ATTACHMENT A

SUMMARY MINUTES

MEETING OF THE ORTHOPEDIC AND REHABILITATION DEVICES

ADVISORY PANEL

OPEN SESSION

September 8, 2005

Hilton Washington D.C. North
Gaithersburg, Maryland

Orthopedic and Rehabilitation Devices Advisory Panel Meeting

September 8, 2005

Attendees

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

Voting Member
Choll W. Kim, M.D., Ph.D.
University of California, San Diego
San Diego, California

Consultants
Brent A. Blumenstein, Ph.D.
TriArc Consulting
Seattle, Washington

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

Michael B. Mayor, M.D.
Dartmouth Hitchcock Medical Center
Lebanon, New Hampshire

Harry B. Skinner, M.D., Ph.D.
University of California, Irvine
Orange, California

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

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

Executive Secretary
Janet L. Scudiero, M.S.

CALL TO ORDER

Executive Secretary Janet L. Scudiero, M.S., called the meeting to order at 8:34 a.m. The panel meeting scheduled for November 3rd and 4th was cancelled. Noting that Dr. John Kirkpatrick was unable to attend, Ms. Scudiero read a statement appointing panel member Sanjiv H. Naidu, M.D., Ph.D. as Acting Panel Chair for the September 8th and 9th meeting. She declared that panel consultants Brent A. Blumenstein, Ph.D., Jay D. Mabrey, M.D., Michael B. Mayor, M.D., and Harry B. Skinner, M.D. Ph.D. had been appointed to temporary voting status for the duration of the meeting. Ms. Scudiero then read the conflict of interest statement. A full waiver had been granted to Michael Mayor, M.D., for his interests in firms that could be affected by the Panel's recommendations.

Acting Panel Chair Sanjiv H. Naidu, M.D., Ph.D., stated that the purpose of the meeting was to make recommendations concerning a PMA, P040033, for the Smith & Nephew Birmingham Hip Resurfacing (BHR) System. He asked the panel members to introduce themselves, after which he noted that the members present constituted a quorum.

POSTMARKET STUDY DESIGN

Susan N. Gardner, Ph.D., Director, Office of Surveillance and Biometrics, talked about organizational changes in CDRH and the review of conditions of approval studies by the Office of Surveillance and Biometrics (OSB). An internal review of the condition of approval studies program revealed that many studies could not be found and that there were no standard procedures for tracking the studies. There was a need for better information about device use in real world clinical settings.

As a result of the review, an automated tracking system was developed, and an epidemiologist will be included on the PMA review team when there's an expectation for a condition of approval study. The epidemiologist will begin developing that study concurrent with the PMA process and will be responsible for crafting well-formulated postmarket questions, designing the study protocol, and evaluating the study progress and results.

UPDATE SINCE THE AUGUST 31, 2004 MEETING

Glenn A. Stiegman, M.S., Chief, Orthopedic Devices Branch, gave an update on activities relevant to the panel. P040006 from the June 2, 2004 meeting for the DePuy Charite artificial disc was approved October 26, 2004 for spinal arthroplasty in patients with degenerative disc disease (DDD), with a post-approval study to document the incidence of complications. Two ceramic on ceramic hips were approved, the Smith & Nephew Reflections Ceramic Acetabular System on December 17, 2004 and on May 4, 2005, the DePuy Dura Option Ceramic Hip System. P010029 for the Nuflexxa one

percent sodium hyaluronate by Savient Pharmaceuticals, recently bought by Ferring Pharmaceuticals, was approved. A humanitarian device exemption (HDE), H030009, the Synthes USA Vertical Expandable Prosthetic Titanium Rib, was approved.

Other significant 510(k) clearances were for Blackstone Medical's Laminoplasty Fixation System and Zimmer Trabecular Technology's Trabecular Metal Osteonecrosis Interventional Implant.

Mr. Stiegman also discussed guidances that had been published since the last panel update as well as staffing changes at FDA.

FIRST OPEN PUBLIC HEARING

Susan Krasny, Ph.D., R.A.C., Vice President, Orthopaedic Surgical Manufacturers Association, urged the panel to focus on the device's safety and effectiveness based on the data provided. While the FDA is responsible for protecting the public from products that are adulterated, unsafe, or ineffective, the agency is also responsible for fostering innovation. Dr. Krasny emphasized the idea of a reasonable assurance of safety and effectiveness and that of valid scientific evidence. According to the regulation and the law, reasonable is defined as moderate, fair, and inexpensive, and there is a broad range of valid scientific evidence that can be used to make a determination about safety and effectiveness.

William G. Maloney, III, M.D., Wright Medical Technology, Inc., made comments regarding the current PMA's study methodology, the issue of conflict of interest, and the idea of compelling medical need. The data under review was a combination of retrospective data and prospective data reviewed retrospectively. There were not predefined follow-up times, standardized clinical evaluations, adverse event report forms, or standardized radiographic evaluations. Also, the only verifiable survivorship data came from a single surgeon, Dr. Derek McMinn, an expert surgeon, and the verification was neither done concurrently nor by an independent study monitor.

Dr. Maloney next discussed the three study cohorts. The Oswestry cohort had no direct patient contact as required for IDE studies, the outcome measure of OSHIP score was unfamiliar, and it was unclear how the Oswestry Outcome Center was funded. As for the McMinn cohort, there was no functional outcome data available for review, and the patients never specifically consented to participate in a research study. Finally, the radiographic analysis for the X-ray cohort was primarily retrospective analysis. Furthermore, a strict analysis of the data in the X-ray cohort would have resulted in a potentially much smaller cohort based on protocol violations.

With regard to conflict of interest, the principal investigator, Derek McMinn, was also the product designer and a co-founder of Midland Medical Technology, for which no precise conflict

information was provided and which was bought by Smith and Nephew for 67 million pounds with a provision to pay another 33 million if the device was approved. Also, Dr. McMinn is apparently a current employee of the sponsor. Significant financial conflicts cannot be mitigated, regardless of the quality of the data or integrity of the investigator.

Dr. Maloney also took issue with the notion that there was a compelling medical need for this product. Conventional hip replacement is a good operation with a long track record. He reminded the panel of the last time this kind of data was accepted, for the Mittelmeier hip replacement, which was a clinical disaster in the U.S. in spite of excellent clinical results from Europe. He avowed that approval of the PMA would set a new precedent for Class 3 orthopedic devices and make it impractical to do future IDEs in this country.

SPONSOR PRESENTATION

Marcos Velez-Duran, Vice President of Clinical and Regulatory Affairs & Quality, Smith & Nephew, Inc., outlined the sponsor presentation and introduced the sponsor presenters.

Derek J.W. McMinn, FRCS, Consultant Orthopedic Surgeon, Birmingham Nuffield Hospital, U.K., discussed the problems with total hip replacement, including dislocation, leg lengthening, acetabular and femoral loosening; in addition, revision surgeries are difficult and expensive and may be recurrent in young patients. Instead of total hip replacement, the worn out acetabular and femoral articular cartilage can be replaced with a hip resurfacing. Hip resurfacing is not a new concept, but historically the procedure has had various problems, including wear through of the socket and head, loosened cups, femoral neck fracture, and collapsed femoral heads. Uncemented models addressed the issued of component loosening but led to osteolysis resulting from polyethylene debris. Dr. McMinn's experience with metal on metal total hip replacements eventually led him to combine the concept of resurfacing with large headed metal on metal.

Dr. McMinn then discussed specifics of the device design. The cup has a porous surface with hydroxylapatite (HA) coating. There is a layer of beads integrally cast with the substrate, meaning the implant does not have to be heated to attach the beads. Therefore the beads are highly unlikely to come off and the carbide microstructure is not destroyed by the heat of centering. The femoral component is cemented with a cementless stem. As the implant is inserted, the high pressure drives low viscosity cement into the peripheral femoral head giving good microinterlock. The stem is tapered so that there is a gap between the stem and the surrounding bone so as to avoid distal loading and proximal stress healing of the implant.

Dr. McMinn discussed some of his patients and studies that were done on metal ion release

which showed no difference between the large-headed Birmingham hip resurfacings and 28 millimeter metal-on-metal total hips.

Tim J. Band, Director, Product Development, Smith & Nephew Orthopaedics, Ltd., presented on the device description and preclinical testing. The device consists of the femoral head and acetabular cup. The femoral head is available in six sizes; it is fixed by use of bone cement with recesses on the inside to assist in stability. There are twelve sizes of cups; they are HA coated and cementless. There is a dysplasia option and a bridging cup with screws to provide primary stability. The material used is a cobalt chrome moybderium alloy. The specifications allow for the head to be smaller than the cup to provide a polar bearing.

The preclinical testing was conducted in accordance with FDA guidance and included wear, friction, and fatigue testing. Kinematics were assessed by simulating range of motion, and metallographic microstructure metrology examinations were performed to characterize the device. The beaded surface was tested for static shear, shear fatigue, and static tensile strength, and the substrate was tested for ultimate tensile elongation and abrasion. The HA coating was tested for environmental stability, coating thickness, static shear, and tensile strength, as well as analysis of the chemical and crystallographic characteristics.

Mr. Velez-Duran presented a summary of the clinical studies. The product was first available in the U.K. in 1997 and has been used in 23 countries for a total of more than 33,000 implants. The evidence for safety and effectiveness was based on a consecutive series of 2,385 cases, though the effectiveness data came only from the first consecutive series of 1,626 based on independent review and follow-up by the Oswestry Center Registry. The radiographic study is based on the first consecutive 124 cases conducted by Dr. McMinn. All of the devices in the 2,385 procedures are of the same design, and the studies relied on surgeries conducted by Dr. McMinn at a single center.

Effectiveness was evaluated in terms of survivorship as well as secondary measures such as the Oswestry modified Harris Hip Score, or OSHIP, and the five-year radiographic assessment. Safety measures included number of revisions as well as all other adverse events. Five-year patient follow-up was 90.8 percent, and survivorship at five years was 98.4 percent.

The Oswestry Center followed a total of 5,000 cases, and the survivorship data from those additional 3,374 cases and 140 surgeons was similar to Dr. McMinn's, 96.3 percent.

The OSHIP measure, a patient self-assessment of pain and function, was validated and compares well with the Harris Hip Score. For the radiographic data there were predefined success and failure criteria, and the five-year success result was 97.2 percent. As for safety, there were 27 revisions in 2,385 cases, a rate of 1.1 percent, and there was low incidence of other adverse events; all were less than

or equal to one percent.

George DeMuth, Statistical Consultant, Stat-Tech Services, LLC, commented on statistical issues. He focused on the unilateral hips from the Oswestry and X-ray cohorts since there was better follow-up data for those groups. There was 98.3 percent survival with a 1.7 percent revision rate. In terms of efficacy, the average OSHIP score increased from 60 to the mid-90s. With regard to satisfaction, almost every patient was pleased with the results.

Mr. DeMuth addressed problems with the study design and pointed out that there was a large sample size, the OSHIP was sensitive to small differences, survival was an objective endpoint, there was external radiographic review, and the results were consistent with other published studies.

He summarized that there were many procedures with good follow-up, the survivorship rate was very good, there were large improvements in OSHIP score, patient satisfaction was high, and the sensitivity analysis showed that the missing baseline data had little impact on the five-year results.

Neal Defibaugh, Director of Clinical Affairs, Smith & Nephew, Inc. – Orthopaedics, discussed approval considerations, including labeling, surgeon training, and post-approval study. The BHR is intended for patients at risk of requiring more than one hip joint replacement; risk factors are age of less than 55 and high activity level. Contraindications for the device are infection, skeletal immaturity, conditions that would compromise implant stability or postoperative recovery, patients with inadequate bone stock, women of child-bearing age, and renal failure. The sponsor anticipates sending a group of core surgeons from the U.S. to the U.K. to view live surgery and participate in lectures and workshops. These surgeons would eventually train others in the U.S. after performing surgeries themselves.

With regard to post-approval study, Mr. Defibaugh was unsure whether it would be necessary given the large patient population already studied and the length of follow-up. The protocol submitted by the sponsor was for a prospective, nonrandomized survivorship study with clinical radiographic evaluations through five years. Post-card would be done in years six through ten, explants returned to the sponsor would be analyzed, and annual progress reports would be made to the FDA.

Dr. Naidu asked the panel for any questions of the sponsor. Dr. Mabrey asked for further details on surgeon training and evaluation. **Dr. Marc Thomas, Senior Marketing Manager, Smith & Nephew,** responded that the initial training would be a two-day course, with a follow-up including a second opportunity to view the surgery. Following that, the surgeons will work on their own patients until they feel they have the proficiency to train their colleagues. Dr. Mabrey asked further whether there would be opportunity for cadaveric dissection as opposed to merely sawbones use, and Dr. Thomas responded that there would be an effort in the U.S. for cadaveric dissection.

Dr. John Rogerson, Orthopedic Surgeon, Madison, Wisconsin, stated that soft tissue dissection was critical and that Smith & Nephew already had extensive experience training surgeons around the world in the use of the device. He clarified that the initial training would be about two months before introduction of the device into the U.S. market and the subsequent session would be right before introduction. The sponsor hoped to send field representatives to observe and assist the core surgeons for their first ten procedures. Once the learning curve had been obtained, the core surgeons would begin training the next group of surgeons in a manner similar to their own training experience.

Dr. Mabrey asked how many surgeries would be needed for the initial learning curve. Dr. Rogerson suggested 30 surgeries would likely be needed, depending on the surgeon's skill and experience.

Dr. Blumenstein asked how many deaths there were in the cohorts, and Dr. Skinner said he thought there had been twenty, which seemed high given the average age of 53 years. **Marie Marlow, Consultant, M Squared Associates**, explained that narratives for each death had been included in the panel packets. Dr. Blumenstein then asked how the deaths were handled with respect to survivorship. Mr. DeMuth responded that they censored at the time of death if there was a revision.

Dr. Skinner wondered about the number of deaths given that apparently none were a result of the procedure. **James Richardson, FRCS MD, Director, Oswestry Outcomes Centre, Robert Jones and Agnes Hunt Orthopaedics and District Hospital NHS Trust, U.K.,** responded that the expected death rate for the age range would be .47 percent for women and .74 for men and that the twenty deaths resulted in a death rate per year for the cohort of about .3 percent, less than predicted. Dr. Richardson noted he had not done a detailed analysis of each age band.

Dr. Mayor asked how the acetabulum was handled during revisions, particularly for femoral neck fracture, and he also asked for clarification of the description of femoral head collapse as distinct from avascular necrosis. Dr. McMinn responded that the acetabulum was left alone provided it was in a good position and there was no evidence at surgery of age loading or wear of the component. He said that it was very difficult to differentiate between collapsed head and avascular necrosis and that some of the cases could have been categorized either way.

Dr. Skinner asked whether the change in the selection criteria regarding less than 50 percent of femoral head involvement in avascular necrosis had led to a decrease in the number of femoral head problems. Dr. McMinn responded that it was true that avascular necrosis was a major problem for femoral head collapse. Whether the femoral head collapses depends on the magnitude of the original femoral head lesion and whether or not then pathology is recurring. He said that collapses have

decreased as a result of experience with femoral head remnants with virtually no bone.

Dr. Skinner then asked how patients were selected to have a resurfacing and to what extent Dr. McMinn's practice was referral based. Dr. McMinn responded that his practice is mainly referral though he does get some local patients referred. Dr. Skinner asked how many total hips he had done in the past seven years, and Dr. McMinn answered between 50 and 100 a year. Dr. Skinner inquired why the pain rate was so high compared to some of the ceramic studies. Dr. McMinn replied that the pain data was gleaned from his notes by an outside group of consultants. He acknowledged that there was less pain reported postoperatively compared with one year out and attributed this to the fact that pain was reported only when worse than anticipated. Following surgery patients were expecting to experience some pain and therefore were less likely to report it than they would be one year later.

Dr. Skinner then asked about the number of patients with a limp one year out. Ms. Marlow responded that the auditors were instructed to record every incident since it was a retrospective review.

Ms. Whittington asked about the extremely high numbers of wound exudates. Ms. Marlow attributed those high numbers to the auditors being instructed not to leave anything out as well. Ms. Whittington then inquired whether there was any correlation between patients who developed late wound infections and those who had revisions. Ms. Marlow responded that the sponsor would have to see if they could find an answer.

FDA PRESENTATION

John S. Goode, Lead Reviewer, Orthopedic Devices Branch, discussed the reasons for the panel meeting and the information the FDA was seeking. He then presented the device description and the preclinical and clinical information. Mr. Goode clarified the three types of acetabular cups, standard, dysplasia, and bridging. Both the dysplasia and bridging cups are for dysplasia indications.

With regard to patient selection, prospective clinical investigations generally predefine the study population with specific inclusion and exclusion criteria so that the results can be generalized. In case series studies such as for this PMA, generalization is more difficult because the patients are not enrolled for predefined conditions. A complete review of Dr. McMinn's patients who either did not have surgery or who had conventional total hip replacements (THR) might have made it possible to retrospectively determine what criteria were used to select for BHR. Instead, the sponsor provided a list of factors that contributed to Dr. McMinn's decision to perform a THR rather than BHR. Factors included advanced age, low activity level, and poor bone stock.

The device is intended for patients requiring primary hip resurfacing due to inflammatory and non-inflammatory arthritis and for joint replacement in those at risk of future revision. He mentioned

the contraindications already discussed by the sponsor and also addressed problems resulting from notching the femoral neck and from placing the femoral component in varus. Mr. Goode then highlighted parts of the definition of valid scientific evidence.

He then discussed the study and noted that five implantations in the McMinn cohort were performed before April 2002 and should have been included in the Oswestry cohort. The three cohorts were pooled into two, the overall McMinn cohort, which included the X-ray, Oswestry, and McMinn cohorts, and the X-ray/Oswestry combined cohort. The overall McMinn cohort was used to assess safety, the X-ray cohort was used for the radiographic assessment, the X-ray/Oswestry cohort contributed to the assessment of survivorship and patient satisfaction, and the 1,111 unilateral hips in this combined cohort were used to assess pain and function data.

Mr. Goode noted that the pain and function data for the McMinn cohort were collected using the Oxford Hip Score and not OSHIP. These data were not tracked by the Oswestry Outcomes Center, but by the National Health Services Center, so the sponsor did not have access to the Oxford Hip Score data. The sponsor included data from 3,374 cases performed by 140 other surgeons worldwide, but the sponsor had no way to independently verify any of this data, and it was not a primary source for the PMA.

Safety data was collected from the Oswestry Outcomes Center (OOC) by annual questionnaires completed by the patient and from the McMinn Center based on post-operative patient visits and information provided by primary care physicians to Dr. McMinn. Eleven percent of the Oswestry/X-ray combined cohort was missing at least the last follow-up evaluation, but the OOC continued to attempt to contact these patients. The sponsor also included an analysis of the literature on metal ions, which incorporated an unpublished report by Daniel Zee and Dr. McMinn.

For effectiveness, the primary measurement was survivorship for procedures with a minimum of two years postop. Data were available for 90.8 percent of these procedures eligible for five-year follow-up. Data was collected using the same methods as for the safety data, and there was also data on the independent radiographic review of the X-ray cohort. Five-year AP and lateral view radiographs were compared to baseline radiographs, and success was defined as absence of radiolucencies or radiolucency in any one or two zones, component migration less than or equal to two millimeters, and change in acetabular angle less than five degrees.

Pain, function, and movement data were collected using the OSHIP scoring system, a patient self-assessment without direct physician evaluation. If the data were not collected, the score for any missing item was assumed to be zero, the lowest possible. The OSHIP system was designed to allow for long-term and large sample follow-up without the need for physician assessment and to eliminate the

potential for the bias physician administered surveys are susceptible to. The lack of physician assessment is the main difference between OSHIP and Harris Hip Score. The sponsor provided literature references to justify the use of the OSHIP score and asserted that the close correlation of the OSHIP and Harris Hip scores and the tendency of OSHIP scores to be somewhat lower suggest that OSHIP is a close and conservative estimate of the Harris Hip Score.

Mr. Goode then presented the results. In terms of safety, there were 27 revisions, ten due to femoral neck fracture, six femoral head collapse, one dislocation, two AVN, and eight due to infection. There were 2,912 adverse events in 1,669 of the 2,385 procedures, a rate of 70 percent. Mr. Goode returned to the metal ion literature analysis to state that there was not conclusive evidence that elevated cobalt and chromium levels have detrimental health effects.

For effectiveness, 98.4 percent of procedures were estimated to be free from revision at five years, and the only marginally statistically significant difference was between patients with osteoarthritis at 98.8 percent and avascular necrosis at 92.1 percent. From the radiographic data, three of the 108 procedures, 2.8 percent, were failures at five years. For pain and function data, based on the 1,111 unilateral procedures in the Oswestry/X-ray cohort, the mean OSHIP score improved from 60 to 94.8 at five years. For patient satisfaction, 99.5 percent were pleased or very pleased after five years.

The sponsor submitted two literature controls by D'Antonio and Garino. They appeared to have significant differences compared to the data for the BHR device, including the different evaluation scoring systems, length of follow-up, mean baseline pain and function scores, and indications for use.

Mr. Goode then discussed the applicability of the data, collected outside the U.S. by a single investigator, to the target U.S. patient and orthopedic surgeon populations. The sponsor provided a comparison of the racial and ethnic distributions of the U.K. and the U.S., but no such data on the patients studied for the PMA. The sponsor also provided a comparison of the demographic and diagnostic indications for the BHR study and the D'Antonio literature reference. The sponsor described Dr. McMinn's practice as similar to the standard in the U.S and provided a protocol for a post approval study

Chang S. Lao, Ph.D., Division of Biostatistics, Office of Surveillance and Biometrics, gave a presentation on the statistical summary. The basic statistical issues were generalization from data from one surgeon at one center to the U.S. surgeon population, the lack of control group, the nonrandomized nature of the study, and the combined retrospective and prospective data. Sample size justification for generalization to the general patient population is neither pre-specified hypothesis testing nor based on the confidence interval approach.

Dr. Lao next discussed the PMA statistical analysis. Looking at the five year survivorship data,

the real, non-hypothetical percentage who made it to the five year follow-up was about 21 percent. Dr. Lao discussed the issue of intermittent missing, that is, that many patients did not return for follow-up at one year, two years, etc., but did return for the five-year follow-up, and cautioned that one had to be careful making assumptions about what the complete data set would have looked like for those years.

The final issue from the statistical analysis was the correlation between OSHIP and HHS scores. One difference is that OSHIP evaluates the patient in three different areas, pain, function, and hip movement, and HHS has the additional area of domain of deformity. Dr. Lao showed the correlation between the two for each individual component. The overall correlation was 91 percent with a 95 percent confidence interval. However, there was a potential for bias due to the masking and randomization issues. Linear regression analysis was done to see how well HHS could be predicted from OSHIP. Dr. Lao looked at other ways to compare the two scores, including total mean score and binary outcomes.

Dr. Lao summarized the basic statistical issues. Because of the single investigator, generalization to other physicians or centers could not be justified. Also, the post-hoc justifications for sample size, patient selection, and inclusion/exclusion data could not be statistically evaluated. There was no pre-specified masking, HHS/OSHIP order randomization, or sample size determination for correlation studies. Another issue was the incomplete or missing OSHIP data and the fact that assumptions about this data could not be statistically tested.

The statistical conclusions based on the available data were mean age of 53 with a range of 12 to 86, 27 revisions with two occurring after the five-year follow-up, over 98 percent survivorship, mean OSHIP score at five years of 94.8 percent, 92.8 percent excellent or good at five years, and .91 correlation coefficient.

PANEL DELIBERATIONS AND FDA QUESTIONS

Dr. Mabrey gave a presentation comparing resurfacing with total hip replacement. In a total hip, the femoral neck is replaced and there is no femoral stem. Advantages of resurfacing are the conservation of bone and thus a reproduction of anatomic hip mechanics and easier revision than with total hip athroplasty. Dr. Mabrey discussed the evolution of design of hip resurfacing arthroplasty beginning with the Smith-Petersen Mold.

Femoral neck fractures usually result from a femoral head defect or an error in implantation. The surgical technique is demanding. Appropriate angle of implantation of the head must be maintained, and one must avoid notching the femoral neck and impingement. When implanting the acetabulum, exposure is more challenging than in a total hip since the femoral neck and portions of the

head remain in place.

A key concern is differences in stress distribution. Resurfacing concentrates stress at the femoral neck. Thinning of the medial femoral cortex can result from stress shielding, and acetabular fixation can also be a problem.

Another issue is metal on metal ion levels. Levels in patients with resurfacings have been shown to be significantly higher than those in patients with metal on metal total hip arthroplasty. Dr. Mabrey discussed a study of metal on metal hip replacement by Harlan Amstutz.

In summation, Dr. Mabrey stated that metal on metal hip resurfacing is prone to high concentrations of cobalt and chrome ions, and femoral neck fracture is a problem unique to this family of devices. He also pointed out that similar devices were currently being tested within the U.S. and that femoral head resurfacing arthroplasty is not a standard procedure taught in U.S. orthopedic residency programs.

Dr. Mayor asked about the carbon content and surface roughness and about the screws locking into the threaded lug in the final phase of insertion. Mr. Band declared that the carbon content was indeed between .25 and .35 percent weight and the surface roughness was maximum .05 microns RA. He also acknowledged that the dysplasia screw engages in the cortical bone but noted that as it enters the acetabular component the thread is timed for full engagement so there is no leverage of the dysplasia. Dr. Mayor then asked whether the cobalt chrome beaded surface was really a coating, and Mr. Valez-Duran agreed that it was a fully integrated cast surface. Dr. Mayor then inquired whether it was fair not to have done abrasion testing, and Mr. Band said that abrasion testing was done. Mr. Goode stated that the sponsor had said the strength of the surface would be similar to the substrate as a justification for not doing abrasion testing exactly as described by Dr. Mayor.

Dr. Mayor asked about one component that showed considerably higher wear rate. **Anthony Unsworth, Ph.D., Professor of Engineering and Director of the Centre for Biomedical Engineering, Durham University, U.K.,** said that some specimens, though produced to the same specifications, do show higher wear rates but that they normally restore themselves after many cycles. Dr. Mayor then asked about surface topography only being measured in the polar region. Dr. Unsworth stated that it was difficult to get the lens inside the cup since the topography is done by a non-contacting method so as not to damage the surface.

Dr. Mayor then asked why a resurfacing BHR would not be done on 70 year old person with favorable bone stock and habitus given that revision is so much easier than with a total hip arthroplasty. **Cecil Rorabeck, Orthopedic Surgeon, Professor of Surgery, University of Western Ontario, London Health Sciences Center, Ontario, Canada,** stated that the procedure should be done on

patients with bone stock that's reproducibly good with time, meaning males under age 65 and females with normal DEXA scans, likely less than 60 years of age. He stated that there wasn't scientific evidence for that, but given that patients are likely to become more osteoporotic over time and the potential for neck fracture, the procedure should be restricted to patients under 65 with normal bone density.

Dr. Mayor then asked about the potential for a saturation problem with regard to the metal ion concentrations in light of data from Dr. Josh Jacobs that showed that patients with bilateral total hips had more than twice the serum levels as unilateral patients. **Joseph Daniel, FRCS MS, Staff Orthopedic Surgeon, Birmingham Nuffield Hospital, and Director of Research, McMinn Centre, U.K.**, said there was a confounding factor in the article which showed that resurfacings produced higher levels of ions and that Dr. Jacobs had found no difference between a 28 millimeter replacement and a larger diameter resurfacing. With regard to the renal threshold for metal ions, Dr. Daniel stated that research was ongoing that seemed to show that blood levels did not increase as much as urine levels when patients who had one resurfacing came back for a quadrilateral. He also pointed out differences in the techniques they were using compared to Dr. Jacobs. Dr. Daniel admitted that the levels did more than double, and Dr. Naidu asked for clarification. Dr. Daniel stated that the urinary excretion of metal ions went up three times, not the whole blood levels, suggesting that the kidneys still had capacity to take in and excrete the ions.

Dr. Mayor finally asked whether the sponsor had designed a revision system to assure that a conversion from a resurfacing to a total hip stemmed implant would yield a good fit between the head and cup. Mr. Band replied that there was a full modular system for such a purpose.

Dr. Skinner returned to the issue of renal function. He observed that the sponsor had not addressed cobalt with regard to high activity levels and wondered whether the device should be contraindicated in patients likely to have renal failure. Dr. Daniel replied that they had found no correlation between activity and cobalt or chromium levels. Mr. Velez-Duran said that the sponsor was planning to contraindicate the device for patients with borderline renal failure. Dr. Skinner then pointed out the connection between diabetes and hypertension and thus renal problems. Mr. Velez-Duran replied that the sponsor would discuss that issue with the FDA.

Dr. Skinner asked Dr. McMinn whether, given the rather sizable incision required for adequate exposure, the procedure should be relatively contraindicated for a mini incision. Dr. McMinn said that he had been doing mini incision resurfacing for some years. The sponsor found no correlation between incision length and the objective data recorded. Patients who had had a resurfacing done both ways almost uniformly preferred the smaller incision. Dr. McMinn stated, however, that the mini incision

was more difficult and that he instructs surgeons not to use it until they are really proficient. Dr. Rogerson stated that patients seem to have less pain with larger incisions and that patients are generally not concerned with the size of the incision.

Ms. Whittington questioned whether there was screening done to determine a patient's level of kidney disease and proposed that the labeling information should be more detailed about renal insufficiency, as well as avascular necrosis, so patients would understand why the procedure was not indicated for them. Mr. Velez-Duran stated the sponsor would work with FDA on those concerns. Dr. McMinn said that his average patient age was 53 and that it was rare to find significant renal problems in fit 53 year old individuals. Ms. Whittington returned to the idea of a screening since people with chronic kidney disease are not always aware of their disease. Dr. McMinn stated that all patients have creatinine and urea screenings before surgery.

Ms. Adams inquired whether the labeling the panel had was for physicians only or whether it would also be the labeling that consumers would see. Mr. Velez-Duran said that specific patient labeling would be developed. Ms. Adams reminded the sponsor about questions asked previously regarding patient deaths and whether there was a correlation between infections and revisions. Ms. Marlow said the average age of the patients who died was 63 and presented a table showing age at time of death and cause of death. Ms. Adams asked whether any deaths had been associated with the device, and Ms. Marlow said that none had. Mr. DeMuth addressed the question about infections and said there were more revisions in patients that did not have wound exudates, and in only one of the four patients with wound exudate and a revision was there a relation between the exudate and the revision.

Ms. Adams then asked whether there was any financial disclosure or conflict of interest information related to three letters that were submitted. Ms. Scudiero said that the letters were received without any additional information. Ms. Adams then asked the sponsor whether they had made the appropriate financial and conflict of interest disclosures for the PMA. Mr. Velez-Duran stated that the appropriate disclosures were submitted to the FDA, and **Mark Melkerson, M.S., FDA**, stated that the PMA would not be before the panel if the disclosures had not been made.

Dr. Kim inquired about the learning curve and how many cases one would need to do before one was able to perform the surgery reliably. Dr. Rorabeck stated that after all the necessary training perhaps ten procedures would need to be done before a surgeon got to a level of comfort, though he noted that it would depend somewhat on patient selection. Dr. Kim then asked if there was a quantitative value in terms of adequate bone stock. Dr. Rorabeck replied that a patient with Type A or B bone stock would probably be a good candidate for resurfacing. Dr. Kim asked about what metal ion concentrations would be detrimental to health. Dr. Rorabeck stated that the sponsor did not know the

answer but that the concentrations fell within acceptable levels established by ministries of labor in various countries. Dr. Daniel presented data from a study that tracked 579 metal-metal total replacements for 30 years and found no difference in cancer rates as compared to the general population and also from one publication that showed blood serum metal ion levels were not recordable in umbilical cord blood.

Dr. Mabrey sought clarification of whether all of the acetabular cups evaluated were HA coated, and done so using the same application technique, and Mr. Band stated that there had been no design changes. Dr. Mabrey then asked what percentage of cases the sponsor anticipated would require use of the dysplasia cups. Dr. McMinn replied that he had used 176, a rate of around seven percent, but said that it would depend on the experience and confidence of the surgeon in terms of what he or she was willing to take on. Dr. Mabrey asked whether the labeling would be restricted as to the Crowe type, and Dr. McMinn said that it would be left up to the surgeon. Mr. Velez-Duran suggested that it could be addressed in the surgeon training. Dr. Mabrey brought up the high incidence of diabetes in the Mexican American population. Ms. Marlow said that it was a good point to consider and that cities with high Mexican American populations might need to be selected for the post approval study.

Dr. Blumenstein gave a presentation on the statistical issues. He first addressed minor issues, such as that estimation of survivorships was wrong because competing risks were either lost to follow-up or, in the case of death, censored. Also, data collection practices in the study were substandard, the criterion for success was unplanned, and there was a single site in another country with a single surgeon. Dr. Blumenstein then addressed the idea of an unmet medical need, which is the type of situation where a cohort or case series study would be appropriate. Though the BHR was the first device in its class, it was not the first intervention for the disease. In fact, there was an effective predicate intervention, and safety and effectiveness could not be adequately characterized without comparison to the existing intervention.

The highest standard for comparing interventions is the randomized clinical trial, but the PMA used a single cohort study with comparison to historical data. The differences in effect are confounded by cohort differences. He referred to meta analysis and described the study before the panel as the least valid sort.

Dr. Kim asked about the relation between the ten percent loss to follow-up in some of the groups to the survivorship of over 95 percent and wondered what effect that ten percent could have if it included a high percentage of failures. Dr. Blumenstein replied that there were actuarial methods to estimate what the survivorship would be and said that the estimate used was not valid because deaths were censored. He stated that incomplete follow-up, in and of itself, was not necessarily a problem. Dr.

Kim then asked the sponsor what the survivorship would be if one were to assume the worst case scenario for those lost to follow-up.

Mr. Velez-Duran responded to Dr. Blumenstein's presentation by stating that the literature controls were selected after a full review of the available literature and that the scarcity of randomized clinical studies published on orthopedic devices would limit any meta analysis. He also pointed out that whatever method was used to calculate survivorship, there were only 27 revisions in a very large cohort. Dr. Rorabeck addressed the issue of a randomized clinical trial and said the problem is that patients come in requesting a specific procedure, so there are potential ethical issues involved with randomization.

Dr. Skinner asked whether a patient's death would tend to make the survivorship better since that patient would no longer be at risk for a revision, and Dr. Blumenstein said that was correct and that the methodology for estimating survivorship was wrong.

1. Please discuss the evaluation methods used to collect safety data (i.e., data on revisions, adverse events, deaths, metal ion literature analysis) and whether or not these methods are reliable to assess the safety of the device.

Panel members were divided on this question. Some panel members stated that although the data were imperfect, the methods were adequate given FDA's definition of valid evidence. Others said that the lack of prospective design and methods used to extract the data from the records were inadequate or that the data was representative of Dr. McMinn's skills and not that of a larger group of surgeons. Other panel members said that it was adequate given Congress's mandate that FDA find the least burdensome ways to bring devices to market. The sponsor clarified that the registry and the method to collect the data were set prospectively in 1997.

2. Please discuss the evaluation methods used to collect effectiveness data (i.e., data on survivorship, OSHIP score, radiographic, and patient satisfaction) and whether or not these methods are reliable to assess the effectiveness of the device.

Panel members agreed that it was appropriate to collect data from the patient self-assessment in that this would eliminate the potential for bias with physician-administered questionnaires. One panel member took issue with the use of OSHIP as opposed to the Harris Hip Score and with the sponsor's statement that the data was collected prospectively given the three different cohorts. The sponsor replied that the cohorts were simply a means of identifying which patients had which data and said that the Oswestry Center had developed the OSHIP questionnaire because patient self-assessment had been proposed in the literature as a potentially better assessment of pain and function. Another panel member wished there had been other scores by which to judge whether the OSHIP was equivalent to the Harris Hip Score. One panel member stated that the methods would have been adequate for an unmet medical

need but that there was not enough compatibility to allow for cohort comparison. Another panel member stated that the data demonstrated the effectiveness of the device as used by the single investigator.

3. Please discuss whether or not the foreign data from a single investigator and U.K. practice of medicine is applicable to the target U.S. population and practice of medicine.

Panel members were not concerned that the data came from the U.K., but a majority thought the data was not applicable to the general practice of orthopedic surgery given that the data came from a single investigator. Some panel members thought that the study was done very similarly to how it would have been done in the U.S. as far as using a highly skilled surgeon in a referral practice except that there would have been more than investigator. Another panel member was concerned about the single investigator but thought the additional data from140 other surgeons was reassuring, as well as the extensive training plan proposed and the sponsor's offer to do an extensive post approval study.

4. Based on the safety data in 2,385 patients in the Overall McMinn Cohort (i.e., data on revisions, adverse events, deaths) and the analysis of the metal ion literature, please discuss whether or not you believe that the data contained in this PMA provide reasonable assurance of safety.

Panel members were in agreement that the data provided a reasonable assurance of safety.

5. Based on the:

- **5-year survivorship analysis of the 1,626 procedures in the X-Ray/Oswestry combined effort;**
- **5-year radiographic data of the 124 procedures in the X-Ray cohort;**
- **5-year pain and function (OSHIP) data of the 1,111 unilateral procedures in the X-Ray/Oswestry combined cohort; and**
- **5-year patient satisfaction analysis of the 1,626 procedures in the X-Ray/Oswestry combined cohort;**

Please discuss whether or not you believe that the data contained in this PMA provide reasonable assurance of effectiveness.

The panel was in general consensus that the data provided a reasonable assurance of effectiveness. One panel member thought the methodology was significantly flawed such that an effectiveness determination could not be made. One panel member thought that data would have showed efficacy if the device were treating an unmet medical need but thought it should have been compared to predicate devices.

6. Do the patient selection methods and data presented on the BHR device support the proposed labeling indication?

Please comment on any other aspects of the product labeling, such as:

- **Contraindications**
- **Warnings**
- **Precautions**
- **Potential Adverse Effects on Health**

The panel generally believed that the data presented supported the proposed labeling indication but expressed concerns regarding metal ion release and renal insufficiency. One panel member said that

the labeling should indicate the lack of information on the adverse health effects of metal ion release. Another panel member said that the patient labeling should be effective for the patient since physicians do not read patient labeling to their patients. Another panel member reminded the sponsor of the panel's concerns regarding GFR and creatinine.

7. A reasonable assurance of safety and effectiveness as defined in questions #4 and #5 above must be demonstrated for device approval. If you believe the data in the PMA demonstrate a reasonable assurance of safety and effectiveness but think there are remaining specific questions regarding this device that should be addressed in a post-approval study, please identify those questions.

Some panel members thought that there should be long-term follow-up in a post approval study. Some panel members thought the proposed study was poorly controlled and recommended a randomized clinical trial or further follow-up on some of the single investigator's first patients. One panel member urged that a study should evaluate issues with the learning curve.

SECOND OPEN PUBLIC HEARING

Craig Thomas, Orthopedic Surgeon, Washington, D.C., addressed the issue of learning curve with respect to surface arthroplasty. He stated that there was a learning curve but that it could be improved. He also addressed the issue of limp and stated that limp was common for all hip patients both before and after surgery. He addressed the question of age limit and said that it would be inappropriate to put a limit on the procedure. Dr. Thomas agreed that resurfacing could be done with small incisions and that surgeons should not be initially trained to use a small incision. With regard to avascular necrosis, he said that the decision should be left to the physician and patient and that the final decision could be made intraoperatively.

Dr. Thomas thought the panel was overly critical of the data given that each of the components of the device could be used separately as FDA-approved devices and could be used together if not for the presence of the stem.

FDA AND SPONSOR SUMMATIONS

The FDA had no further comments. Mr. Velez-Duran thanked the panel members for their time and effort.

PANEL VOTE

Ms. Scudiero read the voting options. Dr. Naidu called for a motion. Dr. Mabrey moved that the PMA be approved with conditions, and Dr. Mayor seconded the motion.

Dr. Mabrey moved that the first condition be a post approval study with some radiographic follow-up at ten years; Dr. Mayor seconded the motion.

Dr. Blumenstein asked for a friendly amendment that the size of the study be based on statistical principles and criteria for success. Dr. Mabrey and Dr. Mayor accepted the amendment.

Dr. Skinner said that the ten year data would not be available until after the procedure had been abandoned or been found widely adopted and suggested that long-term data should come from further follow-up of Dr. McMinn's patients.

Dr. Naidu restated the first condition as post market approval study as proposed by the sponsor plus radiographic and clinical follow-up at ten years which is statistically significant. The motion was approved unanimously.

Dr. Blumenstein moved for a randomized controlled trial to compare to a predicate device. Mr. Melkerson pointed out that a need for new clinical data to support efficacy would be a reason to not approve the device.

Dr. Kim moved for limited release of the product based on the statistical need of the numbers of patients required for the post market approval study. Mr. Melkerson stated that approval of a product is approval for general distribution, and Dr. Kim retracted his motion. Dr. Mabrey asked the sponsor to clarify whether their roll-out plan would initially restrict the device to fifteen champion surgeons, and Mr. Velez-Duran said that was correct then retracted his statement. Dr. Marc Thomas clarified that the sponsor would not limit it to fifteen surgeons but rather would seek a geographical representation of U.S. surgeons to train in the U.K. so they could return and eventually train their fellow surgeons.

Dr. Naidu called for a vote on the motion to approve with one condition. The motion passed 3-2.

Dr. Skinner stated that data showed the device was safe and effective. He noted that although he thought the post market study was unreasonable, it was better than the alternative, and he held the same position with regard to the motion that was passed.

Dr. Kim said the technology was promising and that there was a need for an alternative for younger, more active patients likely to outlive a total hip replacement, but he felt the data provided was insufficient to make conclusions about safety in terms of the learning curve with regard to widespread use and about safety and effectiveness when used by the general U.S. surgical population. Dr. Kim urged device sponsors in general to collect more meaningful and compelling data which is applicable to the U.S. population.

Dr. Mabrey said the clinical efficacy had been demonstrated and thanked Dr. Thomas for his comments regarding the learning curve and applicability to U.S. surgeons. He made an analogy to the use of mini incisions for total hip replacements, which had a steep learning curve and required no FDA

approval, and noted that the early adopters of that practice passed on knowledge learned from their own early mistakes.

Dr. Blumenstein echoed Dr. Kim's comments especially with regard to the lack of information on variability among surgeons and reiterated his view that there was not an adequate control.

Dr. Mayor stated that regardless of the design of the study he had been reassured of the device's safety and effectiveness. He also noted that future applicants should not assume that money can be saved by following the example of this PMA.

Ms. Adams reiterated her comments regarding the Congressional mandate for safe and timely introduction of new medical products and emphasized FDA's goal of considering alternatives to randomized controlled trials, valid non-U.S. data, paper PMAs, and literature controls.

Ms. Whittington noted that the public is always interested in better therapies and that the post market study would ensure that the device was safe across sites. She emphasized education of practitioners and the public about use of the device in the right person at the right time.

Dr. Naidu stated that he supported approval of the device because there was enough valid scientific evidence in spite of problems with the study design. He observed that PMAs based on a retrospective design based on a single surgeon's experience had been previously approved and noted that it was an innovative device that was needed.

ADJOURNMENT

Dr. Naidu adjourned the meeting at 4:22 p.m.

I certify that I attended this meeting of the Orthopedic and Rehabilitation Devices Advisory Panel Meeting on September 8, 2005 , and that these minutes accurately reflect what transpired.

Janet L. Scudiero
Executive Secretary

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

Sanjiv H. Naidu, M.D., Ph.D.
Acting Chairperson

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