these subgroups, once again. In terms of the leg pain, the severe, the patients that had severe back pain, in terms of how many patients did we measure leg pain in, in this group? It was 54 percent of the CC population. It's not a small group. And in that 54 percent of the CC population, you can see we had a very nice reduction, 0.0123. It's not a chance event.

And in terms of back pain, once again, that's 61 percent of the CC population. Not a small population. And, of course, both those numbers are significant in the ITT and in the CC. So if we simply talk about patients with severe back pain, if we talk about moving forward -- patients with severe back pain, providing this device to them, it's a large percentage of the patients, and you can see there is indeed confidence that these patients will benefit from this product. Next slide, please?

In terms of the successful study, treatment magnitude effect, once again, I'd like to point out that they're very large treatment effects, in terms of the magnitude, based on the same populations that I alluded to a moment ago. In terms of the entire population, taking out severe back pain, we're not talking about 1 or 2 percent. These numbers are

large. 11 to 14 percent of all patients -- you can see there, in fact, is a very nice magnitude of effect in all patients. We stressed the 34 percent, obviously, because it was over the request by FDA for 33, but looking at all patients, indeed, there is a very nice treatment effect, in terms of the size of the benefit. Next slide?

And so, in ending, I think it is very important to consider that, indeed, this is a very safe product. It's been established around the world, and it's clear in our own pivotal study. This is an unmet need. A number of the Panelists have addressed this. The clinicians here have addressed this. And we just don't have anything else.

So we think that there is no FDA-approved surgical adjuvant that's indicated for the reduction of pain and neurological symptoms in lumbar surgery. We think we've shown in a straightforward way that, in fact, Oxiplex fulfills this need.

Thank you, Dr. Mabrey for your time.

DR. MABREY: And thank you. Before we proceed to the vote, I would ask Ms. Connie Whittington, our consumer representative, and Ms. Elisabeth George, our industry representative, if they have any additional comments.

Ms. Whittington?

MS. WHITTINGTON: In representing the patient, we certainly need something to help reduce pain both in the immediate postoperative and long term postoperative period. And this product does, in some populations, it seems, has some hope to do that. And, certainly, the volume of patients that have been done, that have utilized this device internationally would represent that, and I appreciate the information that was brought forward about that.

There's still some issues that I had today, as you all have heard about, about the studies that were done. There is potential for it in the future. I would encourage you to continue to focus on the patient's outcome and your LSOQ as your quality metric and measurement of effectiveness. I think that that's critical to development of any product or project.

DR. MABREY: Thank you. Ms. George?

MS. GEORGE: I think that the Sponsor just tried to clarify many of the open questions that we brought up and that all of you brought up regarding the analysis of the data of all versus the severe back pain patients. And I think that along with that analysis, as well as the earlier gentleman that spoke

from Belgium, the many published papers that have been identified in the safety and effectiveness data -- I believe there were 9 or 10 different papers with more than 300 patients each, you know? And the 100,000 patient use I think clearly shows us the safety.

I think that the fact that it is -- efficacy has also been shown, I believe, through those papers, based on the information that's included there. So I think that we have enough data to show us that it is a safe and effective product. I think that if there is any question on people's part, that they want more data, then I think the post-market surveillance could be evaluated, the study. But I also would voice that the standard post-market surveillance systems that are in place in the U.S., as well as internationally, in China, Japan, Canada, and the EU, there is sufficient data, and the expectation is, as a medical device manufacturer with certified quality systems and registered quality systems, it is our requirement to be monitoring that data consistently and taking severe actions as appropriate.

DR. MABREY: Thank you. We are now ready to vote on the Panel's recommendation to the FDA for

this PMA.

Panel members, I would ask that you refer to the voting options flow chart in your folders, the multicolored chart, which has evolved over the last several Panel meetings.

DR. MABREY: Dr. Jean will now read the Panel Recommendation Options for Pre-Market Approval Applications.

Dr. Jean?

DR. JEAN: The Medical Device Amendments to the federal Food, Drug and Cosmetic Act, as amended by the Safe Medical Devices Act of 1990, allows the Food and Drug Administration to obtain a recommendation from an expert advisory panel on designated medical device pre-market approval applications 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. The definition of safety, effectiveness and valid scientific evidence are as follows.

Safety, as defined in 21 C.F.R. 860.7(d)(1). 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 probably risks.

Effectiveness, as defined in 21 C.F.R., Section 860.7(e)(1). There is reasonable assurance that a device is effective when it can be determined, based on valid scientific evidence, that in 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.

Valid scientific evidence, as defined in 21 C.F.R., Section 860.7(c)(2). Valid scientific evidence is 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 a marketed device, from which it can fairly and responsibly be concluded by qualified experts that there is reasonable assurance of 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:

Approval. If there are no conditions attached.

Approvable with conditions. The Panel may recommend that the PMA be found approvable subject to specified conditions, such as physician or patient education, labeling changes or a 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 the data do not provide a reasonable assurance that the device is effective under the conditions of use prescribed, recommended, or suggested in the proposed labeling.

Following the voting, the Chair will ask each Panel member to present a brief statement outlining the reasons for his or her vote.

DR. MABREY: Are there any questions from the Panel about these voting options before I ask for a main motion on the approvability of the PMA?

(No response.)

DR. MABREY: Is there a motion for either approval, approvable with conditions, or not approvable from the Panel? Dr. Hanley?

DR. HANLEY: Mr. Chairman, it is my understanding that the PMA must stand on its own merits with regard to safety and effectiveness data in the application or from publicly available information. I do believe there is reasonable assurance that the device is safe. While it is possible that this device may be effective in certain subgroups, the data did not provide a reasonable assurance that the device is effective under the conditions of use prescribed, recommended, or suggested in the proposed labeling.

Hence, I propose the motion that the PMA for Oxiplex by FzioMed is not approvable.

DR. BLUMENSTEIN: Second.

DR. MABREY: And it's been seconded. Let me switch over to my non-approvable.

It has been moved and seconded that the PMA P070023 for the FzioMed Oxiplex/SP gel be found not

approvable. With a show of hands, please indicate if you concur with the recommendation that the above-named PMA be found not approvable. Keep in mind that those members who are raising their hands are indicating that they concur with the recommendation that the above-stated PMA is not approvable.

Let me back up one moment. We need to have discussion on the motion before we can vote.

Is there any discussion on the motion?

(No response.)

DR. MABREY: Not seeing any hands for discussion, we'll move on to voting. With a show of hands, indicate if you concur with the recommendation that the above-named PMA be found not approvable. Keep them up while I check. Okay. Thank you.

The voting members who are raising their hands indicating that they concur with the recommendation that the above-stated PMA is not approvable are Dr. Hanley, Dr. Horlocker, Dr. Rao, Dr. Evans, and Dr. Blumenstein.

DR. MABREY: With a show of hands, please indicate if you oppose the recommendation that PMA, P070023 be found not approvable? Okay.

The voting members who are raising their hands indicating that they are opposed with the

recommendation that the above-stated PMA is not approvable are Drs. McCormick and Sang.

DR. MABREY: I don't think anyone's abstaining from the vote.

It is the recommendation of this Panel to the FDA that the PMA P070023 for the FzioMed Oxiplex SP gel be found not approvable.

The motion carried 5 to 2 with no abstentions.

DR. MABREY: I will now ask each Panel member to state the reason for his or her vote, starting with Dr. Hanley.

DR. HANLEY: I think I explained those earlier and in the proposed motion. I think this material is safe, and I think it possibly is effective in certain subgroup of patients or possibly can be, but I think the statistical analysis does not prove superiority of this over a control of no therapy in the surgical group. I think the major issue here is proving the primary endpoint. And we need to base our decisions on, first, absolute proof, statistically, of the primary endpoint, and then secondary analysis of the secondary endpoints and sort through those.

So while I, deep down, as a spine surgeon,

want to approve this stuff, the statistics mandate that I don't even if I believe the Sponsor's statistical analysis completely. I have to reject this based upon the training and the principles of the FDA-approval process. You can't pick out little things. It either is or it isn't. And it's statistically significant and clinically significant or it's not.

So I think there is a need for something like this, and it may well be that in certain patients it can be helpful. But I'm obligated not to vote for something that's not statistically validated through the PMA process. You can't get around that.

DR. MABREY: Thank you. Dr. Horlocker?

DR. HORLOCKER: It's hard to come up with something so beautifully stated to even add to that. I, too, agree that we have enough data to say that this is safe, but as far as efficacy, it may be in some patient populations somewhat helpful. And I think we need to actually prove that both statistically and then determine if there is even a clinical relevance. We don't even know if there is a statistical difference if that's going to be a clinically relevant difference, too. So I think there are two things that the Sponsor has to do.

And, as Dr. Hanley stated so beautifully, that start with a primary endpoint and then go on from there to the secondary endpoints once you've proven that you do have that efficacy.

DR. MABREY: Thank you. Dr. Rao?

DR. RAO: I believe that the product is going to be safe. However, the lack of a statistical significance using the primary and secondary effectiveness endpoints is what led me to not approve the product.

In addition, I have concerns regarding the randomization process, deviation from the list of exclusions.

And, finally, my biggest concern is the lack of a clear basis of physiologic efficacy. We ought to be a few decades away from using devices with no clear or proven basis of efficacy.

DR. MABREY: Thank you. Dr. McCormick?

DR. McCORMICK: So I didn't vote for the non approvable motion, and the reason is that -- I had trouble with the study. It's a very highly selective group, very unusual group in the high incidence of low back pain, severe low back pain. They call this a challenging group. This represented the majority, which I just don't see that. I think

most surgeons don't see that either. The improvement that was seen was small.

But, on the other hand, there was no harm with the treatment. And I think that there is a, if not scientifically valid, at least strongly suggested by this that there might be some patient population in whom there may be some benefit for this treatment. And as a practicing surgeon who looks these patients in the eyes on a weekly basis, I'd like to have that option open to me.

I want to say I would not have voted for to approve it but would have voted for approval with conditions. And those conditions would have been that the proposed indication, which would have been put on the package or the indications would have to be very narrowly constructed to reflect this highly select group and this unique patient population with severe low back pain. Under those circumstances, I would have voted for approval.

DR. MABREY: Dr. Evans?

DR. EVANS: I think I agree with what was eloquently stated by Dr. Hanley. My concern is that the Type 1 error rate I believe has been compromised, and I don't -- and I'm concerned that it's been compromised in enough -- in a way that we can't

quantify it. And, therefore, I don't really have confidence in -- you know, I'm worried about the false positive rates.

I was not particularly concerned with the safety data. It looks like a very safe device, and this does not rule out the possibility of effectiveness, but I do believe that we've lost control of the error rates in such a way that we're not quite sure where we are. And so I think we need more data.

DR. MABREY: Thank you. Dr. Sang?

DR. SANG: I actually agree with all of the comments. The study was methodologically flawed. It was unblinded. It was uncontrolled. And the data analysis plan was questionably not consistent with the FDA's recommendations.

And, despite that, I voted against not approving because I do believe this is safe. I see patients with failed back. And I'm hoping that -- I had been hoping to vote approvable with conditions. And the condition would be to then demonstrate in a systematic way with a completely new design and new outcomes in a double-blinded, not single-blinded, and controlled fashion with an appropriate control group on effect.

And, you know, once again, what tipped me over the edge was the safety profile, which I think the data from Europe probably support. We did not hear enough of the details, but I'm making the assumption that this has been shown to be safe in over 100,000 Europeans, or 100,000 outside the U.S.

So, thank you.

DR. MABREY: And Dr. Blumenstein?

DR. BLUMENSTEIN: I voted for not approvable. I think we're going to have to teach Dr. Hanley the statistician secret handshake because he seems to be moving towards qualification for that.

The reason that I voted not approvable was that for the analyses for which I could feel confident about knowing the false positive probability, there was no efficacy. And for the analyses for which I was uncertain and quite concerned about, the false positive probability, while those were suggestive of an effect, I couldn't find a way to approve it.

DR. MABREY: Thank you. Since the Panel has voted to recommend that the PMA is not approvable, as part of a general discussion as an aid to the FDA and also to the Sponsor in future applications, I would now ask each Panel member,

starting with Dr. Hanley, what would it take? And this is a discussion.

DR. HANLEY: Well, I'm frequently asked about these studies, and study design is where you win or lose in these things. And with something like this, where there is no effective treatment, a superiority study is obviously the best way to go.

I think getting an adequate sample size, controlling your study population through the sites a little tighter can often give you better information. The issue as a surgeon, the whole question is here can you reduce lower extremity radiculitis discasthetic pain in a nerve root operated on thought to be related to postoperative adhesions, so called scar -- tethered root. That's the question. So that's the one that needs to be addressed for this particular problem.

Now, I think the average orthopedic or neurosurgical spine surgeon thinks the biggest problem in spine surgery is regular old discogenic back pain. That's the tough thing. But that's a whole different kettle of fish. You start mixing those two up and you can get into trouble.

I think there's a not unreasonable chance this stuff might work. But I don't think there are

enough numbers. I think there was too much variability, and I think the thing got mucked up in a statistical conundrum, which I think was not understandable. Not that I couldn't -- I definitely couldn't understand it, but I also believe that I will never be able to understand it. And I think there's a problem. Keep it simple. Keep it clean. Keep your study and your control groups clean. Get an adequate number of patients. Don't overdo yourself with too many study sites doing too few patients.

DR. MABREY: Thank you. Dr. Horlocker?

DR. HORLOCKER: Well, I would just add kind of a comment to what Dr. Rao said earlier. Without knowing what the mechanism of this is, it's hard to know exactly how to construct a study to know what your patient population should actually be, and it would be wonderful if you had some of the mechanistic -- how it works, so then you know how you could evaluated its efficacy or not.

Other than that, just from the standpoint of larger numbers and keeping it to more of a clear and simple statistical analysis that follows what was recommended and then a secondary analysis if that's justified by the primary analysis.

DR. MABREY: Dr. Rao?

DR. RAO: I think your pilot study may have been on the right track. I think you ought to focus on peridural fibrosis and the potential leg pain that results postoperatively. That's the only clear rationale that exists with peridural fibrosis, relief or causation of leg pain. So your study should be geared towards leg pain.

Postoperatively, I would exclude any potential structural causes of leg pain besides peridural fibrosis, and then you have a clean sample of patients with just peridural fibrosis. And then you assess whether or not the use of this device helped and relieved their leg pain. That would be the cleanest study. You have to have a clear basis of efficacy, and then you have to have a clean sample without associated structural pathology that may be contributing to their postoperative leg pain.

It would help if you had additional variables where you could rule out patient selection or psychological factors and get a cleaner sample still. Thank you.

DR. MABREY: Dr. McCormick?

DR. McCORMICK: Well, the one thing, at the very least, listening to the other Panel members,

what this study generated was a very compelling hypothesis, to suggest that in a very distinct patient population there may be a very clear-cut benefit to this treatment. And, to me, efficacy overrules generalizability. And so I think short of doing a new trial, where you only select patients with severe back pain, I just can't imagine how any other study is going to get through this Panel, based on a heterogeneous -- patient population. So that's the only thing I would suggest.

DR. MABREY: Thank you. Dr. Evans?

DR. EVANS: I guess what would convince me is a randomized trial in people with high back pain, stratify randomization on important potential confounders, control for those covariates in design and make sure that you control error rates in analysis and so that, you know, you know exactly what your error rates are. You know, I think, you know, any analyses you do is put within context of everything else you do. And so I guess that's, you know, what would be my recommendation.

DR. MABREY: Dr. Sang?

DR. SANG: I do think that there are pre-clinical data to support your hypothesis that this reduces peridural fibrosis in the long term or

perhaps other similar barriers, types of barriers. I think that these are such difficult studies to run. I would recommend, if I were advising you, to first do a small bridging study, a proof-of-concept study in a highly select group of subjects with radiculitis. I would review -- I would run this in a very small number of sites. I would have your investigators review records, review MRIs. And, frankly, I would exclude those with significant compression of the nerve root.

But, anyway, I would recommend a bridging study. I might recommend even a small amount of local anesthetic in a selected nerve root block to demonstrate that it's clean radiculopathy. But some small study to show proof-of-concept.

And then, as I was running this, I would design -- plan to move forward with a pivotal trial, assuming that that study gave you a go. And I think your pivotal trial has to be -- it has to be double-blinded, randomized controlled. It has to incorporate a treatment, a real placebo, whether it be an injection of saline with -- not an injection, but an application of saline instead of your gel. It's not ideal. I'm sure there is something you can figure out. But the surgeons have to be blinded.

The surgeons are making decisions. And surgeons, with high volumes, of course there's a possibility that they may not know who got what. But the chance is good that surgeons can remember in whom -- for whom they injected an exciting new gel.

At any rate, I would either stratify it by pain intensity, by pain severity, or I would exclude patients without sufficient pain, you know, patients, for example, who have at least a 5 out of 10 or on the Likert Scale, or a certain number on your composite scale, or whatever your primary outcome is chosen. And I would incorporate some of the more standard pain measures as secondary endpoints. I would incorporate measures that have shown to have treatment responses in other -- even though they're pharmacological trials, they're at least sensitive to treatment effects. I would consider including an intensity measure, another -- well, I like the BPI because it's a composite measure of intensity and function and it looks at intensity in different ways, but you can decide what pain measure to use, also function and activity measures that you already have incorporated and you know are important. I would consider a responder analysis. That would potentially help you in your analyses.

I would certainly look at opioid use soon after -- every point following surgery and also other concomitant medication use because it is the standard of care in these patients who have persistent pain following a laminectomy to -- or discectomy to be put on any number of anticonvulsants or antidepressants.

So I would include all of those potential confounders that could have served as one of many potential sources of variability that could have affected your treatment effect in this study. Of course, a disability instrument that you've already, you've already, you've already proposed.

So, you know, I think these are really difficult studies to run successfully. And, therefore, I think a bridging study to show proof-of-concept would be very, very useful for you.

DR. MABREY: Dr. Blumenstein?

DR. BLUMENSTEIN: I've said a lot already that hint at suggestions towards perhaps a new study. I would like to emphasize that you've heard from several people, and it took something that I kind of wondered about myself, in the idea of double-blinding the study seems to bother more than just me. The other thing I would mention is that whatever primary endpoint is chosen, I think it should be more ITT-

friendly.

DR. MABREY: Thank you. I'd also like to invite comments from Ms. Whittington and Ms. George.

MS. WHITTINGTON: I don't have any further comments. I've already offered my thoughts.

DR. MABREY: Ms. George?

MS. GEORGE: I guess I would just like to say as a manufacturer, first, I want to thank you all for your -- on behalf of industry for your input and your insights. It's been very interesting listening to the suggestions of structuring the study, et cetera, since that, in fact, was done in partnership with the Sponsor and the FDA and planned.

And it's also interesting listening to the comment about having many more patients or stratifying the data and focusing the release, because other Panels I've been on have been the opposite, where a Sponsor has come in with a much narrower intended use or indications to use. It gets rejected for the inverse reason that it's too narrow a use and it doesn't -- doctors want to have more patients be able to use it.

I also think that what we need to remember is, is that hindsight is 20/20. So all the proposals and suggestions that you all made, I believe that the

Sponsor mentioned that the study was developed many years ago, and so as time passes, also clinical practice changes. It's very difficult to get patients.

And so those are all the things that as a manufacturer that we have to try to, you know, we try to balance. We want to make sure that we're making the largest population. We want to make sure that we're meeting the intended use, obviously partnering with the FDA to ensure that it's safe and efficacy is met.

But I think the other thing that we want to remember is, is that there's at least 100,000 patients outside of the U.S. that are getting potentially better medical care made available to them than we're affording our patients. So that's it.

DR. MABREY: Thank you. Well, I would like to -- oh, well, I was going to thank the Panel first.

Dr. Hanley, Dr. Horlocker, Dr. Rao, Dr. McCormick, Dr. Evans, Dr. Sang, Dr. Blumenstein, Ms. Whittington, Ms. George, thank you for all the time that you've put in this.

Dr. Jean, thank you for the organization that you've provided for today's Panel.

I would like to thank the FDA for their presentations, and I would like to thank the Sponsor as well for putting this together and educating us on this product and on this study.

Mr. Melkerson, does the FDA wish to say anything or add anything?

MR. MELKERSON: Just echoing the thanks both to the Sponsor and their presentation and their efforts, and as well as the staff, and as well as I would also like to thank the Panel; and just, again, recognizing Ms. Whittington's and Ms. Adam's efforts for the Panel, and we hope to see them in other avenues and venues.

DR. MABREY: Well, then, the July 15, 2008 meeting of the Orthopedic and Rehabilitation Devices Panel is now adjourned.

(Whereupon, at 5:00 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

July 15, 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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