SUMMARY MINUTES

MEDICAL DEVICES ADVISORY COMMITTEE

ORTHOPAEDIC AND REHABILITATION DEVICES PANEL

July 17, 2007

Hilton Washington DC North
Gaithersburg, MD

ORTHOPAEDIC AND REHABILITATION DEVICES PANEL MEETING
July 17, 2007
Attendees:

Chairman:
Jay D. Mabrey, M.D.
Baylor University Medical Center

Industry Representative:
Melissa Walker, M.S., RAC
Stereotaxis, Inc.

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

Voting Members:
Stuart B. Goodman, M.D., Ph.D.
Stanford University

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

Paul C. McCormick, M.D., M.P.H.
Columbia University

Deputized Voting Members:
Stephen J. Haines, M.D.
University of Minnesota

Edward N. Hanley, M.D.
Carolinas Medical Center

John Kirkpatrick, M.D.
University of Florida College of Medicine

Sanjiv H. Naidu, M.D., Ph.D.
Penn State Fredericksen Outpatient Center

Christopher H. Schmidt, Ph.D.
Tufts-New England Medical Center

Executive Secretary:
Ronald P. Jean, Ph.D.

FDA Representative:
Mark N. Melkerson, M.S.

CALL TO ORDER

Chairman Mabrey called the Panel to order at 8:11 a.m. The purpose of the meeting was to make a recommendation to the FDA on Premarket Approval Application (PMA) P060023, for the Medtronic Sofamor Danek Bryan Cervical Disc Prosthesis, which was indicated for skeletally mature patients with cervical degenerative disc disease (DDD) at one level from C3-C7. He noted the presence of a quorum and that the members had received training in FDA device law and regulations.

Dr. Jean read the appointment of temporary voting members and conflict of interest statements into the record. Drs. Hanley, Kirkpatrick, Naidu, and Schmidt were appointed as temporary voting members. All members were in compliance with conflict of interest laws. Waivers had been issued to Drs. Goodman, Hanley, and Kirkpatrick.

FDA UPDATE

Theodore Stevens gave the update. Panel meetings are tentatively scheduled for September 18-19 and November 13-14. There are not yet any specific matters scheduled for the dates. Since the last meeting, three PMAs have been approved. P050004, the EMS Swiss Dolorclast, an extracorporeal shock wave therapy device for the treatment of chronic plantar fasciitis was approved without going to Panel. P050016, the Corin Medical Cormet 2000 Hip Resurfacing from the February 22 Panel meeting was approved on July 3. On July 5, 2007, the Exactech NOVATION Ceramic Articulation Hip System, P050039, was approved without going to Panel. Medtronic's Prestige Disc was approved the day before the meeting.

Two reclassifications went to Panel on June 2, 2006. Of those, the intervertebral body fusion device, 888.3080 was reclassified to Class 2, effective July 12. The reclassification petition for non-invasive bone growth stimulator, docket number 2005-0121, was withdrawn by the petitioner on April 2, 2007.

A guidance document has been published to go with the reclassification of spinal fusion cages. A draft guidance for preparation of investigational studies for cartilage therapy and replacement is out for public comment through October 9. Both are available on the FDA website. Guidance documents on artificial discs, femoral stem testing, and hip stems are in the final stages of approval.

Staff additions include an engineer detailed from the Office of Compliance, a permanent secretary, and a summer intern. Four engineers have left the branch. The CDRH e-Copy initiative is ongoing. Another initiative is that, in the future, the Panel will be presented updates on the status of Post Approval Studies (PAS).

OPEN PUBLIC HEARING

Dr. Mabrey opened the floor for the public hearing. Dr. Jean read the public hearing statement, encouraging disclosure of financial interests related to the PMA.

Dr. Susan Krasny of the Orthopedic Surgical Manufacturers Association (OSMA), a trade association of over 30 member companies. OSMA did not endorse the device but expressed its interest in the ongoing availability of safe and effective medical devices.

She reminded the panel of the FDA's dual role: to protect the public from unsafe or ineffective products and to foster innovation. She emphasized two points: reasonable assurance of safety and effectiveness as the standard to be met and the meaning of valid scientific evidence.

Michael Rudicule, a study patient, spoke on his experience with the device. The sponsor paid for his travel. Mr. Rudicule had a waterskiing accident as an adolescent. The injury resurfaced when he was 30. For 12 years, he experienced recurrent, severe neck pain, which was treated with steroids, muscle relaxants, pain medication, and physical therapy. In 2002, his body stopped responding to physical therapy and he lost sensation in his left hand. He had avoided vertebral fusion due to concerns about loss of mobility, arthritis, and impact on adjacent discs. After surgery with the investigational device, the pain was gone and feeling returned to his left hand. He checked out of the hospital the day after the surgery. After two weeks, he could run and lift weights. After six weeks, he was playing golf. He said the device has changed his life by eliminating his back problem and urged the panel to make the device available to others.

SPONSOR PRESENTATION

Kathryn H. Simpson, PhD, Manager of Clinical Regulatory Affairs, introduced the presentation. The Bryan Cervical Disc consists of two titanium alloy shells, which sandwich a polyurethane nucleus. The nucleus is in a polyurethane sheath attached by titanium retaining wires. Vincent Bryan, MD, began designing the device in 1992 and began marketing the device in Europe in 2002. Worldwide, 15,000 devices have been implanted. Medtronic purchased Spinal Dynamics in 2002 and assumed management of the study.

Stephen White, Vice President of Research and Development, addressed design and preclinical testing. The device is a multi-piece articulating metal and polyurethane device that is inserted into the cervical disc space, using the standard anterior cervical approach. The titanium shells have a porous titanium coating, which obtains bony fixation between the vertebral body and the device. The inner surfaces of the shells are polished and articulate with the polyurethane nucleus. The device allows for 2 mm of physiologic anterior/posterior translation and behaves similar to a normal disc. The polyurethane sheath facilitates one-piece insertion, retains the saline lubricant, and prevents acute soft tissue ingrowth into the articulation area. The device allows for internal and external rotation, 11 degrees of flexion/extension motion, and 11 degrees of left/right lateral bending.

The metallic shell components use titanium and titanium alloys compliant to ASTM standards. The metal has a long history of orthopedic use and proven biocompatibility. Additionally, it distorts imaging less than other materials. The nucleus is molded from silicone-modified end group polycarbonate polyurethane, a material chosen for its resistance to wear and its lubricious and compliant properties. The material is in use in cardiovascular, neurological, and spinal products.

The mechanical testing simulated worst case in vivo scenarios. The shell was tested for fatigue, coating shear, coating abrasion, and coating friction torque. The

nucleus was tested for static compression, compression fatigue, creep, and durability. The sheath was tested for tensile strength. The implant's stability was tested for antepulsion and retropulsion, cadaver shear, and with an RSA analysis. The device was extensively tested in wear durability machines. It withstood a 10 million fatigue cycle load of 1,000 N. The normal load is 130 N. It withstood 10 million cycles of a 300 N shear force, 2.5 times the normal shear load. The shell coating exceeded all relevant mechanical criteria. In testing the nucleus for compression, the device was subjected to 10,756 N. For creep, it was cyclically loaded for 10 million cycles at 285 N. Stability tests showed it took 270 N to cause antepulsion, 429 to cause retropulsion. All acceptance criteria were met.

Eight adult chimpanzees implanted with the device showed normal behavior and range of motion and no neurological or physical changes. There was no subluxation, migration or loosening, and all components were in good condition when removed. The animals were followed for 3, 4, 6, and 6.5 months. Average bone ingrowth was 30 percent.

A study was also done in goats, out to 12 months. Goats commonly butt heads, and particles were found at 6 months in local and spinal tissues. Particles from the nucleus and sheath were injected into rabbits, which were examined for reactions to the particles. There was no evidence of neurotoxicity, systemic toxicity, or local effects. A review of two explanted devices showed limited wear, good adherence of tissue to the surface, glossy finish, and evidence of biomechanical stability.

Rick C. Sasso, MD, a clinical investigator, presented the results of the clinical trial, a prospective, randomized, multi-center, controlled trial with the standard of care, anterior cervical disc fusion (ACDF) with parallel end plates, an allograft in the interspace, and an ATLANTIS plate and screws as the control. The primary objective was to demonstrate overall non-inferiority in overall success. The secondary objective was to show superiority in overall success. Patients admitted to the study had single-level, systematic cervical DDD, noted by disc herniation with radiculopathy, spondylitic radiculopathy, disc herniation with myelopathy, or spondylitic myelopathy. The diseased segment had to be mobile, free of significant osteophytes and facet arthrosis on CT scans. Additional inclusion and exclusion criteria included age, mental competency, medical history, and existing medical conditions. Patients were evaluated preoperatively, at surgery, and postoperatively at 6 weeks and 3, 6, 12, and 24 months.

A total of 242 patients received the device, 221 the control. Patient follow-up compliance exceeded 85 percent at all of the centers. After study completion, FDA approved continued access to the investigators, and there were 29 continued access patients at the time of the PMA submission, none of whom had reached 24 months. Patients in the investigational and control arms had similar demographic characteristics and preoperative conditions. The mean operative time was 48 minutes longer for the device than the control, possibly due to end plate preparation and the newness of the procedure. Blood loss was low, but higher than in the ACDF cases, possibly due to operating time. The mean hospital stays were nearly identical, about one day.

Safety was assessed as a function of neurological observations, the nature and frequency of adverse events, and the occurrence of second surgery procedures. In these, the device was shown to be non-inferior to the control. Neurological status was assessed

by measuring motor function, sensory function, and reflexes. Success was based on the postoperative condition being no worse than the preoperative condition in all three parameters. At 12 and 24 months, the results of the device and control were nearly identical. Reported adverse events were assessed by nature and severity by World Health Organization (WHO) criteria. Investigators reported all adverse events, device-related or not. The number of overall events was not statistically different, 83.5 percent for the device arm, 78.7 percent for the control. WHO grade 3 and 4 events, considered serious, were also similar, 26.4 percent for the device, 24.9 percent for control. Only 2.9 percent of device patients had implant or procedure-related adverse events, compared to 5.4 percent in the control arm. Comparing adverse events in the two arms of the study, statistical differences were only found in two areas; the device showed fewer non-unions and pending non-unions. There was no category of adverse events in which the device group was statistically higher than control. The frequency of adverse events was typical for a patient population undergoing an anterior cervical inter-body procedure. Secondary surgeries were low and similar between the treatment groups, 6 in the device arm, 8 in the control arm. Resurguries were due to residual pain, trauma, and failed fusions. Due to similar neurological success rates, adverse event rates, and secondary intervention rates to the standard of care, the sponsor deemed the device safe for its intended use.

The success criterion was a composite variable, "overall success," which consisted of an improvement of 15 points or more on the Neck Disability Index (NDI) and three safety considerations: neurological maintenance or improvement, no serious implant or procedure-related adverse events, and no need for a second surgery. A second surgery indicated failure. The overall success rate for the device group was significantly higher at 12 and 24 months after surgery than control.

NDI scores were consistently lower in the device arm, lower being better. Bryan findings showed an improvement of over 65 percent from baseline. At 24 months, the device's superiority over control in the rate of patients with an improvement of 15 points or more is statistically significant. Secondary effectiveness endpoints included neck pain, arm pain, global perceived effect, and SF-36. For neck and arm pain, Bryan patients had better results than control patients. At both 12 and 24 months, more Bryan patients said they were either completely recovered or much improved; at 24 months, this was about 92 percent of device patients compared to 86 percent of control. The SF-36 questionnaire indicated general health status. The results were similar for both groups. Radiographs by two independent reviewers showed that functional spine height success rates exceeded 90 percent in both groups, and non-inferiority was demonstrated. Radiographs also demonstrated a sustained lateral bending ability of an average of 7.7 degrees out to 24 months in the device group. No device patients had bridging bone, and only six had osteophytes. The advantage of the device over the control was demonstrated: maintained level of motion. In the ACDF patients, motion is not desired. Patients showed a higher level of satisfaction with the device than control, and they returned to work a median of 13 days sooner. The device's overall success rate was non-inferior, actually superior to the control's, with the benefits of pain and neurological symptom relief with the maintenance of motion.

Stephen Papadopoulos, MD, a clinical investigator with a financial interest in both the investigational device and the control device, presented on clinical cases. For both the

Bryan Disc and the control, a standard anterior cervical approach is performed, followed by a discectomy and neural decompression at the index level. Patients randomized for the control were given ACDF. For Bryan patients, the end plates were milled to match the device face. The device is installed with a simple press fit technique, and the device's design provides confidence in the technique. Friction on the bone/implant interface eliminates forces directed toward migration.

He reviewed three typical patient cases. The first one, a 45 year old female with severe arm pain and weakness due to a herniated disc and osteophyte formation at the C6-7 level, was treated with the device. The surgery was uneventful, and she was discharged the next day. Two years postoperative, her lateral flexion/extension and lateral bending x-rays showed maintenance of normal motion and good positioning of the device. Her NDI and arm pain improved quickly after surgery and continued to improve out to two years. SF-36 and MCS scores showed sustained quality of life improvements. An x-ray taken at 4 years showed the Bryan Disc maintaining alignment and motion.

Three patients in the IDE study underwent Bryan Disc removal. One was a 40-year old female who presented with radiographic evidence of degenerative changes at multiple levels. C5-6 was thought to be most significant and was the only symptomatic level, and it had extensive osteophyte formation. She did well initially, but she developed recurrent neck and bilateral arm and shoulder pain. An MRI showed significant disc bulge at C6-7 with neurologic compression and foraminal encroachment. The C5-6 level, where the Bryan Disc was installed, appeared to be decompressed. Examination could not fully rule out the possibility of recurrent compression at the implant level, so the surgeon removed the Bryan disc and applied ACDF. The removal and revision was without complication. The explanted device was in good condition.

In a 41 year old female treated with the device at C5-6 for severe arm pain and weakness due to a herniated disc, lateral flexion-extension films showed segmental motion well-preserved at 6 years.

Hallett Matthews, MD, Vice President of Medical Affairs, presented the sponsor's proposed PAS. The sponsor felt that the purpose of the post-approval study would be to gather longer-term data. Currently-enrolled IDE and continued access patients would be followed and evaluated at 4, 5, and 7 years post-operative to collect the same safety and effectiveness data collected in the IDE study, all primary and secondary data. The post-approval study population would include at least 200 patients, half from each arm of the study. The final statistical analysis would be similar to that performed for the PMA. Success would be based on showing non-inferiority of the Bryan Disc group to the control group at 7 years. Study reports would be submitted to the agency at six month intervals for the first two years, then annually out to completion and the final report.

He then addressed the FDA's question to the Panel on the PAS. FDA's concerns about motion measurements at treated and adjacent levels as well as adjacent level disease would be addressed by the continued collection of all measurements from the IDE study. FDA asked whether measures of heterotopic ossification (HO) and kyphosis should be added to the post-approval study. The sponsor said these were short-term events that would be observed in the early postoperative period, so long-term data would not be meaningful. Finally, FDA asked whether new patients should be enrolled. The sponsor believed the existing number of patients to be sufficient.

Dr. Simpson returned to present concluding remarks. She said the data submitted demonstrated reasonable assurance of safety and effectiveness. She addressed some of the questions FDA would present to the Panel. On the adequacy of the pre-clinical testing, she said Medtronic had performed numerous preclinical and animal studies to show the design's strength, wear properties, function, and the effect of wear particles. The results showed the device was strong and stable, and the IDE results supported this finding. To the FDA's question about motion measurements, she said the device demonstrated motion at the treatment level throughout the postoperative course. Adjacent level motion was the same in both arms of the study. To FDA's question on the adequacy of the labeling, she responded by referring to the submitted draft labeling, which summarizes the study and necessary cautions. The operative time is included with the other surgical data. FDA also asked about the inclusion of C3-4 level in the indication, since there were few such patients in the study. She said there are no safety issues associated with upper cervical levels and some surgical advantages to the level. The number of implantations at that level was consistent with the low frequency of occurrence. She said safety and effectiveness were demonstrated and the device showed superiority to ACDF in overall success at 12 and 24 months. The device failure rate was 33 percent lower than the fusion failure rate.

Chairman Mabrey opened the floor to questions from the Panel. Dr. Naidu asked about the 510(k)-cleared spinal devices made of polyurethane. Dr. White said the two devices were for posterior stabilization and fusion, Medtronic's Agile device and a device made by a competitor. Dr. Naidu asked why the polyurethane disc in the explanted device was yellow. Dr. Papadopoulos said the disc was stored in formalin post-retrieval. Dr. Naidu noted that, in the six-year follow-up film, it appeared that the polyurethane had shrunken.

Dr. Kirkpatrick asked about device removal in the animal studies. Dr. Jeff Rouleau, Medtronic's Senior Manager of Research, said, due to changes in the porous coating, only 2 chimpanzees had the final version of the device. Those animals showed 10 to 50 percent bone in-growth on histologic sections. The devices were removed with standard osteotomes, and the revision was uneventful. Dr. John Heller, a consultant, said that the device cracks free of the bone, pulling off only bone that shears at the interface. The revision is not technically challenging, and there is no need to remove or destroy more bone. Members presented other questions to be addressed later in the day.

FDA PRESENTATION

Ann Ferriter, a reviewer in the Orthopedics Spinal Devices Branch, presented the preclinical and clinical issues. FDA brought this device before the panel because it was the first polyurethane on titanium articulation in a disc prosthesis and included a novel method of bone fixation. Additionally, the shell and nucleus constraint was unique, as was the sheath encapsulation design. She pointed out that the nucleus is made of bionate polyurethane and the sheath is made of biospan polyether polyurethane. Two features of interest on the shell are the porous coating and the perpendicular wing.

The pre-clinical issues were device wear, response to generated particulates, device migration or expulsion, device reliability, and joint encapsulation. The wear tests

showed no nucleus cracking or generation of large particles. In the clinical trial, the explanted devices showed minimal wear, and in radiographs, wear was insufficient to show decreased height. The goat study showed nucleus wear and titanium particles.

The sponsor evaluated the response to the generated particles. Most particles were less than one micron in diameter. Particles from the nucleus and shell were injected into rabbits. The materials were found to be non-irritant and non-toxic. In the explants, evaluations were performed on the perioperative tissues. Polymer particles were observed and metal particles in one patient, but there was no observed adverse reaction. The sponsor concluded that the results were typical of a polymer on metal implant.

Device expulsion or migration was a concern due to the novel device fixation mechanism. The sponsor provided a series of tests and demonstrated that the horizontal pull force required to dislodge the device was above 100 N of horizontal force. No radiographic evidence was found of expulsion or any migration greater than 3.5 mm. There were no clinical study failures or reoperations due to migration or expulsion.

Device reliability was the fourth issue. The device showed no radiographic failures or observations of failure in explanted devices, and the device met test acceptance criteria. The final preclinical issue was joint encapsulation. The device met acceptance criteria in the bench tests. In both the animal and clinical studies, particles were found in the device and the perioperative tissue.

In the clinical trial, Bryan patient follow-up compliance was consistently higher. Patient demographics were similar between the device and control arms, as were baseline assessments. One concern of the FDA was that only 3 Bryan patients and no control patients were treated at C3-C4, leading the FDA to wonder if effectiveness at that level was demonstrated.

In the clinical trial, 12 patients randomized for the device got the control, 5 due to disc space smaller than 14 mm; 4 due to poor intraoperative visualization at C6-7; and one each due to a prominent clavicle preventing device placement, retraction of the airway at C4-5, and inadequate fit at C6-7. Operative time and blood loss were greater in the device arm. Overall success for the first 300 subjects at 24 months was 80.6 percent for Bryan, 70.7 percent for control. The device and control had similar adverse event rates. The device preserved motion at the treatment level and ACDF did not. Motion at adjacent levels was similar for the two groups at preoperative, 12 months, and 24 months.

In the literature, there are reports of HO in up to 18 percent of patients treated with the Bryan disc in Europe. Though it was not a study endpoint, the sponsor reviewed the clinical data and found a lower rate in US Bryan patients; 6 device patients showed osteophytes in their radiographs.

Jason Schroeder, PhD, presented a statistical review. The Bayesian interim analysis was scheduled for when 300 patients had 24 month data. Patients were randomized 1:1. Randomization was stratified by center with a fixed block size of 4. Of the 463 patients to receive treatment, 12 were randomized to the device but received the control; 1 patient randomized for control received Bryan instead, and 117 patients were randomized but never treated (37 Bryan, 80 control). Of the 80 potential control patients, 32 dropped out due to dissatisfaction with the randomization. None of the potential Bryan patients dropped out for this reason. No clinically relevant demographic or baseline differences were seen between the 463 study and 117 non-study patients.

The primary endpoint was overall success at 24 months. The non-inferiority hypothesis, with a non-inferiority delta of 10 percent, was that the overall success rate for Bryan was not lower than control by more than 10 percent. The device was non-inferior to control if the posterior probability of non-inferiority was at least 95 percent. If non-inferiority was met, the superiority hypothesis followed. Bryan would be considered superior to control if the posterior probability of superiority was at least 95 percent.

The PMA was based on the results of a Bayesian interim analysis. At the time of the interim analysis, 333 patients, 168 Bryan and 165 control, had reached 24 months. Of these, 300 patients had observed overall success outcomes, 160 in the Bryan group, 140 in the control. Patients who had 12 month data at the time of the analysis were included. Patients with neither 12 month nor 24 month data (2.1 percent for the device, 7.7 percent for control) and patients with major protocol violations (11.2 percent in the device group, 21.7 percent in the control) were excluded. This left 210 device and 160 control patients in the analysis. In both the primary analysis dataset and the per-protocol dataset, the posterior probability of non-inferiority was 99.9 percent. Sensitivity analyses using conventional frequencies assessed the impact of the missing data. Even if every missing Bryan outcome were counted as a failure and all missing control data counted as success, Bryan would still be non-inferior. The sponsor then tested the superiority hypothesis. The posterior probability of superiority was 96.9 percent for the primary analysis dataset, 94.4 percent in the per protocol dataset. Dr. Schroeder concluded that the data supported the claim of non-inferiority, with respect to overall success at 24 months. However, the results were inconclusive on the claim of superiority.

Dr. Cunlin Wang, MD, PhD, summarized and discussed the sponsor's proposed PAS. He reminded the members that the discussion was not a recommendation of approvability by the FDA and that a PAS cannot lower the threshold for PMA approval. Based on the PMA study, there were issues that were important to assessing the long-term safety and effectiveness of the device: survival of the implant, overall success of the device compared to arthrodesis, effect on adjacent levels, new complications from particles and wear debris, and reported complications that may affect the long-term use of the device, such as anterior/posterior disc migration, HO, and kyphosis of the functional spinal unit.

FDA has a few issues to discuss with the sponsor on its PAS. The study must be device-driven with a non-inferiority design. FDA will work with the sponsor to define the appropriate delta level. Although the primary outcome is the same composite endpoint, the criteria for NDI improvement has not yet been defined. FDA would like to see radiographic measurements as part of success. Additionally, the PAS only follows patients from the IDE and continued access studies. If no new patients or physicians are recruited, FDA cannot assess the representativeness of the PMA patients and physicians. Inclusion of new patients and surgeons would increase the generalizability of the results. The sponsor stated a minimum of 200 patients to be recruited from the PMA cohort. FDA and the sponsor will discuss how those patients will be selected, whether this is a sufficient size, how to avoid losing patients to follow-up, and what is to be done if the number falls below 200 during follow-up. If the Panel did recommend a PAS, FDA would like the Panel to discuss the issues listed in question 7.

Chairman Mabrey opened the floor to questions from the Panel. Dr. Haines asked if an intent to treat analysis was done. Dr. Schroeder said the patients were analyzed as they were randomized. The 117 patients not treated were not analyzed. Dr. McCormick asked if any allowances were made for the numerous tests of significance. Dr. Schroeder said there was no multiplicity adjustment. Dr. Naidu asked if the 510(k)-approved polyurethane devices were load-bearing. Dr. Melkerson said the existing devices were similar to pedicle screw systems with a metal rod.

PANEL DISCUSSION

The discussion began with Drs. Kirkpatrick, Naidu, and Schmidt commenting on the device. **Dr. Kirkpatrick** discussed the preclinical and clinical studies. In the preclinical tests, the device was only tested in the neutral zone, a part of the spine that sees very little stress. That area does not see extremes of motion. Therefore, the device was not tested in a worst case scenario. While 90 percent of the particles in the wear test were less than one micron, only 57 percent of the particulates were less than one micron in the biocompatibility tests. He was also not sure that the shapes and injection backgrounds accurately simulated debris from wear. In three rabbits in the study, there were five pathologic changes in the kidneys that were found at three months, and that required clarification as to whether or not the kidney changes were related to particulate dose.

He then discussed the stability of the bone/implant interface, patient enrollment, and his perspective on safety and effectiveness. The literature shows varying degrees of kyphosis, possibly surgeon-related. This may impact training requirements. Because there was no change in position of the device from 6 to 24 months, it seemed relatively stable. The fact that 15 percent of the 117 patients who were randomized but not included got better without treatment suggests that the entry requirements were too loose. Distribution among sites and time between randomization and surgery could be other factors. Attention to detail in preoperative selection could also have prevented the 12 patients randomized for Bryan who got ACDF. The patient randomized for ACDF but getting Bryan was difficult to understand.

With the presented data, the device was comparable in safety to the control. Though dysphasia and dysphonia rates were not statistically significant, Dr. Kirkpatrick considered it a known complication. This may be attributed to surgery time and instrumentation. His other safety concern was unknown, long-term effects on the kidneys. For effectiveness, he said that the criteria of 15 points on NDI was a meaningful difference, and the mean improvement in device patients was higher than 15.

The indication used the words, “degenerative disc disease.” The term was too broad, since the study looked at reconstruction for a defect left by anterior compression, and neural compression was one of the inclusion criteria. Therefore, the patient information should indicate that the goal of the surgery is decompression of the nerve or spinal cord and that the device is an option for reconstruction. The information should also indicate that long-term performance is unknown. The package insert should also indicate that the device is indicated for reconstruction of a single disc space after decompression for radiculopathy or myelopathy. He was curious about the finding of higher adjacent section motion in the device group and long-term consequences. Finally, he did not see clear evidence on the life span of the polyurethane.

Dr. Naidu spoke primarily on the structure of the polyurethane and the polypropylene, elastomer degradation in vivo, and the application of the specifics to the PMA and preclinical studies. The bionate nucleus is polycarbonate urethane (PCU). The sheath is polyether segmented polyurethane, (PEU).

His first concern was a lack of literature review for the polymers used. The literature shows that one percent oxygen by weight in the elastomer bulk can degrade the elastomer's fatigue propagation by twofold. Elastomer aging by oxidation leads to inferior fatigue crack propogation and fissuring of elastomers in general. Bionate's structure contains at least six sites of double-bonded oxygen. Dr. Naidu suggested that the explanted disc was yellow due to more than formalin.

Though there is clinical experience with similar polyurethanes in other implanted medical devices, those devices PCU do not subject the PCU to the compressive, tensile, and constant loading this device does. All studies to date on all PCUs, bionates, and PEUs subjected to compressive loading show degradation in number average molecular weight (MN) and weight average molecular weight (MW). With the device, the elastomer is subjected to compression and tensile strains in an oxygenated environment. The sponsor did not address the biomaterials literature or present evidence that the PCU and PEU in the device can maintain elastomeric and polymeric integrity in vivo.

Literature shows that bionate is susceptible to biodegradation. Monocytes form foreign giant body cells on bionate. Those adherent cells release reactive oxygen, which oxidizes polyurethanes. The literature further shows that MW and MN decrease significantly with application of stress in an oxidative environment; those studies included the PCU in the device. PCU is shown to degrade in an oxidative environment with stress. Additional literature shows that PEU degrades under dynamic load and oxygenation. The oxygenation can cause a brittle, pitted surface layer, and cracking occurs in fatigue studies. The sponsor's wear test showed nuclear surface cracking at 10 million compressive loads of 130 N. PCU particles broke, and 18 mg of wear debris was noted, 90 percent of which was less than one micron. The presence of submicron particles will induce chronic inflammation.

Second, the Bryan Disc has several moving parts, including the metal/PCU articulation. This is a high-friction interface, even higher than metal-on-metal articulation. There is not enough data to demonstrate that the PCU/titanium interface will not be a source of particulates. The discs explanted from humans were not tested to see if the nucleus was intact.

The third point was PCU biocompatibility. He had significant concerns with biological response, particularly kidney reactions in the rabbit study and debris found around the implant and in the spinal cord in the goat study. Hemorrhage occurred in one of the goats. In human explant analysis, foreign body giant cells and macrophages surrounded the polymeric debris. The sponsor did not look at the extent of inflammation histologically or measure tissue cytokine. The preclinical studies are inadequate on biocompatibility. He concluded that the PMA had not convinced him that the PCU used in the device was safe.

Dr. Schmidt gave his statistical perspective. He noted that the sponsor had used a noninformative prior and that selection of the prior is an important aspect of performing a

Bayesian analysis. Generally, there are two types of priors: skeptical and enthusiastic. The enthusiastic is generally performed by the sponsor, the skeptical by the regulatory agency. The compromise between the two was noninformative.

The sponsor used 12-month and 24-month outcomes in its analysis. Since 12 months was an interim analysis, many patients with 12-month outcomes were missing 24-month outcomes. That partial information is useful if 12-month outcomes correlate to 24-month outcomes. The missing 24-month outcomes can be estimated using a Markov model, since the data eliminates 2 of the 4 possible outcomes. The Bayesian analysis allows the sponsor to use information from patients with incomplete data. The uninformative prior was used to not let information outside of the trial affect the analysis.

The Panel members asked more questions, which were addressed after the lunch break. When the Panel reconvened, Dr. Donald Barry, the sponsor's biostatistics consultant, addressed the Panel's statistical questions. He agreed with Dr. Schmidt's assertion that the 12-month data was an interval analysis and that 12-month data was set in a 2 by 2 table. To Dr. Propert's question about the intention to treat for the 117 patients not included in the study, he said the effect was unknown. However, those patients were similar to the patients in the study, so similar success rates would be expected.

Dr. Sasso addressed questions about postoperative instructions. He said the 12 crossover patients received the control because it was part of the protocol to do so if the Bryan Disc could not be placed. Most commonly, this was due to the inability to radiographically view the disc segment, which is done in the operating room. The cross-over from control to device was due to a clerical error caused by randomization and blinding. With the exception of two weeks of NSAIDs for the device group, postoperative protocol was identical between the arms. He said he was more cautious with his device patients than with his ACDF patients in terms of when they could return to work. The placebo effect is unlikely because there was a robust control and objective data was gathered. In response to the question on the pseudoarthrosis rate, the finding required bridging bone, no motion, and no lucencies across the graftose junction. With an allograft, literature shows a 7 percent pseudoarthrosis rate. In response to the question on operating time, he confirmed that each surgeon performed the last five operations faster than the first five.

Dr. Harry Genant addressed the question on angular range of motion measurements. He said the sponsor used images digitized at 100 microns and electronic workstations that could measure to a tenth of a degree.

Dr. White addressed the materials questions. He said the device is made of the proper materials. An FDA summary had a paragraph that stated that the wear tests showed no cracks deeper than 2 mm. That did not mean that there were 2 mm cracks in the nucleus. Rather, that language was an artifact of an acceptance criteria listed for the test. The sponsor saw no cracking, severe delamination, or deformation from the test. The ten million cycle test had six specimens, three saturated with saline. The device is tested to plus or minus 4.9 degrees of flexion-extension. He said the titanium in the device is not titrided, that the finish is 3RA, and that the wear rate with the device has been very low, one cubic mm per million cycles. Since the sheath is permeable, the device will not lack for lubrication. This is a third generation polyurethane material that is low-wear and proven in hip replacements as a load-bearing material.

Steven Kurtz, a sponsor consultant, presented a summary of the retrieved cores and noted that some of his data was new. Chairman Mabrey noted that the Panel was to consider only PMA data. Mr. Kurtz said the explanted devices showed no evidence of damage consistent with the oxidative mechanisms raised by Dr. Naidu. When shown a slide comparing a new component to a six year old component, Dr. Naidu noted that the older one was yellowed. Dr. Michael Ebert from Medronic said the discoloration could have come from protein or blood absorption. Chairman Mabrey asked how permeable the sheath is. Dr. Ebert said the sheath is water and lipid permeable and that body fluids will permeate. Mr. Ward of the Polymer Technology Group said permeability was low to anything the size of glucose or larger. This is a dense membrane with no permanent pore structure, so permeation is due to activated diffusion.

Dr. Paul Anderson, a consultant to the sponsor, said the explantations and revisions in the chimpanzee studies were without complication. Two explanted devices, one in for 3 months, the other for 9, were sent for chemical analysis and compared to specimens that had been vacuum sealed. FTIR spectroscopy showed curves identical to the controls and no evidence of oxidation. Gel permeation chromatography showed little difference in molecular weight of the polymer, in the nucleus or the sheath. There was no evidence of fragmentation or oxidation. Dr. Naidu asked if a volatile gas analysis was done. Dr. Anderson said it was not. Dr. Naidu asked the extent of the surface analysis. Mr. White said it included a visual analysis, macroscopic analysis, and optical SEM, showing no cracks at 6 years. The extractions showed pristine nuclei and polished surfaces. He said the dynamic spinal stabilization system uses polycarbonate urethane and has ten years of clinical use. Explants show degradation over time, but it does not go deeper than 100 microns, and there are no significant changes in function or molecular weight. In the Bryan device, the silicone in the polymer is used to prevent even surface cracking in Biospan, and the polycarbonate urethanes were chosen for their oxidative stability. He said the silicone-modified polycarbonate urethane offered a unique combination of mechanical strength and biostability.

Dr. Jeffrey Toth, a consultant to the sponsor, said his laboratory at the Medical College of Wisconsin conducted host response retrieval analyses on 4 explanted devices. Polymeric particles were seen in .5 to 1 percent of the microscopic fields. It was also rare to find particles in the histology. When particles were found, foreign body giant cells were common.

Dr. Rouleau spoke to concerns about the rabbit study. The veterinary pathologist noted five changes in the kidneys (three in one animal, and two others with single changes) and diagnosed all the changes to be consistent with an Encephalazum canaliculi infection. The parasite is common among laboratory rabbits. Changes were not found at later timepoints. Regarding Dr. Goodman's question of the consistency between particles in the simulator and those injected, fluoroscopy showed that the particulate carrier media traveled from the lumbar region to the cervical spine and through the entire epidural space. Particles were made as consistent to the simulator tests as possible. The cryomilling process to create sub-micron particles is lengthy and difficult. Particles from the simulator could not be used, since they were not sterile.

Dr. Heller addressed Dr. McCormick's question of which of the control patients received NSAIDs and whether some of the study patients had continued NSAIDs beyond 2 weeks, which could account for early improvement. Dr. Heller said 13 of the 221

control patients took NSAIDs, which are generally not used with a fusion. NSAIDs are believed to be associated with lower rates of ossification and spontaneous fusion. There have only been small studies of unknown value on the matter.

Dr. Papadopoulos observed that during the follow-up a woman with a Bryan Disc at C5-6 was in a serious auto accident. Though there were long bone fractures, pelvic fractures, and spine fractures adjacent to the disc, the disc was secure and did not migrate. Responding to Dr. McCormick's questions about pseudoarthrosis and adjacent level revisions, he said 5 control patients with symptomatic pseudoarthrosis received surgery for it. One Bryan patient and 2 control patients had adjacent levels addressed in subsequent surgeries.

PANEL QUESTIONS

Ms. Ferriter read the FDA's questions to the Panel.

1. The sponsor has provided a combination of engineering testing, biocompatibility testing, functional animal studies, device retrievals and analysis, Radiographic follow-up and clinical observations to address the degree of constraint, materials of articulation, and other design features of the Bryan Cervical Disc Prosthesis. Please discuss the testing, the data, and the clinical observations regarding:

* **device wear**
* **material and particulate reaction**
* **device expulsion or migration**
* **implant durability and reliability and**
* **sheath purpose and function.**

Panel consensus was that the testing, biocompatibility testing, functional animal studies, device retrievals and analyses were adequate and to the Panel's satisfaction. However, the Panel had two issues: one in relationship to the kidneys and a concern over patients in renal failure who might receive the device, a second from the Panel's biomaterials expert regarding some material properties of polyurethane as a bearing material against titanium and requested more specific data, such as on the coefficient of friction.

2. The sponsor has presented radiographic data to demonstrate preservation of motion at the index level in the patients receiving the investigational device. Motion at the index level did not correlate with clinical success.

Further analysis has demonstrated that the motion, as measured by dynamic radiographs, was not significantly different at adjacent levels for the investigational device and for controls.

Please discuss how index level and adjacent level motion contribute to the effectiveness of the investigational device.

Panel consensus was that the sponsor demonstrated preservation of motion at the operated level. In adjacent segments, the Panel expressed questions regarding the

importance of maintaining or preserving motion in adjacent motion segments and indicated that time will tell whether or not it is a clinically significant advantage.

3. **Please discuss the adequacy of the of the device labeling.**
What information related to mean operative time should be included in the labeling?
What information related to cervical levels should be included?

Panel consensus was that the operative time is not a significant issue to be mentioned in specific labeling but should be mentioned as part of a procedure description. Surgical training will be important, at least initially. Questions were raised about the nomenclature of degenerative disc disease; the Panel clearly stated that there should be no mention of adjacent level disease as there was no information available supporting it.

4. Under CFR 860.7(d)(1), safety is defined as reasonable assurance, based on valid scientific evidence, based on valid scientific evidence, that the probable benefits to health under conditions of the intended use, when accompanied by adequate directions for use and warnings against unsafe use, outweigh any probable risks.

Considering the adverse event rates for the subject device, please discuss whether the clinical data in the PMA provide reasonable assurance that the device is safe.

Panel consensus was that the device, within the timeframe studied, is safe. The Panel expressed interest in clarifying the intended use, meaning intended use over several years. There were suggestions of longer-term follow-up. Based on the data presented in the PMA, the device is safe.

5. Please discuss whether the clinical data in the PMA provide reasonable assurance that the proposed device is effective.

The majority opinion of the Panel was that the device is effective for its intended use. However, there were concerns from many members as to long-term effectiveness.

6. The sponsor has presented comparisons of the investigational and control procedures based on a variety of datasets (e.g. as randomized, as implanted). Please discuss whether these pre-specified secondary analyses support the sponsor's claim that the investigational device is superior to the control procedure with respect to the overall success endpoint.

Panel consensus was that the device did not demonstrate superiority over the control, standard of care.

7. Please discuss the following issues related to a potential post-approval study.

Is it necessary to recruit new patients/physicians in the PAS or to use an alternative approach to evaluate the device's "real-world" performance after approval?

Is 7-year followup appropriate for this device?

Should treated level and adjacent –segment motion and the occurrence or progression of adjacent-segment disease be assessed in both groups of the PAS?

Should the rate of HO and kyphosis after Bryan Cervical Disc implantation be investigated in the PAS?

The Panel unanimously supported a post-approval study should the device be approved. On recruitment, some Panelists felt a database on the existing cohort was sufficient. Others argued for a larger patient database or expanded collection of data on existing patients. The Panelists unanimously agreed that the treated and adjacent levels and rates of HO should be studied.

OPEN PUBLIC HEARING

Chairman Mabrey called for public comment. Hearing none, he closed the session.

FDA AND SPONSOR SUMMATIONS

FDA had no further comments. For the sponsor, **Dr. Simpson** gave closing comments. She said the Bryan Disc presents several novel device features that contribute to its clinical performance. The study demonstrated how the features contribute to device success. The device showed no migration, subsidence, or expulsion. She said the polyurethane materials have a long history of safe use and were tested for their mechanical properties, safety, and biocompatibility. Bryan proved non-inferior and superior by endpoints and hypotheses pre-defined in the approved protocol. She expressed the importance of accurate labeling and further post-approval study.

PANEL DELIBERATIONS AND VOTE

The Chairman asked for comment from the Industry and Consumer Representatives. Ms. Walker thanked the FDA and sponsor. She reminded the Panel of the discussed post-approval activities and conditions. Ms. Whittington seconded those thanks and expressed interest in packaging, physician education, and patient informative materials. She hoped to see them as they are developed.

Executive Secretary Jean read the panel recommendation options into the record. Chairman Mabrey called for a motion. **Dr. Kirkpatrick moved that the Panel recommend that the PMA is approvable with conditions. Dr. Goodman seconded the motion.**

Dr. Haines moved the condition that there be no mention of adjacent level motion or disease in the product literature or labeling. Dr. Goodman seconded the motion. Dr. Kirkpatrick proposed an amendment, that the numbers may be reported, but without conjecture as to future effects on the adjacent segments, since the labeling will discuss the IDE, and there is no need to edit the data out. Dr. Haines accepted the amendment, saying the information was not relevant to the safety and effectiveness of the device but should not be eliminated from the findings. Dr. Hanley suggested that the issue was removing claims of superiority from the labeling and the condition represents non-permission to claim superiority. Chairman Mabrey suggested that may be for another motion. Dr. Haines declined the amendment. **The motion carried**, 5 to 2, with Dr. Naidu abstaining.

Dr. Kirkpatrick moved that there be a pre-approval study on the rabbit particulate model, with no protozoan infection, to ensure that there is no risk of early nephrotoxicity. Chairman Mabrey pointed out that a pre-approval study cannot be a condition of approval. **Dr. Kirkpatrick amended his motion to require that the study be performed as a post-approval study, within six months of approvability. Dr. Goodman seconded the motion**. Dr. Hanley said he thought the condition too specific. Dr. Kirkpatrick said that the kidney problems found at three months had not been resolved scientifically. Dr. Goodman offered an amendment, that "within six months" be replaced by "expeditiously. Dr. Kirkpatrick accepted the amendment. Dr. Goodman seconded. Dr. Kirkpatrick restated his motion as the condition that within an expeditious timeframe a rabbit study simulating the three-month particulate study that had the nephrotoxic results. **The motion carried** 5 to 2. Dr. Naidu abstained.

Dr. Haines moved the condition that no claim of superiority of the treatment be included in the labeling or literature. Dr. Kirkpatrick seconded the motion. Ms. Walker suggested that the motion should not limit FDA and sponsor from discussing smaller scale claims that may be appropriate as the data is presented. Dr. McCormick asked for clarification on the term, literature. Dr. Haines said he meant documents accompanying the device or marketing material. **The motion carried** 7 to 0. Dr. Naidu abstained.

Dr. Hanley moved that appropriate training for surgeon users be a condition of approval. Dr. Kirkpatrick seconded the motion. Chairman Mabrey clarified that the FDA and sponsor would work out the details of the training. **The motion carried** 7 to 0. Dr. Naidu abstained.

Dr. Goodman moved that there be appropriate patient education modules or information made available. Dr. McCormick seconded the motion. Chairman Mabrey asked for Ms. Whittington's comments. She said the materials had to be age-level appropriate, truthful, and transparent. Dr. Kirkpatrick said the motion should incorporate the Panel's earlier discussion on patient education material. **The motion carried** 7 to 0. Dr. Naidu abstained.

Dr. Kirkpatrick moved that the device indication be changed to read that the Bryan Cervical Disc is indicated in skeletally mature patients as an alternative for reconstruction following single level decompression for cervical radiculopathy or myelopathy between C3 to C7, eliminating the wording on degenerative disc disease. Dr. Goodman seconded the motion. Chairman Mabrey asked if the motion could be summarized as a motion to eliminate the reference to degenerative disc disease. Dr.

Kirkpatrick said he liked the motion as it was. Dr. Hanley said he did not want to approve a motion on semantics or language. Dr. Haines noted that there is no clear and specific indication in the PMA. Ms. Walker suggested amending the motion to require negotiation between the sponsor and FDA to make an indication that reflects the data and patient population. Dr. Kirkpatrick declined the amendment as too vague. **The motion carried** 4 to 1. There were three abstentions.

Dr. Haines proposed a post-approval study to address the issues discussed during the Panel's discussion of question 7. Dr. Kirkpatrick seconded the motion. He elaborated on some of the issues: motion at the treated and adjacent levels, HO, kyphosis, analysis centralized to one center, and a 10-year follow-up. Dr. Hanley suggested that the issue of whether or not 200 patients from the study group was appropriate was not for the Panel to decide. Dr. Haines agreed that the Panel should not design the study. Dr. Kirkpatrick added that the fusion patients were less likely to follow up. **The motion carried** 7 to 0. Dr. Naidu abstained.

Dr. Goodman moved that references to NSAID use be stricken from the product literature and patient education materials. Dr. McCormick seconded the motion for the purpose of discussion. He asked the reasoning behind the motion. Dr. Goodman said that NSAID use should be left up to the surgeon. He said NSAID use in not necessarily a part of the surgical technique. However, NSAID use can be mentioned in reference to the studies and describing them accurately. Ms. Walker noted a statement on page 6 of the package insert, which addressed NSAID use in the study without making them a mandatory instruction. Dr. Hanley said that the condition attempted to regulate the practice of medicine. Dr. Goodman said it is not usual for a description of a surgical technique to include a mention of medication. He was not recommending that NSAIDs not be used, only that mention of NSAID be excluded from the description of the surgical technique. **The motion failed** 3 to 2 with three abstentions.

Chairman Mabrey called for other conditions. Hearing none, **he called the question of approval with conditions. The motion carried** 7 to 1, with Dr. Naidu in the minority.

Chairman Mabrey polled the members on the reasons for their votes. Dr. Hanley said the study had shown safety and efficacy, but not superiority. He expressed concern about materials and deterioration over time, so further information should be collected. Dr. Haines said safety and efficacy were demonstrated and that the device will be a good addition to the armormentarium. Dr. McCormick said the data showed the device to be safe and effective in the timeframe and patient population studied. Dr. Goodman urged the sponsor to consider Dr. Naidu's concerns and carry out long-term studies on the materials' properties. Dr. Kirkpatrick shared Dr. Naidu's concerns but voted affirmatively because the analysis was fair and met the legal and regulatory standard.

Dr. Naidu said the study was reasonable for a short term evaluation. However, he expressed concern that the polymer is the weak link in the device. Though the sponsor presented data on strengthening the polymer with silicone, Polydimethylsiloxane oxidizes and falls apart, and the silastomer will age and fragment with time. The nine-month explants in the study did not show degradation due to bulk. He said the device will degrade in the long term.

Dr. Schmidt urged the sponsor to consider potential heterogeneity in the results going forward. Dr. Propert said the device is safe and effective up to two years and that

the conditions will address the other concerns. Ms. Walker thanked the sponsor and FDA. Ms. Whittington urged the industry members to think of the device in terms of whether or not a product is good enough for their own mothers.

ADJOURNMENT

Chairman Mabrey thanked the participants and adjourned the meeting at 4:45 p.m.

I certify that I attended this meeting of the Orthopaedic and Rehabilitation Devices Panel on February 22, 2007 and that these minutes accurately reflect what transpired.

Ronald P. Jean, Ph.D.
Executive Secretary

I approve the minutes of this meeting as recorded in this summary.

Jay D. Mabrey, M.D.
Acting Chairperson

Summary Prepared by

Eric M. Hendrixson
Neal R. Gross & Company
1323 Rhode Island Ave, NW
Washington, DC 20005
(202) 234-4433
Wednesday, August 8, 2007