SUMMARY MINUTES

MEETING OF THE ORTHOPAEDIC AND REHABILITATION DEVICES

ADVISORY PANEL

OPEN SESSION

September 19, 2006

Hilton Washington D.C. North
Gaithersburg, Maryland

Orthopaedic and Rehabilitation Devices Advisory Panel Meeting

September 19, 2006

Attendees

Acting Chairperson
Jay D. Mabrey, M.D.
Baylor University Medical Center
Dallas, Texas

Voting Member
Stuart B. Goodman, M.D., Ph.D.
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Stanford, California

Consumer Representative
Connie F. Whittington, M.S.N., R.N., O.N.C.
Piedmont Hospital
Atlanta, Georgia

Industry Representative
Pamela W. Adams, M.S., R.A.C., C.Q.M.
Etex Corporation, Inc.
Cambridge, Massachusetts

Deputized Voting Members
Constantine A. Gatsonis, Ph.D.
Brown University
Providence, Rhode Island

Stephen J. Haines, M.D.
University of Minnesota
Minneapolis, Minnesota

Edward N. Hanley, M.D.
Carolinas Medical Center
Charlotte, North Carolina

John S. Kirkpatrick, M.D.
University of Alabama
Birmingham, Alabama

Sanjiv H. Naidu, M.D., Ph.D.
Pennsylvania State College of Medicine
Hershey, Pennsylvania

Kathleen J. Propert, Sc.D.
University of Pennsylvania
Philadelphia, Pennsylvania

Executive Secretary
Ronald P. Jean, Ph.D.

FDA Participants
Barbara D. Buch, M.D.
Deputy Director, Division of General, Restorative and Neurological Devices

Mark N. Melkerson, M.S.
Director, Division of General, Restorative, and Neurological Devices

CALL TO ORDER

Executive Secretary Ronald P. Jean, Ph.D., called the meeting to order at 8:26 a.m. The panel meetings scheduled for October 13 and December 11 and 12, 2006 had been cancelled because no agenda items are ready for panel review.

DEPUTIZATION OF VOTING MEMBERS

Dr. Jean read a statement appointing the following as temporary voting members of the Orthopaedic and Rehabilitation Devices Panel: Constantine A. Gatsonis, Ph.D.; Stephen J. Haines, M.D.; Edward N. Hanley, M.D.; John S. Kirkpatrick, M.D.; Sanjiv H. Naidu, M.D., Ph.D.; and Kathleen J. Propert, Sc.D. The statement also appointed Jay D. Mabrey, M.D. as Acting Panel Chair for the duration of the meeting.

CONFLICT OF INTEREST STATEMENT

Dr. Jean then read the conflict of interest statement. Waivers have been granted to Stuart B. Goodman, M.D., Ph.D.; Edward N. Hanley, M.D.; John S. Kirkpatrick, M.D.; and Connie F. Whittington, M.S.N., R.N., O.N.C. Dr. Goodman's waiver involves two consulting interests with unaffected units of competing firms as well as unaffected units of competing firms on topics unrelated to the day's agenda. Dr. Hanley's involves stockholdings in the parents of competing firms. Ms. Whittington's waiver involves her employer's interest in the sponsor's study. Serving as the industry representative, Pamela Adams is acting on behalf of all related industry and is employed by Etex Corporation.

PANEL INTRODUCTIONS

Acting Panel Chair Jay D. Mabrey, M.D., said the panel would make a recommendation on the approvability of pre-market approval application P060018 for the Medtronic Sofamor Danek PRESTIGE Cervical Disc System. He asked those seated at

the table to introduce themselves. Dr. Mabrey noted that the panel members present constituted a quorum.

Dr. Mabrey recognized Janet Scudiero, the former panel executive secretary.

Mark N. Melkerson, Director, Division of General, Restorative, and Neurological Devices, said that Ms. Scudiero would continue as executive secretary of the neurological panel. He then read letters of service from Andrew von Eschenbach, Acting Commissioner, for two outgoing voting members, John Kirkpatrick and Sanjiv Naidu

UPDATE SINCE THE JUNE 2, 2006 MEETING

Barbara D. Buch, M.D., Deputy Director, Division of General, Restorative and Neurological Devices, provided a division update. Reclassifications for intervertebral body fusion devices, noninvasive bone growth stimulators, mobile bearing knees, and metal-on-metal hip joint prosthetics are under review. A PMA was approved in June for Zimmer's Trilogy AB acetabular system, and a post-approval study is being conducted to evaluate long-term safety and effectiveness. The PRODISC-L total disc replacement from Synthes Spine was approved August 14, 2006, and a post-approval study is being performed to evaluate long-term safety and effectiveness. Around 150-200 510(k)s have been cleared since the last meeting. Several guidances are under GGP review.

Dr. Buch explained that the e-Copy Initiative provides that one of the paper copy submissions for 510(k)s, PMAs, IDEs, and 513(g)s can be replaced with an electronic pdf file, for which a specific format is required. She also said they would begin in 2007 to provide updates to the panel on the progress of condition of approval studies currently underway.

Regarding additions to division staff, Dr. Buch said that six reviewers had been added as well as Theodore Stevens as Chief of the Orthopaedic Spine Devices Branch and Jonette Foy, Ph.D., as Chief of the Orthopaedic Joint Devices Branch. There are two new deputy directors for the Division of General, Restorative and Neurological Devices, and a new acting branch chief for the Restorative Devices Branch. There have also been some departures from the division.

FIRST OPEN PUBLIC HEARING

Dr. Jean read the open public hearing statement.

Charles Branch, Jr., M.D., Chairman of the American Association of Neurological Surgeons (AANS)/Congress of Neurological Surgeons (CNS) Joint Section on Disorders of the Spine and Peripheral Nerves, said that AANS and CNS support serious and favorable consideration of cervical disc arthroplasty technology, which is a potential advance in care pending further experience and long-term safety and effectiveness data.

For treatment of symptomatic cervical disc degeneration, the technology appears to have value in relief of symptoms as well as added value in prevention of adjacent level degeneration. Reported experience with cervical artificial disc technology has shown it to be safe, durable, and effective with respect to both preservation of motion and relief of radicular symptoms at least comparable to the current standard treatment of anterior cervical discectomy and fusion.

Sally Maher, President, Orthopaedic Surgical Manufacturers Association (OSMA), said that OSMA has worked cooperatively with FDA, the American Academy of Orthopaedic Surgeons (ASCM), and other organizations to ensure orthopedic medical

products are of uniform high quality and supplied in quantities sufficient to meet national needs. OSMA's membership includes over 30 companies which collectively produce over 85 percent of all orthopedic implants intended for U.S. clinical use.

Ms. Maher urged the panel to base its recommendations on the product's safety and effectiveness as demonstrated by the data provided. She said that FDA is responsible not only for protecting the public but also for fostering innovation.

Ms. Maher emphasized two points regarding the law and regulations, reasonable assurance of safety and effectiveness, where reasonable is defined as moderate, fair, and inexpensive, and valid scientific evidence. She asked for the panel's careful consideration and noted that recommendations for further studies may delay introduction of a useful product or result in burdensome and expensive additional data collection.

Stacy Brickson discussed her experience as one of the first PRESTIGE cervical disc patients at the University of Wisconsin-Madison. A mother of two, graduate student, and competitive Ironman triathlete, Ms. Brickson was involved in two car accidents in 2002 that resulted in a large central herniation at C6-C7. A physical therapist and athletic trainer, Ms. Brickson is a strong advocate for conservative care but also a proponent of exploring surgical options when conservative care fails.

Several hours after surgery performed by Dr. Tom Zdeblik in 2003, Ms. Brickson was able to look over her left shoulder for the first time in months, and the following day she was released. She was asked to refrain from impact activities for six to ten weeks, which she did, but she was able to use a Stairmaster and stationary bicycle several days after surgery. This past summer she completed her first Ironman postoperatively.

SPONSOR PRESENTATION

Bailey Lipscomb, Ph.D., Vice President of Clinical Affairs, Medtronic, began by discussing the development of the PRESTIGE cervical disc, the first artificial cervical disc to be reviewed by the panel. It is stainless steel, fits in the disc space in the cervical spine, and is intended to maintain motion at the treated level. The PRESTIGE device evolved from earlier work of Brian Cummins, a neurosurgeon at Frenchay Hospital in Bristol, England who envisioned the device as a way to maintain motion in the treatment of cervical disc disease. Early implants designed by Mr. Cummins were fabricated in his hospital's machine shop and, in spite of various manufacturing issues, worked quite well.

Medtronic became involved through an agreement in the late 1990s with Frenchay Hospital, refined the design and manufacturing conditions, designed instrumentation, and initiated a comprehensive test program. The PRESTIGE device is supported by clinical data from a multi-center prospective randomized study in which 541 patients had IDE surgeries. Patients presented with cervical degenerative disc disease (DDD) requiring surgery at a single level, the desired indication. The control treatment was the standard of care, plated fusion with a structural interbody bone graft, which is regarded as very successful by spine surgeons and their patients.

Carl Stamp, Vice President of Global Operations, Medtronic Spine and Biologics, began by reviewing the design of the device. It is a two-piece articulating metal device inserted into the cervical spine using a standard anterior cervical approach. The two pieces articulate through a ball and trough mechanism. The articulation is based on the normal kinematics of the cervical spine and allows for flexion, extension, left and right lateral bending, axial rotation within the normal limits of the spine, and up to two millimeters of translation in the anterior/posterior direction. Each component is affixed

using two bone screws which are held in place by secondary lock screws.

The device is implanted following standard anterior exposure, discectomy, and thorough decompression of the neural elements, and the disc space is prepared using a standard Smith-Robinson technique. The components are made from stainless steel conforming to ASTM F-138 and are electropolished and passivated to resist corrosion.

Ten sizes are available, but some were requested by surgeons during the clinical trial and thus were not part of the study though they were added to the PMA. A design change in the flexion relief angle was required to ensure mechanical strength of these new sizes, and this reduced the maximum flexion angle by approximately two degrees in the worst case size. Nevertheless flexion remains well above the initial design requirement and beyond the maximum physiologic flexion reported in the literature.

A battery of preclinical tests was performed to simulate in vivo worst case scenarios. The results support device performance under conditions much more severe than would be expected. Even in the extreme scenario of simultaneous failure of all four bone screws the device remains stable.

Subluxation testing was used to determine the force required to jump the ball from the trough at maximum flexion angles in all motion planes, and the force required exceeded the physiological values in all positions, meaning the device would not dislocate without extensive failure of other anatomic structures. Testing was also conducted to determine the force required for the device to subside into the vertebral end plate. The end plate contact area is larger than many commercially available interbody devices, and thus the loads were in excess of those required to subside a widely used interbody device.

Static compression testing established loads for compression fatigue testing. The device withstood fatigue loads far higher than normal physiologic loads in a simulation of worst case bone implant contact at only the screw flange interface. Biomechanical performance was evaluated using cadaveric spines as harvested and with the PRESTIGE device implanted, and motion performance with the implant was comparable to the intact spine.

Wear tests were conducted under conditions agreed upon by Medtronic and FDA during the IDE approval process. The axial rotation and lateral bending test conditions are equivalent to a person looking both ways to cross a street every three and a half minutes for 16 hours every day for 50 years, and the flexion/extension conditions are equivalent to a person tying their shoes every 1 minute and 45 seconds for 16 hours every day for 50 years. Wear test specimens were compared to a well-functioning explant for similarities in wear pattern and total material lost. Wear patterns appear to be very similar, but the wear simulation may be much more severe than in vivo conditions.

Finally, the particulate injection study looked at the effect of injecting particulate representative of debris generated during wear testing into the epidural space of rabbits. In low dose and high dose bolus injection models there was no evidence of neurotoxicity, systemic toxicity, or local effects.

J. Kenneth Burkus, M.D., Columbus, Georgia, presented the results of the clinical trial. He stated that the primary study objective, establishing safety and effectiveness of PRESTIGE in treatment of DDD, was met. Further, the device was found to be statistically superior to the control for the primary outcome variable.

A total of 276 patients received the PRESTIGE disc, and 265 received the fusion control. Thirty-two centers were involved. Patients in both groups shared similar demographics and preoperative medical conditions.

All patients were past their 12-month postoperative period when the study analysis was conducted, but 24-month data was used as primary supporting evidence. The protocol stipulated that an interim analysis could be done on the first 250 patients with primary outcome results at 24 months, and the study conclusions and effectiveness and neurological information being presented are based on the interim analysis.

Consistent with FDA guidance on spinal implant studies, a composite variable of overall success was created as the primary endpoint. Overall success is comprised of an effectiveness parameter of neck disability index (NDI) as well as three safety considerations: neurological success, occurrence of serious adverse events possibly associated with the device, and occurrence of secondary surgical procedures classified as a failure. Overall success was calculated both with and without functional spinal unit (FSU) height success.

Overall success rates for the PRESTIGE group were considerably higher at 12 and 24 months, and the 24 month rate was found to be statistically superior to fusion. Using FSU height success the difference in overall success rates is larger. The primary trial objective was met and surpassed regardless of the overall success definition.

Safety was assessed based on neurological observations and the nature and frequency of adverse events and second surgery procedures. The PRESTIGE group was found to be as safe as the fusion group. Overall neurological success rates at 12 and 24 months were consistently higher for PRESTIGE patients.

All adverse events were reported, including many which were unrelated to the treatment or device. Eighty-two percent of PRESTIGE patients had at least one adverse event, which is not statistically different than the 80 percent rate for control patients. Rates of serious adverse events were similar for both treatments. The rate of adverse events possibly related to the implant was notably higher in the control group and was related to non-unions. Adverse events were categorized based on their nature, and of the 21 categories there were statistical differences in only four.

The rate of spinal events was statistically lower in PRESTIGE patients. The rate of urogenital events was lower in the control group. There were no deaths among PRESTIGE patients and three in the control group. Five cancers were reported in the PRESTIGE group and two in the control group. The occurrence of cancer was not statistically different, and the incidence rates in the study were in general expected ranges.

Another part of the safety assessment was the number and nature of additional surgical procedures performed. Revisions, removals, and supplemental fixations are considered significant procedures at the treated spinal level, and patients having one of these procedures were typically considered treatment failures. The PRESTIGE group had statistically lower rates of revision and supplemental fixation and a lower, though not statistically, rate of implant removals. Removal of the PRESTIGE implants was mainly due to treatment of pain and neurological complaints. Second surgeries classified as reoperations and other procedures were statistically similar, though the number of invasive second procedures involving levels adjacent to the treated levels was lower in the PRESTIGE group.

Turning to effectiveness, PRESTIGE patients experienced exceptional pain relief with maintenance of cervical motion. NDI was used to measure the effect of neck pain on a patient's ability to manage activities of daily life. Mean NDI scores for the PRESTIGE group were consistently lower, indicating less pain and disability, than the control group. NDI success is defined as postoperative improvement of at least 15 points. NDI success for PRESTIGE patients was found to be statistically equivalent to the control at 24 months.

Secondary clinical assessments were also performed. Of note, statistical non-inferiority was not demonstrated for the mental component of the SF-36 questionnaire, but, since the mean improvement scores were not statistically different, it is not felt that this finding is important.

Radiographic analysis was used to assess FSU height. Success was based on no more than a two millimeter decrease from baseline at six weeks post-op. FSU success rates were very high for both groups, and non-inferiority was demonstrated for the PRESTIGE group at 24 months. Based on an assessment of lateral flexion/extension and lateral bending radiographs the device was found to maintain motion. The two treatments had similar adjacent level motion angulation outcomes, but there was only a modest increase in motion.

Medtronic feels the clinical data support approval of the product. At postoperative visits patients were asked questions about their satisfaction, and there were high levels of satisfaction for both groups at 24 months. Patients in the PRESTIGE group generally resumed a more normal lifestyle earlier. Medtronic provided all available data to FDA, and the study conclusions are not changed. Moreover, these additional data

establish non-inferiority for the mental component of the SF-36, which was not demonstrated in the interim analysis.

Vincent C. Traynelis, M.D., Professor of Neurosurgery, University of Iowa, reviewed a number of case studies. He first talked about the early work of Cummins and noted the procedure was found to be safe and well tolerated. One of Cummins's patients was a 60-year-old man suffering from radiculopathy and myelopathy. Five years after surgery he was found to be active without any significant pain and had excellent range of motion of the cervical spine. Another Cummins patient had congenital cervical stenosis and developed myelopathy due to abnormalities at C3-4 and C5-6, which was successfully treated with two-level decompression and arthrodesis. After doing well for some time, she developed recurrent symptoms from compression at the segment just below the C5-6 fusion, and the segment was reconstructed with a Cummins disc. Eleven years later she is doing well.

The PRESTIGE disc, while similar to the Cummins disc, was refined and is available in multiple sizes. The Cummins disc could be viewed as a worst case scenario of PRESTIGE, but over a decade after implantation patients treated with it are doing well. Dr. Traynelis briefly reviewed the surgical procedures which were very similar.

Turning to IDE patients, Dr. Traynelis described a 43-year-old woman he treated. She was in the hospital less than a day, and her NDI score improved rapidly, falling to zero three months after surgery. Her improvement was long-lasting. The patient experienced an adverse event, a sinus infection, which was not felt to be related to surgery or the implant.

Another patient, a 41-year-old man, began to develop back and bilateral arm and shoulder pain around one year after surgery, and the pain increased in severity in spite of conservative management. He underwent a C5-6 discectomy and fusion, but after continuing to have significant symptoms two months later the PRESTIGE disc was removed and the arthrodesis was extended. Two years after the initial surgery he continues to experience significant symptoms and has been referred to a pain management specialist.

Dr. Lipscomb summarized information pertaining to the FDA's questions for the panel. He stated that the valid scientific evidence presented unquestionably provides reasonable assurance that the device is safe and effective.

Referring to the statistical analysis, Dr. Gatsonis asked about the assumption that was made with regard to the relation between data on patients with 24 month assessment and that on patients with only 12 months and whether the two patient populations were similar. She also asked for more explanation of the statement that if there is not a correlation between the outcomes at 12 and 24 months then the model does not use the data. Dr. Gatsonis inquired about the prior probability of the hypothesis of non-inferiority and of the hypothesis of superiority. Finally she asked about the simulation analysis of the frequentist properties of the Bayesian analysis used.

Dr. Goodman asked if there were any control patients in whom only an excision of the disc was done and why the standard of care is decompression and fusion. He then asked for clarification of why movement is an important part of the treatment of myelopathic patients rather than decompression alone or decompression and fusion. Dr. Goodman also asked for assurances about the changes made to the device. He also asked

about the mathematical calculation used for the wear test equivalents. With regard to the animal model, Dr. Goodman asked where the particles were when the rabbits were harvested. Noting that the implants may be used in young to middle-aged patients, he asked for assurance that the device will last for 30 or 40 years or more. Finally, Dr. Goodman asked why the sponsor used stainless steel rather than cobalt chrome as is now used for most total joint replacements with metal-on-metal articulation.

Dr. Kirkpatrick asked about histology from the retrievals.

Dr. Haines asked if the device is really a treatment for DDD or simply a method of replacing the disc that is removed in the process of treating DDD. He also asked if the operation to treat the disease was any different with the device compared to fusion and if the preparation for the disc replacement was any different and about how that might influence the results. Finally Dr. Haines asked if preserving motion is important to achieving the results presented and if any data support that claim.

Dr. Naidu asked whether compressor fatigue testing was done in an animal or cadaver model, and Mr. Stamp said it was not. Noting the aluminum oxide grit blast of the end plates, Dr. Naidu asked about osseointegration. Mr. Stamp said it was not designed for any particular tissue type. Dr. Naidu referenced a statement from the manual about bone on-growth. Mr. Stamp said they were simply looking for mechanical fixation and the specific requirement of bone on-growth was not evaluated. Dr. Naidu asked if there was any tissue in-growth on the surfaces of explanted discs. Dr. Traynelis said those present for the explants had not seen any growth of soft tissues into the implant.

FDA PRESENTATION

Jonathan Peck, M.E., Reviewer, Orthopaedic Spinal Devices Branch, said the device is the first cervical disc replacement and the first metal-on-metal articulation in the spine. The sponsor modified the design to accommodate new device sizes by changing the anterior cut angle from ten to three degrees. This change reinforces the anterior flange but slightly reduces the range of motion.

With regard to wear testing, Mr. Peck noted the difference in wear rates between the coupled motion and the single flexion/extension motion. Three PRESTIGE devices have been explanted and evaluated to date. They were compared to those that underwent wear simulation, and it was concluded that the explants only showed slight wear, indicating that perhaps 0.1 million cycles in simulation represents one year of clinical use.

Ann Costello, Ph.D., D.M.D., reviewed the clinical data provided. PRESTIGE is indicated in skeletally mature individuals with cervical DDD at one level from C3 to C7. Subjects had to have undergone six weeks of unsuccessful conservative therapy or have signs of progression or spinal cord nerve root compression, and a subject's NDI had to be greater than or equal to 30.

The original efficacy endpoint was based on overall success, which included, among other things, maintenance of FSU height. Because of difficulty visualizing the involved segments, particularly at the C6-C7 level, the sponsor proposed revising overall success to not include FSU. However, maintenance of FSU height may be clinically relevant in treating radiculopathy and myelopathy. Radiographic success was evaluated separate from the primary efficacy analysis, and the sponsor evaluated a number of secondary effectiveness endpoints as well.

Except for alcohol use the subjects in the two treatment groups were fairly similar. Around 80 percent of subjects experienced an adverse event, and most of these events occurred perioperatively and resolved over time. The incidence of trauma events was higher in the PRESTIGE group. There were three deaths, all in the control arm and related to cardiac causes.

Five PRESTIGE patients and two in the control group were diagnosed with neoplastic events during the study. Those in the PRESTIGE group are of note based on the impact of metal ion exposure on patients receiving metal-on-metal implants. Preliminary evidence in the literature suggests that different types of metal wear and corrosion particles may elicit different chromosomal aberrations. Metal ion testing was not performed as part of the original IDE protocol, so the sponsor is testing a limited number of patients from the continued access arm.

There were nine device-related adverse events in the PRESTIGE group compared with 26 in the control group, in which there were 16 cases of non-union. There was implant displacement in two PRESTIGE patients, and subsidence occurred in one.

Moving to the interim analysis, the proportion of success on NDI and neurological assessments was similar between the two groups. The overall success criteria with FSU are based on 95 PRESTIGE and 90 control subjects, and 81 percent of PRESTIGE and 64 percent of control subjects were successes. Using the revised endpoint, 80 percent of PRESTIGE and 71 percent of control subjects were successes.

Data on the number of patients presenting with radiculopathy, myelopathy, or a combination was not collected so subgroup analysis was not performed. Moving to pain assessment, eight PRESTIGE and one control subject had greater than three millimeter

deterioration on their arm pain assessment; ten PRESTIGE patients and seven controls had a greater than three millimeter deterioration on their neck pain assessment.

The proportion of success for secondary endpoints was also similar except for the SF-36 mental component, for which 66 percent of PRESTIGE subjects and 73 percent of control subjects were successes. With regard to radiographic success criteria, 73 percent of subjects met the criteria for angular motion. Mean angular motion and mean translational motion, as measured preoperatively, were maintained at 12 and 24 months. Lateral bending was not measured preoperatively. As to adjacent level motion, mean values for the two groups were similar for the level above the treated segment. For the level below, the pre-op mean values were 8.32 for the PRESTIGE group and 7.7 for the control group. At 12 months the PRESTIGE group value was similar to pre-op while the mean for the controls had increased. At 24 months the PRESTIGE mean value had increased from pre-op and 12 month values.

Telba Z. Irony, Ph.D., Chief, General and Surgical Devices Branch, began with an introduction to Bayesian statistics, which uses Bayes Theorem to modify or update probabilities as evidence accrues. Until recent advances in computational technology, it was very difficult to use in the context of clinical trials. FDA issued draft guidance last May on the use of Bayesian statistics in medical device clinical trials.

In using the Bayesian method for a clinical trial, the uncertainty about the treatment effect is described by what is referred to as the prior probability, which is updated using data from the trial to arrive at the posterior probability. As more data is collected the posterior tends to become more precise. Using an example unrelated to the PMA, Dr. Irony explained how an interim analysis is performed.

FDA evaluates Type 1 and 2 errors for such designs. Type I error refers to approving the device when the proportion of adverse events or failures was actually above the level determined, and Type 2 error refers to an unsuccessful trial even though the criteria were met. Dr. Irony said that a study should not be changed from a frequentist to a Bayesian trial or vice versa but should be planned from the beginning.

Xuefeng Li, Ph.D., Center for Devices and Radiological Health, gave an overview of the statistical review of the effectiveness of the device. The sponsor used uniform priors and no historical data. An implied assumption of the Bayesian model is that the 12 month data may provide information about 24 month data.

Three data sets were used to analyze primary outcomes. The primary data set, consisting of all patients who received the devices and completed surgery, was used for the primary analysis, which was actually divided in terms of whether FSU was evaluated. The per-protocol data set is a subgroup of the primary which excludes patients with major protocol deviations. The third data set is called missing equals failure, another subgroup in which all missing responses are assumed to be failures.

For the primary analysis, the posterior probabilities for all endpoints were greater than the pre-specified success criteria of 95 percent. Similar results were obtained using the per-protocol and missing equals failure data sets. Secondary endpoint analyses provide supporting evidence that the device is not inferior to the control.

Moving to statistical limitations of the primary analysis, Dr. Li noted that the sponsor used different denominators of patient populations. Nine of 137 investigational patients and 26 of 148 control patients did not have 24 month overall success outcomes, so the sponsor conducted a sensitivity analysis to evaluate the effect of losing these

patients using conventional frequentist methods. Even in the worst case scenario non-inferiority is maintained. More patients did not have 24 month overall success rate with FSU, but the sponsor did not provide an analysis for this endpoint.

With regard to poolability of the data, the sponsor used a Breslow-Day test to evaluate site effect, and there was no statistically significant heterogeneity across sites regarding overall success with or without FSU. However the test may lack power since many sites had only a small number of patients. At most sites success rates were higher for the PRESTIGE group.

As to the effectiveness analysis, the study met the primary endpoint, and secondary endpoints provided supporting evidence. However, no firm evidence of effectiveness can be drawn with adequate statistical validity. Limitations of the sponsor's analysis include different patient populations used to define success rates, lack of sensitivity analysis for overall success rate with FSU, and that the probability test may lack power.

PANEL DELIBERATIONS

Dr. Kirkpatrick began by discussing general principles for the application of new technology. Does the application confirm the theory the device was developed for; are clinical outcomes equal or better; and are complications and long-term performance the same or better than the standard of care?

There is currently no evidence that motion preservation prevents adjacent segment degeneration, and literature suggests that five or even ten years of follow-up may be needed. Simulation studies show minimal wear and may come close to replicating in vivo conditions. Extended life is anticipated due to the young age of the patients.

Dr. Kirkpatrick next discussed the conceptual basis for disc arthroplasty. Given the success of the current standard of care, many propose disc replacement to preserve near-normal spine mechanics as a way to avoid adjacent segment disease. A retrospective study by Hilibrand found the incidence of adjacent segment disease to be three percent per year and 25 percent at ten years. There is also proposed decreased surgical morbidity compared to allograft.

As to the benefits of motion preservation, Hilibrand's article suggested that we do not know whether the adjacent segment disease is fusion-induced or the result of the natural history of the disease. His study also found that patients with a multi-level arthrodesis were less likely to develop adjacent segment disease.

Dr. Kirkpatrick then raised specific issues with regard to the study. First is that the sponsor's use of "degenerative disc disease" in the package insert is much broader than their indications in the study. He suggested changing the insert to specify that the device is indicated for intractable radiculopathy and/or myelopathy.

Another concern is that 13 patients with intractable symptoms got better and did not have surgery, which suggests that one or more centers may not have strictly adhered to the indications. Also, only ten percent of patients were from minority groups.

Dr. Kirkpatrick posed two questions: were the 13 patients who got better without surgery evenly distributed among the sites, and are the racial demographics consistent with the populations where the centers are located.

With regard to the removed implants, Dr. Kirkpatrick asked about the duration of implantation, the number of explants, and the location of the tissue samples discussed during the histology presentation. As to neurological status he asked if the failures

correlated to the index level and if axial imaging studies were conducted to ensure adequacy of decompression. There can be difficulties using CT or MRI near a stainless steel device, but there are techniques that can be used with CT.

Turning to rationale, Dr. Kirkpatrick noted that the patient brochure attributes to Dr. Hilibrand the statement that clinical evidence suggests that physical stress to vertebrae involved in a fusion may accelerate disc degeneration elsewhere in the neck. However when asked by Dr. Kirkpatrick, Dr. Hilibrand said that was not one of his findings.

Focusing on effectiveness, Dr. Kirkpatrick pointed to the lack of evidence that prevention of adjacent segment degeneration was actually accomplished. Dr. Kirkpatrick's safety concern involved the potential for debris and reaction of the body to the device. All explants studied showed moderate to marked chronic inflammatory response. While this may be typical for metal-on-metal articulation, other such articulations are associated with bone/implant interface with porous coating and in-growth for long-term fixation, and the complications of metallic debris and chronic inflammation associated with non-rigid long-term fixation are unknown.

Dr. Mabrey moved on to the general panel discussion. Dr. Haines strongly supported Dr. Kirkpatrick's concerns about the statement of indication and the rationale of prevention of adjacent segment degeneration. Dr. Naidu reiterated Dr. Kirkpatrick's concerns, particularly with regard to ongoing motion. Dr. Propert echoed the concern about the specialized population and hoped there would be discussion of possible explanations of the data on return-to-work.

Dr. Hanley noted that although the device has been referred to as breakthrough technology, it is a rather primitive artificial disc. He was also concerned that none of the revision surgical procedures were anterior adjacent segment surgery and wondered whether adjacent segments could be effectively fused or implanted with an artificial disc.

Ms. Whittington was concerned that diagnoses be clear and understandable so that patients will have realistic expectations of device longevity. She was also concerned about clarity and reasonable expectations of activities that patients will be able to pursue.

Dr. Mabrey referred to the device being composed of stainless steel rather than cobalt chrome and supported Dr. Hanley's comments about the lack of sophistication of the device. Noting that the original ball and cup design was changed to a ball and trough, Dr. Mabrey hoped the sponsor would address what type of lubrication would be expected for this type of articulation. He also reiterated concerns about long term use.

SPONSOR RESPONSES TO PANEL QUESTIONS

Donald Berry, Ph.D., MD Anderson Cancer Center, addressed statistical questions. P-values suggest that there are not differences between the early and late patients. As to the modeling correlation between 12 and 24 months, he said a mathematical analysis equivalent to imputing was used which recognizes not only the uncertainty in the prediction about 24 month data but also the tendency, based on looking at the 12 month data for those who completed 24 months, of patients who are a success or failure at 12 months to continue to be a success or failure. The raw correlation coefficient is .56 for the control and .50 for the investigational device, and the kappa is .53 versus .61.

There was another question about prior probabilities. The prior probability of non-inferiority was about .59 and of superiority was .5, but it was described as non-informative because the data essentially dominate the eventual conclusion. Another question concerned the relevance of frequentist calculations which were used at the beginning of the trial to ensure it was adequately powered and had an adequate false positive rate, and Dr. Berry said it was a pre-design stage calculation, not something done after the results were in.

Dr. Gatsonis inquired further about the imputation, and Dr. Berry said they did not do imputation but rather a full likelihood model.

Dr. Traynelis addressed Dr. Goodman's questions which overlapped with others. Regarding the standard of care, he said that most patients are treated with anterior cervical decompressions and fusions with very good results. He said other treatment options may be more appropriate for select patients or are particular to individual surgeons.

Regarding motion preservation, Dr. Traynelis said there is some relationship between myelopathy and movement. He noted that the study only examined patients with single level disease, and he contended that motion is good for most patients particularly those who ultimately have fusion at one or more levels.

Mr. Stamp addressed the question about the device design change. He said it had resulted in a two degree change in flexion only and noted the available flexion was still above the initial design requirement and in excess of the maximum possible physiologically. Turning to the question on wear simulation, Mr. Stamp said it was assumed that about 100,000 extreme motion cycles are used per year for an average

individual. Simple math was then used to calculate how many cycles of what duration there would be per day.

Dr. Goodman referred to Dr. Tom Schmalzried's pedometer studies showing extremely wide variation and asked about the patient profile used in the assumptions. Mr. Stamp said that assumption had not been established and the number of cycles per year was based on the explant analysis. He said the patients were active and only well-functioning devices were used in the comparison. Dr. Goodman noted the potential consequences, given the life expectancy of the patients, of these calculations being a bit off. Mr. Stamp agreed but said that not only was 100,000 cycles likely a conservative number but it may be somewhat less than 100,000 per year.

Addressing the number of removals, Dr. Lipscomb said there had been five removals when the PMA data was submitted, but analysis had only been completed on three.

Dr. Kirkpatrick said wear testing in the spine is still in its infancy and noted that the sponsor used a standard under development with multiple inputs from the standards community.

Steve Kurtz, Ph.D., Exponent, and Department of Biomedical Engineering, Drexel University, discussed the results of explant analysis and showed the wear patterns of the explants. Dr. Kirkpatrick asked if one of the devices shown was one of the changed designs, and Dr. Lipscomb said none used in the study had the change. Dr. Kirkpatrick asked Dr. Kurtz to explain the markings on the device in question. Dr. Kurtz said that while they may appear to be impingement marks they are closer to iatrogenic.

Dr. Mabrey asked about markings on the 25.9 month device. Dr. Kurtz said that device had only been retrieved a couple of months prior, and Dr. Mabrey took back the question since it was not part of the data presented. Dr. Kurtz said the device did show anterior impingement but was not revised for that reason.

Dr. Kurtz discussed results from earlier experiences with ball on trough stainless steel articulation in the cervical spine. Looking at electron microscopy he noted that the wear mechanism was essentially microabrasive both in vivo and in the simulator and that the magnitude of abrasive damage was far more severe on the simulator.

Dr. Goodman asked why wear patterns were mediolateral rather than anterior/posterior. Mr. Stamp said it was probably a function of the ball and trough mechanism as opposed to a ball and socket and said with lateral bending and coupled axial rotation the ball slides in a mediolateral orientation. Dr. Mabrey asked for more detail on the mechanism of articulation. Mr. Stamp said limited posterior to anterior sliding may result from the translatory effect of typical cervical spine motion but more than likely that effect would be taken up by the ball sliding through the trough.

Dr. Kirkpatrick asked if they had actually studied that, and Mr. Stamp said they had and referred to a paper by Dennis d'Angelo. Dr. Kirkpatrick asked if they had verified that the ball rolls anterior to posterior in flexion/extension and slides in lateral bending. Mr. Stamp said that it appears to work that way.

Ms. Whittington asked how many years of wear were replicated in the simulator. Mr. Stamp showed the similarity in wear patterns between a 300,000 cycle simulator and a 3.25 year retrieval, which had a much more subtle pattern suggestive of less wear, so the assumption is that 300,000 cycles might roughly represent three years. Given that

assumption, the wear testing indicates the device is sustainable out to 100 years. Ms. Whittington was concerned they are underestimating the number of cycles required since patients typically limit the mobility of their neck. Mr. Stamp said all of the explants were well-functioning but admitted it was hard to quantify patients' level of activity. He noted, however, that for the simulation they essentially doubled the anticipated angular ranges of motion.

Dr. Goodman asked about the use of stainless steel rather than cobalt chrome. Mr. Stamp noted first that the cervical spine bears much less weight during normal motion than a total joint. Also preclinical testing indicated the material was strong enough for the application. Another issue is biocompatibility and the long history of the use of stainless steel in the spine. Further, it was the material available when Cummins began working on the device, and it was an advantage in that Frenchay Hospital already had a lot of information on the device.

Jeffrey Toth, Ph.D., Associate Professor of Orthopaedic Surgery, Medical College of Wisconsin, talked about the histology. Host response and location of debris varied significantly by tissue. There are typically four or five tissue samples. It was unusual to find debris in posterior samples. Most debris was located in the anterior sample, and there was typically a higher concentration on the periphery of the samples. Where metallic debris was found the inflammatory response was rated as marked to moderate based on ASTM F-981. The typical chronic inflammatory response observed was macrophages with occasional foreign body giant cells. Metallic debris was found with no adjacent inflammatory response. Tissue was never seen attached to the retrieved devices, but it is possible that the bond at the interface was separated during explantation.

Dr. Naidu asked what had been done to quantify stresses at the interfaces. Mr. Stamp said appropriate analysis was done on the strength of the screw and anterior flange area, but he said they had not characterized loads for the interface between the roughened surface and the end plate.

Dr. Jeffrey Lowe, Medtronic, discussed the epidural injection study using rabbits and noted that the epidural space is continuous with the cervical spine where the device is intended to be used. He said they looked at a wide variety of tissue samples but were unable to locate the particles.

Dr. Lipscomb addressed questions raised by Dr. Kirkpatrick. Referring to the comment about the definition of DDD, he said they were willing to incorporate the suggested change to the labeling. As to the thirteen patients who dropped out prior to surgery, the five from the PRESTIGE group were spread across four sites, and the eight control subjects were spread across eight sites. Addressing the small number of minority patients, Dr. Lipscomb said there was no statistical difference in 24 month overall success between white and non-white patients. He also said that a brief analysis of outcome based on cervical level treated showed no statistical difference for neurological or overall success outcomes. As to the issue of misquoting Dr. Hilibrand, Dr. Lipscomb said Dr. Kirkpatrick was right and apologized.

FDA QUESTIONS

1. Please discuss the adequacy of the preclinical testing as provided by the sponsor as an assessment of the long-term function and durability of the PRESTIGE device. Are any additional tests recommended?

Panel members generally felt the interface of the device should be studied further and wanted to know what happened to the particles in the animal model.

2. Please discuss the potential impact of the design change on the function of the device in vivo. Also, please comment on the adequacy of the clinical data collected on the original device design in addressing the safety and effectiveness of the newly proposed device design.

Panel members had concerns about the lack of data on the design change and were somewhat concerned about impingement. Some panel members suggested using an in vivo animal model.

3. The sponsor's approved protocol specified a pre-planned interim analysis once the first 250 patients had complete overall success outcome information. The interim analysis was actually performed when 250 patients had all information except at the functional spinal height, and only 185 had complete overall success outcome information with FSU. Please discuss the appropriateness of making this change from planned analysis.

In general the panel felt it was acceptable to exclude FSU data. One panel member thought FSU was relevant and key information. One panel member said the available data showed that FSU is preserved, but another disagreed with the inference that FSU was preserved in the cases in which it was not measured.

4. There were five neoplastic events in the treatment group as opposed to two instances in the control group. Considering the concerns with metal-on-metal devices, for example particulate wear generation and particulate migration, please discuss whether this raises safety concerns with the investigational device. Please also discuss whether additional data are necessary to address this issue.

The panel was not generally concerned about the incidence of cancer. One panel member returned to the concern about particulate debris and what happens to it. Another noted that it was unknown whether there would be long-term neoplastic issues after ten or twenty years but admitted that was well outside the least burdensome approach.

5. Radiographic motion data was presented by the sponsor. Given the implied benefit of a motion-retaining device, please discuss the clinical meaningfulness of the data provided.

Panel members could not say whether preservation of motion is clinically relevant given the data provided and clinical literature. One panel member said it was clinically meaningful since the purpose of the device is to preserve motion.

6. Please discuss whether the clinical data in the PMA provide a reasonable assurance the proposed device is safe for the specified indications in the intended patient population. If not, what additional data or analyses are needed?

The panel generally felt the data was adequate to establish safety in the short term but was concerned about long-term and felt post-approval studies would be necessary. One panel member referred to the moderate inflammatory response at the bone/implant interface, which, based on other areas of orthopedics, may present problems in the five to ten year range. Another panel member noted two-year data had not been presented for all patients. The industry representative said it was the sponsor's obligation to complete the clinical study.

7. Please discuss whether the clinical data in the PMA provide reasonable assurance that the proposed device is effective for the specified indication in intended patient population. If not, what additional data or analyses are needed?

The overall impression of the panel was that the device is effective if judged by non-inferiority rather than superiority. One panel member noted there was not adequate information on effectiveness in preventing adjacent segment disease.

Question eight was not addressed as it was contingent upon a certain decision.

SECOND OPEN PUBLIC HEARING

No members of the public wished to address the panel.

FDA AND SPONSOR SUMMATION

The FDA had no comments.

Dr. Lipscomb said the preclinical and clinical data presented provide strong evidence that the device is safe and effective. He reiterated that the safety data included all 541 patients, not just the first 250. Although not all patients had reached the two year mark, over 420 had. PRESTIGE was shown to be superior to the control with respect to overall success. Other important differences include higher neurological success rates, lower rates of reoperations at adjacent levels, preservation of motion, and earlier return to work.

With regard to questions whether the data support superiority, Dr. Lipscomb said the analyses, variables, and criteria for non-inferiority and superiority were predefined in the protocol, and the criteria for both were met. He noted that the wear testing simulated up to 50-100 years of in vivo use and 15 years using the most conservative assumptions. The prior development history is one of the key foundations of understanding of the device. Direct experience with the Cummins and BRISTOL devices provides further evidence of long-term safety of a stainless steel implant in the cervical spine.

Dr. Lipscomb said that Medtronic is committed to ongoing longer-term study following device approval.

PANEL VOTE

Dr. Jean read the panel recommendation options and the regulatory definitions of safety, effectiveness, and valid scientific data. Dr. Mabrey asked if they were voting on the device as proposed in the PMA and not just the clinically studied device, and Mr. Melkerson said that was correct. Dr. Mabrey then asked if all of the sizes were modified or just the new ones. Mr. Stamp said it had been requested that if additional sizes were added that the change would be made to all sizes. Dr. Kirkpatrick asked if existing data included data that

was not presented but is presumed to exist. Mr. Melkerson said the recommendation should be made on what is contained in the PMA.

Dr. Mabrey called for a motion. Dr. Kirkpatrick moved that device is approvable with conditions. Dr. Hanley seconded the motion.

Dr. Kirkpatrick moved that one condition be that the indication on the package insert be changed to specify intractable radiculopathy and/or myelopathy. Dr. Haines seconded the motion. The panel unanimously supported the first condition.

Dr. Gatsonis moved to limit approval to claims of non-inferiority only. Mr. Melkerson said that would be part of the limitations of the study data in the package insert. Dr. Propert seconded the motion. Ms. Adams suggested that instead the sponsor and FDA could revisit the superiority claim to ensure there is a valid basis. The panel voted unanimously in favor of the second condition.

Dr. Goodman moved that further animal data should be obtained on the issues discussed, including interface and particle debris. Mr. Melkerson asked if he was proposing that it be collected before or after approval, and Dr. Goodman said he thought it should be done before. Dr. Naidu seconded the motion. Mr. Melkerson noted that requiring data prior to approval necessitates a recommendation of not approvable.

Dr. Hanley said it was an onerous recommendation and suggested that FDA and the sponsor work on getting more information. Dr. Goodman said that was acceptable, and Dr. Kirkpatrick clarified that the motion is now for a post-approval study to be negotiated by the sponsor and FDA to look at the particulates and the interface. Dr. Goodman agreed, and Dr. Kirkpatrick seconded the modified motion.

Dr. Lipscomb clarified that the motion was for an animal study, and Mr. Stamp said they would work with FDA to define the model and determine if it is appropriate. Mr. Melkerson thought FDA could address the panel's comments. The panel voted unanimously in favor of condition three.

Dr. Gatsonis moved to approve only the device as studied clinically. Dr. Hanley said the condition was not compatible with the recommendation to approve the PMA. The motion was not seconded.

Dr. Haines moved for a post-approval study of long-term safety and efficacy. Dr. Kirkpatrick seconded the motion. Dr. Lipscomb reviewed the sponsor's proposed post-approval activity as submitted to FDA. The sponsor proposes to continue to follow the patients in the IDE study as well as those in the continued access arm and collect the same clinical data at five and seven years. He noted this would be longer than what was proposed for the lumbar artificial disc or for other spinal implants.

Dr. Kirkpatrick asked if the minimum of 200 patients was realistic, and Dr. Lipscomb said they certainly hope so.

Judith U. Cope, M.D., M.P.H., Epidemiology Branch, Office of Surveillance and Biometrics, gave a presentation on the principles of and need for post-approval studies and focused on the important post-approval issues. FDA has five main concerns it would like to see addressed: a desire for longer-term safety and effectiveness data; better understanding of real world performance; effectiveness of the training program; subgroup performance; and specific outcomes of concern including metal debris, adjacent segment degeneration, and infrequent adverse events such as heterotopic ossification.

Dr. Cope highlighted key features of the sponsor's proposed plan. Of note, the sponsor does not plan to look at FSU height success.

Returning to FDA's concerns, assuming an annual lost to follow-up rate of 15 percent, 226 patients from each arm would need to agree to continue to participate in order to have 100 in each arm five years later for long-term follow-up. With regard to real world performance, will a subset of current subjects be adequate to assure safety and effectiveness for the broader population, and will the surgeons be representative?

With regard to the training program, Dr. Cope noted there were seven patients who had interoperative vascular complications and said there needs to be an evaluation of the training, learning curve, and surgical volume. As to subgroup performance, she noted that no subgroup analysis of the study population could be very heterogeneous.

Moving to the outcomes of concern, Dr. Cope questioned whether the numbers of subjects and length of follow-up would be adequate to evaluate metal debris and adjacent segmental degeneration. Heterotopic ossification may not be expected with artificial cervical discs, but a study in *Neurosurgery* followed up patients who received a different type of cervical disc and found that 17.8 percent had evidence of heterotopic ossification and associated significant loss of motion after one year.

Dr. Cope asked the panel whether the pre-market cohort would provide sufficient assurance of long-term safety and effectiveness and also to discuss concerns about metal debris, adjacent segment degeneration, and potential infrequent outcomes. Mr. Melkerson also asked if the panel wanted to consider issues related to the design modification.

Ms. Adams felt it was entirely inappropriate for FDA to raise new issues and questions at this point in the procedure when the sponsor has no opportunity to respond.

Based on the data presented on heterotopic ossification and the fact that it had not been seen in any of the patients, Dr. Kirkpatrick was not concerned about it. He agreed with concerns about long-term safety and effectiveness but did not think real world performance should be part of the evaluation. He said it would not be reasonable to require a new study with newly trained surgeons. Dr. Kirkpatrick was also concerned about subgroups but thought the solution would have been to start off with a well-defined population in the clinical trial. He thought five years would be a reasonable balance for evaluating metal debris and adjacent segment degeneration. He asked for better radiographs and a more specific description of what will be studied on the x-rays.

Dr. Haines said it was not inappropriate or unprecedented to monitor real world use for some time. He also suggested another arm of new patients who receive the modified design. Dr. Kirkpatrick suggested that cadaveric studies of motion could answer questions about the modified design. Dr. Haines said they really needed to look at application of the device outside of the investigator pool. Dr. Hanley suggested that was the ongoing function of FDA, and Dr. Haines said it would be wise to give FDA some specific advice and recommendations in that regard.

Dr. Gatsonis said it was a concern that the panel needs to respond to. He also said that evaluation of real world performance could be focused on the device by providing training to surgeons. Ms. Whittington said that while the practice of physicians can't be regulated, specific training can be required.

Mr. Melkerson said FDA was following procedures in having the post-approval study presentation after a vote and recommendation and that the sponsor could address the issues that were raised.

Dr. Lipscomb appreciated the comments about additional patients but noted they had spent three years enrolling 500 patients and following them. He also pointed out that it was really ions and not metal debris that they were looking for. He said they planned to administer a training program that includes both didactic and hands-on portions. He also took issue with comments on the surgical procedure, which he said is very similar to what spine surgeons have been doing for years.

Dr. Mabrey agreed that the procedure used was merely an enhancement of an existing surgical procedure. He attempted to summarize the condition as incorporating the sponsor's plan and asking for better radiographs, post-mortem retrieval of devices, and a training program. He said that the sponsor and FDA would work out all the details. The panel voted unanimously in favor of the condition.

Dr. Kirkpatrick moved that the materials not say that "Clinical evidence suggests that a physical stress to the vertebrae involved in a fusion may accelerate disc degeneration elsewhere in your neck," until it is solidly proven. The motion was seconded.

Dr. Haines was also uncomfortable with discussions of motion preservation in the materials. Ms. Whittington agreed that the patient brochure gives unrealistic expectations. Dr. Kirkpatrick said his motion was to eliminate wording about adjacent segment as a benefit of preserving motion and thought these issues would be covered by it.

Dr. Kirkpatrick clarified his motion to be that no educational material will suggest that preserving motion at one segment preserves the adjacent segment from having disease until that is proven in the literature. Dr. Naidu seconded the clarified motion. The panel voted unanimously in favor of the condition.

There being no other motions for conditions of approval, Dr. Mabrey called for a vote on approving Medtronic Sofamor Danek's PMA P060018 with the conditions voted upon. The panel unanimously voted in favor of the motion.

Dr. Hanley was convinced the device has results at least as good as the control and was not overly concerned about the other issues.

Dr. Propert said the conditions would address the questions remaining.

Dr. Naidu agreed with the previous comments.

Dr. Haines applauded the investigators for carefully and scientifically evaluating the device and hoped similar efforts would be made with regard to continuing follow-up.

Dr. Kirkpatrick said safety and effectiveness had been adequately demonstrated within the time periods and constraints and that long-term concerns would be addressed by FDA's follow-up.

Dr. Goodman agreed the device is safe and effective in the short term and looked forward to seeing further human and animal data.

Ms. Adams appreciated everyone's feedback and particularly Dr. Kirkpatrick's review. She said it was a very balanced group. She also acknowledged the work of the sponsor.

Dr. Gatsonis said the data presented supported the conclusions and looked forward to the post-approval studies.

Ms. Whittington appreciated the depth and breadth of the data presented. She said FDA's presentations were exceptional and noted the significant collaboration between industry and FDA.

Dr. Mabrey appreciated the participation and efforts of the panel members. He thanked the sponsor for an excellent, well-prepared presentation. He also thanked FDA staff for bringing the process to this point.

Mr. Melkerson also thanked the panel members for their time and efforts. He also thanked the FDA review staff and noted this was the first PMA Jonathan Peck has presented.

Dr. Mabrey asked if there was an eighth question that had not been addressed. Mr. Melkerson said it was regarding labeling and that the comments had covered it.

ADJOURNMENT

Dr. Mabrey adjourned the meeting at 4:02 p.m.

I certify that I attended this meeting of the Orthopaedic and Rehabilitation Devices Advisory Panel Meeting on September 19, 2006, and that these minutes accurately reflect what transpired.

Ronald P. Jean, Ph.D.
Executive Secretary

I approve the minutes of the September 19, 2006, meeting as recorded in this summary.

Jay D. Mabrey, M.D.
Acting Chairperson

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