device seem to be low. The biggest risk I would be concerned about would be an infection in the knee, and I think there was only one case of that.

And I think the timeline for tissue in-growth is appropriate.

DR. MABREY: Thank you. Dr. Kelly?

DR. KELLY: Just addressing the questions in order, I think that the histological, clinical description of the new tissue is at least substantially equivalent. It's a more of a kindler, gentler, I think, tissue substrate, although it's not normal tissue it's regenerating.

And the effectiveness of achieving the labeled indications, if the indications are truly for repair and reinforcement, I think it indeed does do that because that sort of connotes a scar or some sort of mending tissue, which, again, is not normal.

The risks, I think, are really more with the application than the device itself, pain, effusion, and so forth. So I think the inherent risks of the device alone itself are minimal.

And I have no comment on the tissue timeline because there really is no data, there's no dose response or any kind of time sequence data available.

DR. MABREY: Dr. Kragh?

COL KRAGH: I think that all these four bullets were addressed as best we could, and I see no outstanding issues.

DR. MABREY: Thank you. Dr. Propert?

DR. PROPERT: I do want to comment on the effectiveness data at some point. Is that going to be in a later bullet? Are we still limiting ourself to fostering the growth?

DR. MABREY: Are we still what?

DR. PROPERT: Is this question limited to fostering the growth of tissue? I do want to make a

comment about some of the other clinical effectiveness data. I wasn't sure where in the list that would come up.

DR. MABREY: We're going to address that in Question 4.

DR. PROPERT: Okay. Then no additional comments on this.

DR. MABREY: All right. Thank you. Ms. Dalrymple?

MS. DALRYMPLE: My only question concerning this, and it's probably because I don't have the knowledge that the surgeons do but on the FDA Slide 15, it says the rehabilitation protocol, and I had asked about that before, about the difference between the control group being two to three weeks rehabilitation versus the six months. And I've heard several times that that's to be expected. But I'm wondering why is it to be expected? Is it because it was an implant versus something else because I'm wondering as far as the patients themselves. Why would they opt for this procedure versus just the control group procedure if they know that the rehabilitation time is going to be long and we don't have any data to show that five years out there is going to be a real potential benefit to them.

DR. MABREY: Well, maybe one of our sports medicine experts who routinely repairs menisci can tell us why someone would volunteer to have restricted weight-bearing for six to eight to twelve weeks in the hopes of --

MAJ KADRMAS: I think any time we repair something be it with the ReGen CS device or meniscal repair, we limit their weight-bearing in an attempt to -- just what the sutures do is they provide opposition for the tissue so they can heal. So you have to give that tissue a chance to heal. With a partial meniscectomy, there is nothing that needs to heal, so they can get back to their activity quicker.

Now, when you ask about why would someone opt for something when there is no great proof that it's going to be any benefit, some people don't. But I think that's the risks and benefits you present to the patient. And if athletes say, "I just want to get back in and start playing again," then they'll opt to undergo the meniscectomy. Others, if they think there is a chance that you will be able to preserve some meniscus, even though we don't have proof that it'll have a long-term benefit to them, will opt to limit their activity in the hope that that will give them benefit down the line. We may

have some data support that later on.

But I think those are -- you give the patient the options and the risks and benefits of each and let them choose as long as they know and accept the longer rehab. But that's the difference in the rehab. You're allowing tissue to heal versus one you don't have to allow anything to heal and you can get them --

MS. DALRYMPLE: Okay. Thank you.

DR. ENDRES: I think another thing to keep in mind is that there is -- I don't think there is a gold standard for rehabilitation after meniscus repair. I think probably each one of us on the Panel who does meniscus repairs rehabs our patients differently. And I expect that would be the case potentially for this device as well. For example, after a meniscus repair, I may allow a patient to weight-bear immediately in extension in a brace. So they aren't necessarily going to be non-weight-bearing for six weeks. It may differ among different surgeons.

MS. DALRYMPLE: Thank you.

DR. MABREY: Thank you. Dr. Spindell?

DR. SPINDELL: Yeah, my only comment is sort on that same line is that in the study that

compared partial meniscectomy, partial and this implant of this surgical mesh, they're different procedures, right? There is one -- one has a lot more activity involved, and, potentially, when you look at the -- that's why it's so hard for us to look at the adverse events rates because I'm not sure that they're comparable surgeries, which is -- would also explain why there's a different rehab. I mean, potentially, and I'll ask the orthopedic surgeons, would the more appropriate comparison be to a meniscal repair as far as timeline, time for rehab, et cetera, and not partial meniscectomy?

COL KRAGH: I think in the study it was irreparable, so for the study purpose, I think it's a moot question, but for the intellectual question is a good one and I think appropriate, and I think that the science of meniscal repair has more complications than partial meniscectomy. So I think is what your gut feeling was to ask the question. I mean, obviously, if there was a predicate device that they had compared it to, that would be the most interesting, but, of course, that's just fantasy. But, yes, I agree.

DR. MABREY: Okay. Dr. Schultz, with regards to Question 2 --

UNIDENTIFIED SPEAKER: -- Dr. Shawen?

DR. MABREY: I'm sorry. I started off --

LTC SHAWEN: That's all right. I don't have any significant comments other than I am surprised at how much of the histologic tissue actually came to look like meniscus at that time point. And I would also say that for the labeled indications, I think the effectiveness is met. The risks involved, again, are low, and then I am actually a little bit surprised at how quickly the in-growth is given that this is a collagen scaffold and not autogeneic tissue.

DR. MABREY: Thank you. Dr. Schultz, with regards to Question 2, the Panel generally believes that the device does foster in-growth similar to its predicate devices, that there does appear to be a lack of inflammation, it seems to meet its indications, and the risks associated with the use of the device seem to be minimal. With regards to the timeline, it appears to be appropriate when compared to other orthopedic procedures of similar nature. The Panel has some concerns about tissue regeneration and also about the varying loads that the device will see depending upon the individual into which it is implanted. Is this adequate for the FDA?

DR. SCHULTZ: Thank you.

DR. MABREY: Thank you. Question 3?

DR. JEAN: Please discuss any clinical issues related to use of the ReGen device in the knee as compared to use of the referenced predicate devices for their cleared indications.

DR. MABREY: I'll start with you, Dr. Potter.

DR. POTTER: I think this Panel was placed with, or faced with, very differing interpretations of the clinical data on both sides. I think most of us can glean just based on reading the *JBJS* article that there was an improvement in function in the chronic group. There was no discernible difference in the acute setting in pain scores. I think one thing that we need to keep in mind on the clinical front is that there is no other option for these patients and that indeed comparing meniscal, essentially a meniscal scaffold to a meniscal repair are apples and oranges, both in terms of rehab that was brought up, but also what we expect in terms of patient function in the perioperative period.

If we compared this to what is available, which is meniscal transplantation, which is a heavy hit to knee with bone plugs put in, slots put in, we

might expect very disparate type of pain and function scores compared to the scaffold, but we don't have those data to review.

So I think part of it we have to interpret based on the fact that we can't compare them as equal groups. They're very different groups, and we have to take away from it -- essentially, what we get is that the chronic group had improvement in function but little difference in pain scores.

DR. MABREY: Dr. Endres?

DR. ENDRES: I think a couple comments. I think in terms of this device as with any procedure, there is no substitute for clinical judgment. I think the Sponsor would agree that this device is not appropriate for every single patient who has a meniscal. And, clearly, clinicians need to use their judgment when discussing the use of this product. And, for example, I may choose not to offer it to an older patient and reserve it for a younger patient to -- a young patient with a subtotal meniscectomy, that's a very challenging, difficult problem. And, as Dr. Potter said, there really is no real good solution right now for that. And this offers potentially an alternative treatment to a meniscal allograft, which has mixed results at best. And,

clearly, you would have a very frank discussion of the risks and potential benefits of this device with the patient before you would ever choose to do it.

I think the second comment is when you look at the potential benefits of this device, I break them up into short-term and long-term. In terms of long-term benefits, I think the ideal goal is delaying or preventing osteoarthrosis of the knee, which has become a significant public health burden in this country and probably will increase as the population ages. I don't think we have any evidence available to us now that this device serves that goal. But the potential is there. I think we need to follow these patients out longer. But in terms of short-term goals, I think that's why a lot of us do this surgery is for pain relief and improving quality of life, which is restoring function. And I think those end results cannot be understated. I think those are very important to patients. And I do think although the data is somewhat limited, there is some data that shows potentially improved function in these patients, and I think that's potentially very important.

DR. MABREY: Thank you. Dr. Kelly?

DR. KELLY: I think clinically, this

product alone offers great promise, alone it is safe. The applications I think, though, are concerning in that what I don't want to see happen is some journeyman arthroscopist say, well, I can help you, ma'am or sir, and do a very, very sort of morbidity-associated elaborate repair.

But I have to say that just thinking out of the box here, anything that increases surface area is probably good for the knee even though it's not perfect tissue. We know that the contact stresses in that compartment are probably going to be less. And I actually received this epiphany that if you look at the allograft data, up to 40 percent of some allografts have resorbed short term.

So the fact that we haven't seen that here I think is a very good thing. And in this generation of growth factors, and so forth, this may be a substrate that could be used in conjunction with other elements. But my concern is the application, that the bar is lowered, and that we could cause more damage to a knee than we could help.

DR. MABREY: Thank you. Dr. Kragh?

COL KRAGH: I think regarding its relation to predicate devices for other body parts, obviously, we can only really speculate on that direct Question

Number 3. But I think I am generally impressed with what we've been given and, you know, knowing the realistic ambiguities, I think we've tried to address them as best we can.

DR. MABREY: Thank you. Dr. Propert?

DR. PROPERT: Nothing more just yet.

DR. MABREY: Ms. Dalrymple?

MS. DALRYMPLE: Yeah, I don't have anything. Thank you.

DR. MABREY: Dr. Spindell?

DR. SPINDELL: No comment, nothing.

DR. MABREY: Thank you. Dr. Shawen?

UNIDENTIFIED SPEAKER: Thank you -- oh, sorry.

LTC SHAWEN: I actually have fewer concerns with this device when I compare it to the predicate devices being compared given that the SIS graft is shown to be very pro-inflammatory and very possibly detrimental in its treatment in the shoulder. And I'm very encouraged, actually, by the lengths that this device has been studied to show that this inflammation did not occur, that we don't have an immune response.

DR. MABREY: Thank you. Dr. Kadrmas?

MAJ KADRMAS: I think most of the issues

have been similarly raised. I think clinical issues compared to predicate devices, I think they have shown adequately that it has provided some tissue within the knee. Whether that functions like meniscal tissue is doubtful, but, you know, like we talked about earlier, meniscal repairs probably don't function as a normal meniscus following healing of the repair. I think they did a good job.

It is a bridging, or another option, like Dr. Potter alluded to. Right now, partial meniscectomy leaves them with no meniscus, and you simply wait on a meniscal transplant, which is a morbid procedure in the young, active population. So another tool in your toolbox, when used appropriately, I think is a good option if it's not going to do any harm, which I think this is not.

DR. MABREY: Dr. Schultz, with regards to Question 3, the Panel generally believes that for this particular clinical problem that patients really have no other choice except for partial resection versus partial repair, and, therefore, it is difficult to compare it with other techniques. Clinically, it appears to offer some promise. The Panel does have some concerns about the device being offered to inappropriate patients and for

inappropriate indications. And the Panel and, I, too, can see this being promulgated as the next latest and greatest thing. And every corner arthroscopist may be offering it to anyone that walks in the door. That was just my editorial comment. Now, is this adequate?

DR. SCHULTZ: Well, let me ask a question. I mean, you've raised the concern. Do you have any suggestions in terms of how to prevent that from happening?

DR. MABREY: Suggestions for?

DR. SCHULTZ: Well, I think several of you have raised concerns about overuse and about the need for appropriate skill in judging who should get this and who shouldn't and appropriate skill in making sure that it's implanted properly. Do you have any suggestions for the Agency in terms of how that might be done?

DR. KELLY: The first thing that comes to mind would be there's a certain shoulder implant that's only allowable if you attend a certain course, and there has to be some qualifiers that the product insert should mention, you know, skilled arthroscopists that are well-versed in meniscus repair techniques. And I would offer that maybe a

course could be offered that would be at least a fulfillment to be able to even use it.

DR. MABREY: I would just add that if this were a PMA, this is the part where we start adding all the amendments for the Sponsor. So chime right in.

COL KRAGH: If I recall, the Sponsor group addressed this issue to a limited degree when they were talking about bringing surgeons to training and doing it in a cadaver and apparently had great results on the first try, implying that the learning curve, essentially, was zero in people that were apparently surgeon researchers interested in this. So that's obviously an extremely small subgroup, but it's hard for me to say how hard this procedure would be having never done it, per se. It does seem to be technically demanding on its first go-round, but it's hard for me to comment any further without speculating.

DR. MABREY: I think from my own personal experience, having been on the Panel that approved the Birmingham Hip and having introduced the suggestion that there be extensive clinical training for surgeons attempting to implant the Birmingham Hip, that held for about six months or so after the

implant was introduced. And then, after that, literally every orthopedic surgeon in the city was putting in Birmingham hips whether correct or incorrect. So my concern would be if this device is offered that there be some type of training program offered and some evaluation of skills because it does appear to be somewhat technique-dependent.

DR. SCHULTZ: Thank you.

DR. MABREY: I haven't had a chance to let the rest of the Panel respond to that. Okay. So I think the sense of the Panel members is that some type of training, some type of evaluation be offered for this whether it's cadaver lab or a wet lab or even surgical visitation, that that be considered as part of the approval. This is just a response to your question, of course. All right. Are we ready for -- is that adequate?

DR. SCHULTZ: It is, thank you.

DR. MABREY: All right.

DR. JEAN: Considering the data provided by ReGen on the collagen scaffold device, the nature of the indication for the reinforcement and repair of chronic soft tissue injuries and your own experience, do you believe that ReGen has demonstrated that the collagen scaffold device is at least as safe and

effective as the predicate devices?

DR. MABREY: Dr. Endres, I'll start with you.

DR. ENDRES: I do.

DR. MABREY: Yes?

DR. KELLY: I'd like to qualify it by saying I'm not crazy about the predicates, but, yes, indeed, it is at least as substantially equivalent.

DR. MABREY: Dr. Kragh?

COL KRAGH: Given what we've got, yes.

DR. MABREY: Okay. Dr. Propert?

DR. PROPERT: I'm going to have to put this here because I don't know where else to put it. I just wanted to comment on the safety and effectiveness in the context of evaluating those clinical results from the trial just to say -- and I'm not going to discuss the safety because I don't feel qualified to discuss the issues there. But in terms of the efficacy, I feel like there isn't adequate data or the data isn't adequately presented in order for me to address that; specifically because issues of missing data and changes in follow-up are not adequately addressed, and I really don't feel like I can assess the effectiveness data.

And I specifically want to highlight the

reoperations data. And I can't address what should be considered a reoperation. I don't have the tools for that. But I can say it makes me very nervous when two different fairly competent groups come up with such opposite answers. It makes me wonder if the data is sufficient.

DR. MABREY: Thank you. Ms. Dalrymple?

MS. DALRYMPLE: I don't really have anything to add about the safety.

DR. MABREY: Okay.

DR. SPINDELL: I'm not a surgeon, so I don't have any experience to go on.

DR. MABREY: Dr. Shawen?

LTC SHAWEN: Yeah, I think I already answered that. Yes.

DR. MABREY: Okay. Dr. Kadrmas?

MAJ KADRMAS: Yes.

DR. MABREY: And Dr. Potter?

DR. POTTER: Safety, yes. I have some questions about effectiveness because there is no real true predicate device that's similar that we have available to evaluate, but what we have is limited. But safety, yes.

DR. MABREY: Thank you. And Dr. Schultz, it is the -- with regards to Question 4 on safety and

efficacy, the Panel generally believes that the device is safe and that its effectiveness may remain to be seen. There does seem to be some holes in the data with regards to efficacy, but there does not appear to be any outright problems with the device. Is that adequate for FDA?

DR. SCHULTZ: Well, I think, you know, I guess I'd like to hear more specifically CS device is at least as safe and effective as predicate devices. So, again, the way you said that, I think I would like to --

DR. MABREY: Well, I think I'm also trying to reflect that we're having trouble with comparing this with predicate devices because they really aren't used in the same way --

DR. SCHULTZ: Are different, right.

DR. MABREY: But as far as one can make those comparisons, I think it's the sense of the Panel that, yes, it is as safe and effective --

DR. SCHULTZ: Thank you.

DR. JEAN: Please comment on an indication of the device for the reinforcement and repair of acute soft tissue injuries.

DR. MABREY: Let's start with Dr. Kelly this time.

DR. KELLY: I think from the data presented, we can say that it is -- reasonable indication would be acute or chronic loss of meniscal tissue, which is at least 60 percent or greater.

DR. MABREY: Okay. Dr. Kragh?

COL KRAGH: Given what we got, I think it's adequate. I think that those that have an acute injury have the most potential benefit given what we understand about the disease process.

DR. MABREY: Thank you. Dr. Propert?

DR. PROPERT: No comment.

DR. MABREY: Ms. Dalrymple?

MS. DALRYMPLE: I'm not quite sure if this is the right place to include this, but, before, we had talked about the explants that had occurred, and the FDA person told us that it had occurred because they first were on a treadmill and then they had to have the explant done, and then the next time was because they were doing I think cycling or something. So I guess my question would be about the compliance of the patients and whether or not they're willing to, you know, go through this process in order to -- does -- okay. You're smiling, so I'm not sure.

DR. MABREY: Being a surgeon and having to deal with compliant and non-compliant patients, as

you bring that up, it would be wonderful if every patient we had did exactly as we told them to do. But if that were a requirement to get any type of approval from the FDA, then there would be no devices on the market ever.

(Laughter.)

DR. MABREY: So I think compliance of the patient is an important factor. And that goes into one of the points that was brought up earlier and that is patient selection. You have to find someone who is both motivated but will listen to instruction as well, and especially, and we have a lot of sports medicine docs here, being highly motivated doesn't necessarily mean that your patient is going to listen to your instructions. They want to get back and run and play football or do whatever they're doing. So I'm not sure that patient compliance is an issue as much as patient selection.

MS. DALRYMPLE: Um-hum. Well, that was the second part of my comment is maybe initial warnings to the patient as far as what their physical activity was before injury versus whether or not they're able to have that six-month window there, and then just the patient population. My other concern is if they're very elderly, then possibly, you know, they

wouldn't be a good candidate either because they would need to maintain mobility. So --

DR. MABREY: If they're very elderly, then they usually come to me.

(Laughter.)

DR. MABREY: Sorry about that.

Dr. Spindell?

DR. SPINDELL: No comment.

DR. MABREY: Okay. Dr. Shawen?

LTC SHAWEN: As far as an acute injury, given that there is a paucity of data, long-term data saying that this is going to be good or bad, I have a problem saying that that would be a primary indication.

DR. MABREY: I'm sorry, you said you do or don't?

LTC SHAWEN: I do have a problem that that would be a primary indication for acute injury given that there is a paucity of long-term data.

DR. MABREY: Okay. Dr. Kadrmas?

MAJ KADRMAS: I think based on the data and the risks involved, I do think that the ReGen CS device should be indicated for repair of acute injuries. I don't see a big downside to that. And making a patient wait until they've had one, two,

maybe three surgeries before they're a candidate I don't think is completely appropriate either.

DR. MABREY: Okay. Dr. Potter?

DR. POTTER: I agree. I think that we need some means by which to deal with the patient that unfortunately has a subtotaled meniscectomy, and we can't just wait for them to develop osteoarthritis. That being said, my concern on the chronic side is that the indication has to be very carefully controlled, that in addition to the patient, the surgical learning curve, you have to think about the biologic environment that this implant is being put into. And, specifically, in your initial exclusion criteria, you excluded Grade 4 lesions. But if you have diffuse Grade 3, the contact pressure is already extraordinarily high in the knee.

So my sense is that you have to be very careful about indications with regards to the degree of osteoarthritis in the knee, that any patient, for example, that has any kind of pre-existing adverse synovial response, and that doesn't necessarily mean RA, that can mean an OA patient with synovitis, that's a toxic biologic environment for this type of a device.

So I think, yes, acute and chronic

indicated but with strong caution given the surgical community and their predilection for new devices and putting it in every environment. I think we have to be very careful about selection.

DR. MABREY: Thank you. Dr. Endres?

DR. ENDRES: I think the indications for using it in an acute scenario should be extremely narrow. I don't think there is any evidence to show -- it's essentially implying that this should be performed prophylactically because you're expecting the patient to develop symptoms. And although a large number of patients do go on to develop symptoms, not all of them do, and there is certainly no evidence, for example, that doing a meniscal allograft prophylactically is indicated at all. But I do think in the setting of a young patient who has for whatever reason a subtotal meniscectomy and especially if they have any mal-alignment of the lower extremity, I would consider that, but that would essentially be the only indication.

DR. MABREY: Thank you. Yes?

DR. KELLY: One comment that came to mind is that if you look at the lateral meniscectomy data, it turns out that older patients do far worse. If you take out a lateral meniscus in a middle-aged

person, they go down the hill very rapidly, and it's been, I think, clearly shown the young patients actually do okay for several years. So I think that when we consider this product we should not consider age so much as a factor. I think it may, as Hollis said earlier, sometimes that's all you can give them. So if a middle-aged person loses their lateral meniscus, this actually may potentially slow down that better than an acute, younger.

DR. MABREY: Yes, Dr. Shawen?

LTC SHAWEN: May I comment. One of the things, what if you have a surgeon out there that this small meniscal tear -- now they're going to take out a huge area of this meniscus in order to put in this implant. I think that that would have to be qualified. If this were to be considered for an acute type of thing, you definitely would have to have specific qualifications, and I think that Dr. Kadrmas and Dr. Endres kind of alluded to that.

DR. KELLY: I think -- absolutely correct. In fact, I mention I published a study years ago looking at just mulberry knots causing chondrosis. I mean, everything we do has morbidity. So you have to have very, very, you know, limited indications, and most important of all, in the right hands. This is

not to be the Holy Grail for meniscal surgery. Then it'll be abused.

DR. MABREY: Any other comments from the Panel?

(No response.)

DR. MABREY: Dr. Schultz, with regards to Question 5, the Panel generally believes that there is an indication for the device in the repair of acute soft tissue injuries. However, that feeling is not unanimous. There is also a very strong concern throughout the Panel with regards to patient selection, with patient compliance, and specific qualifiers for the operation. Is that adequate for the FDA?

DR. SCHULTZ: Thank you, yes. I would say that I -- we may come back to some of you or all of you for some additional assistance in helping us to further guide us towards some of what you're calling qualifications and a little bit of assistance in that regard, but I don't think we need to do that today. Thank you.

DR. MABREY: Well, at this point, I would like to thank everyone on the FDA Panel, especially our three military members, point out that it's Army two to one over Air Force --

(Laughter.)

DR. MABREY: Three to one if you count me. And, again, thank you for taking your time out for this very special Panel meeting on extremely short notice in some cases.

Dr. Schultz, do you have anything to add?

DR. SCHULTZ: I don't except to add my sincere and overwhelming thanks to all of you for, again, doing this on short notice, and thank you for what I think was a very, very high-level and thoughtful discussion of all the issues and for providing your input to the FDA and to the American public. Thank you very much.

DR. MABREY: We've now provided the FDA with our responses to their questions related to the ReGen Collagen Scaffold. The November 14, 2008 meeting of the Orthopedic and Rehabilitation Devices Panel is now adjourned. Thank you all.

(Whereupon, at 3:03 p.m., the meeting was concluded.)

C E R T I F I C A T E

This is to certify that the attached proceedings in the matter of:

ORTHOPEDIC AND REHABILITATION DEVICES PANEL

November 14, 2008

Gaithersburg, Maryland

were held as herein appears, and that this is the original transcription thereof for the files of the Food and Drug Administration, Center for Devices and Radiological Health, Medical Devices Advisory Committee.

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DOMINICO QUATTROCIOCCHI,

Official Reporter