SUMMARY MINUTES

MEDICAL DEVICES ADVISORY COMMITTEE

ORTHOPEDIC AND REHABILITATION DEVICES PANEL

February 22, 2007

Hilton Washington DC North
Gaithersburg, MD.

ORTHOPEDIC AND REHABILITATION DEVICES PANEL MEETING
February 22, 2007

Attendees:

Chairman:

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

Industry Representative:

Pamela W. Adams, M.S., R.A.C., C.Q.M.
Etex Corporation, Inc.

Consumer Representative:

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

Deputized Voting Members:

Michael B. Mayor, M.D.
Dartmouth Medical School

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

Sharon-Lise T. Normand, Ph.D.
Harvard Medical School

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

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

Executive Secretary:

Ronald P. Jean, Ph.D.

FDA Representative:

Mark N. Melkerson, MS

CALL TO ORDER

Executive Secretary Jean called the meeting to order at 8:10 a.m. and read the Appointment of Temporary Voting Members and the Conflict of Interest Statement into the record. All members were found to be in compliance, and Dr. Mayor was granted a waiver to allow his participation. Dr. Mabrey was appointed the Panel's new Chairperson; Dr. Propert was appointed a Voting Member.

Chairman Mabrey introduced the meeting on the approvability of PMA P050016 for the Corin Cormet 2000 Hip Resurfacing System, intended for use in resurfacing hip arthroplasty for reduction or relief of pain and/or improved hip function in skeletally mature patients with non-inflammatory degenerative arthritis or inflammatory arthritis. He had the members introduce themselves and noted the presence of a quorum.

DIVISION UPDATE

Dr. Jonette Foy gave an update on the Orthopedic Joint Devices Branch's activities since the last meeting. Upcoming Panel meetings were tentatively scheduled for March 27 and 28, 2007 and May 22 and 23, 2007. Several items were under review or had recently had FR notices published on them. There was a reclassification for bone heterograft, an exemption petition for cranial orthoses, and a reclassification petition for non-invasive bone growth stimulators. Guidance documents were in the works on several subjects: interbody fusion, cartilage, artificial discs, femoral stems, and clinical data on hip systems. Though coming from outside of the branch, the guidance documents on sterility and post-approval studies would affect Orthopedics. She gave an update on staff changes and encouraged participation from individuals outside of the agency.

OPEN PUBLIC HEARING

Executive Secretary Jean read the conflict of interest statement for the public hearing, urging speakers to disclose any conflicts or relevant financial relationships.

Dr. Justin Cobb of Imperial College in London said he has been using the Cormet device for 4 years. In Britain, where hip resurfacing is a common procedure, he has performed 188 resurfacings. He said the procedure was safe, especially compared to the alternatives. His lab measures safety by three categories: revision rates, function, and metal ions. Chromium levels are elevated in the blood of metal-on-metal (MOM) patients, but the ions appeared to have no effect. The function of the device is good, and it allows activity that increases overall health, compared to hip replacement. The revision rate matched the learning curve, and appropriate training would minimize the learning curve. His travel was paid for by the Sponsor, and the Sponsor is a backer on one of his projects.

Mr. Steven Kahn, representing OSMA, said the FDA serves a dual role: to protect the public and to foster innovation. He emphasized that the Panel should look for reasonable assurance of safety and valid scientific evidence in its deliberations. He asked the Panel to remember that the standard of reasonable assurance involves balancing risks

with safety. He said he had no ties to the Sponsor and appeared on behalf of his association.

Anna Benson-Gyles, a device patient, said she developed hip problems in her 50s and had a Corin resurfacing in 1996. Due to bone wear and osteolysis, the implant came loose, and she had a hip replacement and bone graft in 2005. The metal used in 1996 was double heat treated, causing increased wear. Of 1996 Corin patients, one third were showing signs of impending failure and 14 percent had hip failure. The Cormet 2000 was derived from the McMinn Corin resurfacing she had, and the double heat treating was still being used in the PMA device. She noted that the 1994-1995 patients received resurfacings that were not double heat treated and showed much better results. She paid for her own travel from England and said she had no affiliation with the Sponsor.

Dr. Michael Mont of Sinai Hospital of Baltimore said he had performed 1,200 resurfacings, 650 MOM, and that all resurfacings were similar in design, application, and quality. In his participation in the Wright Medical IDE, he recalled that there were a number of fractures in the first 50 patients until the indications and techniques were improved, which virtually eliminated fractures. Education was the key to avoiding device failure and adverse events, so he urged eliminating the learning curve with an education program for surgeons. He said he had consultant relationships with several companies but did not think he had a conflict in this case.

Eric Miller, a device patient, said that he was happy with the results. The device has changed his condition from nearly crippled to mobile. His device was three years old, and he acknowledged the need for long-term studies. He said that if the device lasts only ten years, that's a decade of increased mobility before a total hip replacement is needed. He had no other affiliation with the Sponsor.

SPONSOR PRESENTATION

Richard Sharp, Regulatory Affairs Director, introduced the presentation and presenters. In 2005, Stryker Orthopedics and Corin entered a strategic alliance. Stryker assisted with the PMA and the presentation.

Simon Collins, PhD, Technical Director, presented on the device description and preclinical testing. Cormet is a MOM resurfacing system for conservative treatment of the hip. It has been in clinical use outside the US since 1997. It is a hybrid device, with a cemented resurfacing head component to articulate in a cementless monoblock acetublar cup. The device is manufactured from a high carbon cobalt chrome molybdenum alloy. The resurfacing heads are available in five sizes, from 40 mm to 56 mm. A centrally distally polished stem is used to prevent distal fixation and minimize proximal stress shielding. Three internal anti-rotation spines aid torsional stability. The cups are available in sizes from 46 mm through 62 mm. The design employs 2 sets of external anti-rotation spines, usually in the ischium and the pubis. A dual plasma sprayed layer of hydroxyapatite is deposited over a titanium alloy coating to complete cementless fixation. The head is a predefined amount smaller than the cup to promote lubrication. The surfaces are highly polished, and sphericity is tightly controlled. This results in a low-friction, low-wear device. The device complies with ASTM F74 and ISO 5832-4 for biocompatibility and metallurgy. The material has been used in orthopedics for over 50

years. The device is investment cast, then double heat treated. The process improves mechanical properties, reduces microporosity, and promotes homogeneity.

Preclinical tests included range of motion studies, coating characterization, mechanical tests for failure loads and modes, frictional torque tests, wear tests, and luxation tests. Two major wear studies were published, one looking at head diameter for effects on adverse and standard gait, the other looking at wear channels between as-cast and heat-treated bearings and finding no difference. A range of motion analysis by CAD and sawbone simulation showed the device to exceed ISO 21535 requirements. The titanium coatings were test-validated and are in accordance with the FDA's 2000 guidance document on metallic plasma spray coatings for orthopaedic implants. The hydroxyapatite coating was validated in accordance with the 1995 guidance document for hydroxyapatite-coated orthopaedic implants.

He concluded that the device is based on robust design principles and previous experience, which allowed improved metallurgy over previous generations. The preclinical studies showed that the device met standards and should perform well in vivo.

Bernard Stulberg, MD, a clinical investigator in the IDE and a consultant for Stryker, discussed the history of hip resurfacing in the US and the study design. Hip resurfacing arthoplasty has arisen through three generations. The first generation was mold/interpositional arthroplasty introduced in the 1920s and used through the '60s. In the '70s, the second generation, cemented metal/poly resurfacing hip arthoplasty, was introduced. The first and second generation devices proved unsatisfactory in device performance and implantation technique. The third generation is the MOM hybrid hip arthoplasty. The Cormet was introduced in 2001, employing improved manufacturing technologies and improved understanding of implantation. Over 12,000 have been implanted worldwide.

Hip resurfacing in the USA started with the 1996 Wright Medical IDE. The Cormet IDE began in 2001. Worldwide published experience with third generation resurfacing became available in 2004, after the Cormet IDE's enrollment ended. The publications helped identify important risk factors: female gender, small component size, bone quality, and large femoral cysts. The trial design preceded the availability of this data. The radiographic criteria were changed to be more consistent with current practice and recent literature. The timing also affected the control, since young patients were unwilling to be randomized between the device and total hip arthoplasty (THA). He said that the study results confirmed conclusions in the literature identifying the appropriate patient population and that the clinical and radiographic results were good to excellent.

The study was designed to assess the safety and effectiveness profile for the Cormet device by evaluating peri-operative and post-operative performance, including complications. Additionally, it was to demonstrate the non-inferiority of the Cormet Implant System relative to a THA control with regard to likelihood of clinical success at 2 years. The study was a prospective, multi-center, non-randomized, controlled study. The primary endpoint was a composite clinical success (CCS) of improvement in Harris Hip Score (HHS), radiographic success, absence of revision, and absence of device-related adverse events. CCS was evaluated at 2 years. Eligibility criteria were that the patient have reached skeletal maturity, be a candidate for THA, have no severe infection, have no severe osteoporosis, not be morbidly obese, and have a peri-operative Harris Hip Score (HHS) below 70.

As the study evolved, the control group was changed and two of the CCS criteria changed. Since patients eligible for resurfacing would not accept THA, a historical control was applied, the Howmedica Osteonics Alumina-Bearing Couple (ABC) using the Omnifit System, which was approved in 2003 and is targeted to the same population as Cormet. The original CCS HHS criteria defined a 20 point or greater improvement from baseline to two years as success. Since a patient could have an improvement of 20 but still have a low score, the criterion was changed to a HHS of 80 or better. The radiographic criteria were modified, since a femoral tilt of less than one degree is not radiographically reproducible and meaningful as a clinical parameter. The revised radiographic failure criteria looked for a shift in the stem and radiolucencies in the three Charnley DeLee zones and the modified Gruen zones. This was consistent with the literature and the criteria used in the control's PMA. The changes made the CCS and control more relevant and challenging.

The final PMA study was a prospective, multi-center, non-randomized controlled study. The ABC ceramic on ceramic total hip was the control. The primary endpoint was the modified CCS: a HHS greater than or equal to 80, radiographic success as redefined, absence of revision, and absence of device-related adverse event. CCS was evaluated at 2+ years. The Cormet and ABC IDE studies were comparable.

Marybeth Naughton of Stryker Orthopaedics presented a summary of the clinical studies. Clinical success was established through the analysis of clinical study results in a pivotal unilateral patient group of 337 subjects enrolled between 2002 and 2003 at 12 sites. The control group enrolled 266 subjects at 13 sites between 1996 and 1998. The target follow-up, 85 percent, was met. The baseline characteristics of the ABC and Cormet subjects were well-matched in age, gender, mean weight, diagnosis, and mean pre-operative HHS. Nearly 77 percent of the heads in the study were size 48 or larger, and size was highly correlated to gender, females using smaller femoral heads.

HHS assesses pain, function, absence of deformity, and range of motion. It is a 100 point test, and it weighs pain and function heavily. Both Cormet and the control showed excellent HHS improvements. Cormet had a mean 50.1 score at baseline, 96.7 at month 24. ABC showed a mean 49.7 at baseline, 96.2 at 24 months. More than 95 percent of patients in both groups had an improvement of 20 points or more and a HHS score of 80 or more.

In the radiographic success criteria, patients with revisions were excluded. At month 24, over 98 percent of the 281 Cormet patients evaluated had no reportable radiolucencies. On the acetabular side, two patients had radiolucent lines in zone III, though none had lines in all three zones. One patient had radiolucencies in all three zones on the femoral side, leading to revision. One patient had a radiolucency in the tip only. No acetabular component migration and tilt was seen. Under the modified criteria, 96 percent of the femoral components were a radiographic success. Nearly 75 percent of the patients had a femoral tilt of one degree or more. However, tilt did not seem to affect clinical results.

As for adverse events, 51 percent of Cormet patients and 65 percent of control patients experienced a complication. In the Cormet group, 83 patients had hip-related events, 32 of which were device-related, 28 serious. These events were all post-operative. The control group had 81 adverse events, 21 device-related, of which 6 were operative, 15 post-operative. The events reflected the different risks inherent to

resurfacing and THA. Cormet events were similar in magnitude and nature to those associated with hip resurfacing in the literature. When patients from both the unilateral and bilateral studies were combined, the Cormet group showed a 5.1 percent device-related event rate, the control showed 7.7 percent. Cormet had 2.3 percent femoral neck fracture, compared to 2 percent in ABC. Cormet had a dislocation rate of 0.2 percent, compared to 2.9 percent in the control. All adverse events were comparable to the literature and raised no new issues for THA or resurfacing.

Kathy Trier, PhD, Director of Clinical and Regulatory Affairs, spoke on the CCS and revision analysis. The primary objective was to demonstrate non-inferiority of Cormet with regard to clinical success at 24 months relative to control. CCS proportions were compared using a non-inferiority delta of 8 percent. Both Cormet and control showed an 86-88 percent success rate for CCS. The observed differences between the two groups were small, always below 8 percent. This demonstrated noninferiority.

Supporting analyses included sensitivity analyses to assess the impact of out-of-interval clinical assessments and other assumptions, propensity scores to assess selection bias, and multiple imputation analysis to assess the effects of missing clinical outcomes. The sensitivity analysis showed a less than 5 percent difference between Cormet and control in all 4 analysis populations. Non-inferiority was demonstrated in 3 of the 4 populations. The propensity analysis was designed to adjust for selection bias due to age, gender, weight, baseline function, or baseline pain. The adjusted differences were smaller than the unadjusted differences. Any difference in the populations did not affect the non-inferiority conclusion. The multiple imputation analysis minimized bias due to missing data. Differences among the imputations were not significant, and non-inferiority was met using a multiply-imputed cooled confidence interval. Potential bias from missing clinical outcomes did not affect the non-inferiority conclusion for CCS. These supporting analyses demonstrated the robustness of the non-inferiority conclusion.

At month 24, the Cormet study had 16 revisions, 4.7 percent. The pivotal unilateral study had 7.1 percent revisions; the all- enrolled group had 3.8 percent. (The unilateral study had longer follow-up, so the numbers are not comparable.) ABC had 3 revisions, 1.1 percent. Revision analysis demonstrated that 4 factors were significant predictors of revisions: small component size, a diagnosis other than osteoarthritis, preoperative leg length discrepancy, and HHS scores below 44. Multiple risk factors had a cumulative effect on risk of revision. When risk factors were taken into account, survivorship of the device was comparable to control. Site 5 had a significantly higher revision rate than other sites, but that site had a high occurrence of risk factors.

Richard Sharp reviewed the proposed labeling. Hip resurfacing arthoplasty is the primary joint replacement for patients at risk of requiring more than one hip joint replacement over their lifetimes. It is impossible to predict whether or not a patient will require a future hip joint revision, but several factors increase the risk, such as gender, age, weight, and activity level. The device is contra-indicated in patients with active or suspected infection in or around the hip joint, bone stock inadequate to support the device, skeletal immaturity, distant foci of infection, a mental or neuromuscular disorder that would create an unacceptable risk of prosthesis instability fixation failure or complications in post-operative care; obesity, moderate or severe renal insufficiency, and known or suspected metal sensitivity. Women of childbearing age are contraindicated,

since the effects of metal ion release on the fetus are unknown. Appropriate patient selection and surgeon training are important for a successful outcome.

Cindy Schawe from Stryker Orthopaedics addressed surgeon education. The training and education of surgeons would be predicated on the US clinical experience and would focus on appropriate patient selection. Dedicated learning centers would provide a multi-tiered curriculum, including surgery observation, computer simulation, didactic presentations, a cadaver program, and dry bone and soft tissue dissection. The faculty to student ratio would be high, 1:2, with a mentoring program to provide ongoing support.

James C. Kudrna, M.D., Ph.D. of Northwestern University gave a risk/benefit review. The risks of MOM hip resurfacing are femoral neck fracture, femoral head loosening, potential revision, and metal ion release. In the study, 48 percent of revisions were due to femoral neck fracture. Proper patient selection and proper surgeon training and technique (careful templating, correct femoral neck centering, and avoiding notching the femoral neck) can reduce this risk. Femoral loosening caused revision in 1.2 percent of study patients. Proper patient exclusion and surgeon training reduces this risk as well. Appropriate surgical technique should include cementation and proper component placement. The release of metal ions can be reduced by quality control in device production and proper cup placement during surgery. However, no adverse health effects have been reported due to elevated metal ions. The benefits of the device are the preservation of bone stock, reduced proximal stress shielding, low wear compared to metal on polyethylene, enhanced stability, and improved options for revision. The device shows fewer operative complications than control, a lower rate of dislocation, better and quicker return to function, and a low revision rate in appropriate patients.

PANEL QUESTIONS FOR THE SPONSOR

The Panel asked a number of questions for the Sponsor to address in the afternoon. **Chairman Mabrey** asked about patient selection. **Dr. Schmalzried**, a consultant to Stryker, said patient selection evolved, giving surgeons access to information that allowed them to select the patients best suited to the procedure. The change in inclusion criteria reflected that progress. Patients are more likely to demand the procedure than before, but surgeons should make patients aware of the unique risks.

FDA PRESENTATION

Elizabeth Frank, M.S., Lead Reviewer, introduced the FDA Presentation. The purpose of the meeting was to request guidance from the Panel regarding some concerns with the Cormet study. Originally, the IDE proposed to enroll concurrent control subjects, but the PMA was based on a historical control. The primary safety and effectiveness endpoints were modified. FDA was also concerned with the revision rate.

The IDE protocol was conditionally approved in 2001 and fully approved in 2003. The original design was a prospective, multi-center, non-randomized, concurrently controlled clinical study to test the non-inferiority of the device compared to conventional MOM and metal on polyethylene THA, two control groups. No patients were enrolled in either control group. As a result, the Sponsor chose the Howmedica Osteonics ABC Ceramic on Ceramic System as the historical control. This control was chosen in 2006,

after the study was completed. No MOM historical control was used. The post-hoc selection of the control concerned the FDA.

The Sponsor also revised the CCS, changing the HHS endpoint to a score of 80 or higher, rather than the original 20 point or better improvement. The category of adverse events was not clearly defined until 2006, after discussions with the FDA. The radiographic measurement technique changed with every submission to the agency, and the radiographic success criteria changed between the IDE and the PMA. Acetabular radiolucency success criteria changed from not being present in any zone to not being present in all zones. The femoral subsidence axis femoral canal and femoral tilt varus/valgus categories were combined so that both must be present for failure. The new criteria appeared less stringent.

She pointed out differences between the inclusion/exclusion criteria for the device and for the control. The Sponsor had deformity of femoral head as an exclusion criterion at the investigator's discretion, which the control did not. Cormet patients were required to have a preoperative HHS below 70 points, but the control did not. Inflammatory arthritis patients were included in the Cormet group but not in the control. The Sponsor had asserted that the differences favored the control.

The approved protocol defined specific windows around each timepoint. The Sponsor did not abide by these and used expanded follow-up periods to evaluate patient success. This made time comparisons with the control difficult. At 24 months, follow-up was 60 percent. The Sponsor was allowed to evaluate subjects after 24 months to get follow-up rates up to 84.8 percent. Control follow-up was 96.5 percent.

The Sponsor's all-enrolled cohort consisted of 1,030 subjects 1,148 procedures. The pivotal study had 53 device patients with bilateral treatment, 102 procedures, and 83 control procedures. The unilateral group, considered the primary group for evaluating effectiveness, had 337 device subjects and 266 control subjects. In the unilateral cohort, the investigational study had more males than control (67.7 percent compared to 62.0 percent) and a higher rate of osteoarthritis (85 percent versus 83 percent). However, the only significant difference was age (a mean of 50.1 in the investigational arm, of 53.3 in the control). The all-enrolled cohort had demographics similar to the pivotal cohort.

Neven Popovic , D.V.M., M.D., Ph.D., addressed the clinical results of the study, focusing on HHS, radiographic evaluations, CCS, adverse events, and safety issues. HHS for patients with unilateral procedures at 12 months, both the investigational and the control arms, showed about 94 percent of the readings above 80. At month 24+, an improvement of 20 points or more was shown in 98.6 percent of the device patients and 95.8 of control patients. At month 24+, both device and control showed most of the patients at 80 or higher HHS (96.1 vs. 95.3 percent).

The radiographic success/failure criteria at month 24+ showed a 1.2 percent failure rate by the original criteria, but if radiolucency in all acetabular components is required for failure, there was no failure. Radiolucency was any femoral zone is present in 8 patients; radiolucency in all zones occurred in 2 patients. Cup migration and tilt was rare. Subsidence of the femoral component occurred in 3.7 percent of patients. Stem tilting of 1 degree or more was noted in 73.8 percent of patients, but the rate of tilt in combination with subsidence of the femoral component was 3.7 percent. Anteroversion of the head was observed in 21.3 percent of patients, retroversion in 33.8 percent. Lysis in any zone was 4.5 percent. The composite radiographic failure rate reported by the

Sponsor was 3.9 percent. While the CCS criteria changed over the course of the study, no appreciable difference was seen between the old and new criteria if radiographic success changes were not taken into account.

More neck-notching was seen with the device than control. At month 24+, there were higher instances of bursitis, femoral radiolucency, post-operative hip pain, leg length discrepancy, limp, apparent muscle weakness, and implant squeaking or clicking; however, the device showed fewer fractures and less soft tissue trauma than the control. Heterotrophic bone formation and infection rates were similar between the arms. Device-related adverse events showed higher rates of acetabular loosening, femoral loosening, femoral neck fracture, and femoral subsidence, compared to the control, which had more dislocations, femoral fractures, and ceramic insert chipping. The all-enrolled cohort had 44 total revisions. There were 24 in the pivotal unilateral cohort, 16 of them before 24 months. There were 5 revisions in the control group. Most device revisions were due to femoral neck fracture, femoral loosening, acetabular loosening, infection, or dislocation. Only one center showed evidence of a learning curve affecting revision rates.

Phyllis Silverman, M.S., gave the statistical review of the PMA. She first addressed the changes made to the control group and success criteria after IDE approval. Multiple analysis cohorts have an inflated probability of type 1 error. The validity of inferences drawn from statistical hypothesis testing is based on the integrity of the study design, conduct, and analysis. Changes made to the protocol weakened the validity and usefulness of the study. She noted that the non-inferiority delta was changed from 5 percent to 8 percent. A well-designed trial does not deviate from the original specifications.

In testing the non-inferiority hypothesis, the primary endpoint was the difference in CCS between Cormet and ABC. FDA asked the Sponsor to test the non-inferiority hypothesis using the original radiographic and HHS success criteria. Under the original radiographic criteria, approximately 75 percent of the Cormet patients failed, making them CCS failures; non-inferiority was not met. Using the post-hoc change of radiographic criteria but the original HHS criteria, all analyses but CCS in-window at month 24 met the non-inferiority delta. Using the modified HHS and radiographic criteria, non-inferiority is not shown at month 24+ but not at month 24.

It is important in a non-randomized study that the baselines of the two treatment groups be comparable. The investigational and control populations were similar and differed significantly only in age. The Sponsor had said the difference was clinically insignificant. A propensity score analysis was done to validate the comparability of the groups and showed that the two groups were comparable in gender, age, weight, marked pain at baseline, and HHS at baseline. However, that was only five covariates, and more would have been better. The propensity score analysis was not comprehensive enough to ensure comparability of the treatment groups, due to unavailable control data.

The revision rate was statistically lower in the control than in the Cormet group at 24+ months. For the all-enrolled group, the Kaplan-Meier Analysis showed fewer revisions in the control than in Cormet at 24 months; implant survival was 99.1 percent in the control, 95.8 percent for Cormet. For the pivotal study unilateral cohort, the revision rate was 5 percent at 24 months, 8.1 percent at 36 months.

Missing data for CCS at month 24 was addressed, when it could be, by rollback imputation. In 44 Cormet and 10 control patients, missing data made this impossible.

Four other methods of imputation were used, and most methods of imputation showed the device meeting the non-inferiority criterion. Since most imputation methods showed the same conclusions, the missing data should not be a major concern.

PANEL DELIBERATIONS

Dr. Mayor discussed the clinical perspective on the device. He noted the changes in control and the safety and effectiveness endpoints. The modified radiographic criteria were less stringent, and the control was chosen post-hoc. Complications and device-related events raised doubts as to the ability of the device to efficaciously solve hip disease problems, though rates of dislocation were low with the device. Since there were signs of instability between months 24 and month 24+, he wondered if the Kaplan-Meier survival curve, which shows no further losses at 60 months, projected accurately. The device was likely to be used in the younger part of the population. Though the device was asserted to preserve femoral bone, it does not preserve acetabular bone, and the femoral neck remains at risk for fracture.

Dr. Propert gave a statistical comment. She noted that this was a confusing study with many population subgroups and differing follow-ups. The small number of revisions might mean that the analysis of that data might not be useful for identifying risk factors. The propensity score analysis was incomplete. She said a longitudinal analysis would have helped to clarify changes over time.

Chairman Mabrey opened the Panel's general discussion. **Ms. Whittington** asked about surgeon transparency in communication with patients who may have self-selected the procedure. **Dr. Schmalzried** said that all patients would be given an informed consent document developed with the investigators, the hospital IRB and the FDA. The document includes inclusion and exclusion criteria. **Dr. Mayor** said that a total hip replacement as a revision to a resurfacing might not perform as well as a primary THA. **Dr. Schmalzried** said that in the 22 conversions, surgical parameters and short-term outcomes were similar to a primary hip.

Dr. Propert asked about the change in the non-inferiority delta from 5 to 8 percent. **Dr. Silverman** said it happened early in the IDE, before any results were seen. **Dr. Naidu** asked about the radiographic changes. **Ms. Frank** said they changed after the original PMA submission, in January of 2006. **Dr. Normand** asked how the noninferiority delta was chosen and for more data on HHS. **Dr. Buch** of DGRND said that deltas are chosen based on the literature, the control group, and the Sponsor submission; deltas for this kind of device range from .1 to 10 percent. **Dr. Kudrna** said the pain and function components of HHS were gathered primarily by a physician-administered questionnaire. Range of motion was measured by the surgeon. The score was weighed in favor of the questionnaire. **Mr. Maislin** offered more information on the non-inferiority delta. The 8 percent delta was chosen because 90 percent success at 85 percent compliance would need 273 patients to show 80 percent power. For a 5 percent delta, 1,400 patients would be needed.

Ms. Naughton said the changes in control group and radiographic analysis were done in conjunction with meetings with the FDA and with the intent of providing the best analysis. **Dr. Gruen**, a Sponsor consultant and radiologist, said the original radiographic criteria were made without the benefit of a 2004 paper on measuring MOM resurfacings

by x-ray. The modifications were made for better measurements and better indicators of revision.

Dr. Skinner commented that the cup and the stem were similar to many devices on the market and that the variables and outcomes were identified sufficiently to correct the variables in practice. **Chairman Mabrey** noted that hip resurfacing offers more natural movement than THA.

Ms. Whittington asked about metal debris from the devices. **Dr. Kudrna** said the devices that produced debris were a different model. The current devices are carefully monitored, metal ion releases are low, and the metals are not toxic at the doses found. Neither device failure nor metal-related disease had been seen. **Dr. Krikler**, a Sponsor consultant, said he'd followed a cohort of patients for up to 10 years. Ion levels rose in the first two years, then declined. Hypersensitivity has not been an issue.

Dr. Trier said Corin was conducting an IDE study for a larger-diameter MOM head that articulated with the cup. **Ms. Granger** noted that if the head were prepared before the insertion of the cup, a total hip could be inserted if a conversion were necessary during surgery. **Dr. Gross** addressed femoral notching and femoral neck fractures. The risk factors for surface replacement were not yet well defined. Low bone density was the most important of many factors. The femoral component must be installed in the valgus position, since too much tilt can notch the neck. There was little data on notching and no indication of the degree of risk, but it could create a point where the bone would be more likely to break. **Dr. Mayor** asked about avascular necrosis. **Dr. Gross** agreed that the vascularity of the femoral head is compromised by surgery, but he said most people heal from it.

Dr. Schmalzried said the implants are in 4 mm increments, with two acetabular sizes for every femoral size. Surgeons try to use a large head and thin acetabular side. A submission was being made for 2mm size increments. **Dr. Collins** addressed retrieval of explants. Though there is no retrieval protocol, Corin sends the implants to two laboratories to be examined for indicators of failure and a wear analysis. **Dr. Schmalzried** said that strike wear was not seen in MOM devices, but in vivo lubrication was important to wear rates. Suboptimal positions or interposed third bodies could cause unintended wear mechanics, resulting in debris. Metallic debris and ions were different issues. The ions were not known to be problematic, since cobalt chrome is not highly inflammatory. Osteolysis was being researched as an ion-related issue. Debris was a sign of a malfunctioning joint. In revision surgery, debris and osteolysis was common. Debris tended to include metal, bone, and cement. The osteolysis in the study was all on the femoral side and was so small that some would contest the finding.

Dr. Normand had asked about the number of patients in the control group with one or fewer risk factors. **Ms. Naughton** said the risk factors were for resurfacing, not total hip replacement, so the factors did not apply to the control. **Dr. Normand** said she was concerned about comparability throughout the study. **Dr. Schmalzried** said the control used was the best available, the same one used in the Birmingham data. **Dr. Normand** asked about the propensity score analysis and how it related to risk as well as about site variability. **Mr. Maislin** said that the important thing about the scores was how they overlapped in the two groups. Odds ratios were not his goal. He added that correlations within a site could not impact non-inferiority conclusions and concluded that there were no systemic within-site correlations among patient outcomes. **Dr. Naidu**

followed up on the risk factors. **Dr. Schmalzried** said the comparison of the risk factors had not seemed relevant, so they were not available. **Dr. Naidu** said that determination is better made after a comparison; **Chairman Mabrey** agreed with **Dr. Normand**, that it was a matter of group comparability. **Dr. Naidu** asked for the numbers of patients with greater than three risk factors in the all-enrolled and pivotal groups. **Dr. Trier** referred the Panel to slide 71, page 24 in the Panel packet. In the pivotal group, 16 patients had 3 risk factors, 25 in the all-enrolled. No patient in either group had 4 risk factors. **Ms. Naughton** said that the data on risk factors could be submitted at a later time.

PANEL QUESTIONS

1) The applicant planned to conduct a prospective, non-randomized concurrently controlled clinical study to evaluate the Cormet 2000 Hip Resurfacing System. The control subjects were to receive a cleared metal-on-metal or metal-on-polyethylene total hip replacement. However, no subjects were ever actually enrolled in the control arm of the study. In the original PMA submission, the applicant proposed and used metal-on-metal hip data as a historical control. In subsequent amendments to the PMA, the Sponsor re-analyzed their clinical data using another device, the Howmedica Osteonics ABC ceramic-on-ceramic system (Alumina Bearing Couple, approved in PMA P000013 on February 3rd, 2003) as the historical control.

Please discuss the impact of changing the controls during the study progression, and after the original data analyses were performed on the ability to interpret the data as valid scientific evidence to support the safety and effectiveness of this device. Please also comment on the relevance of using the Osteonics ABC ceramic-on-ceramic system as a control for a clinical study using the Cormet 2000 Hip Resurfacing System as the investigational arm.

The Panel expressed a variety of opinions, ranging from frustration with the inability to pick out an appropriate control group to acceptance that in the current reality such a control group may no longer be selectable.

2) Various radiographic measurement techniques and criteria have been used to evaluate the success/failure of resurfacing hip devices. The original IDE approved protocol included the following radiographic success criteria:

a) Acetabular component:
- Migration<5mm vertical or horizontal
- Migration <5 degrees in varus/valgus
- No new or progressive radiolucencies>1mm in **any** zones

b) Femoral component:
- Subsidence<5mm
- Tilting<1 degree in varus/valgus
- No new or progressive radiolucencies >2mm in **any** zones

In amendments to the PMA submission, the Sponsor provided a new radiographic technique and then analyzed the radiographs according to the following revised endpoints:

a) Acetabular component:
Migration <5mm vertical or horizontal
Migration<5 degrees in the varus/valgus
No new complete radiolucencies >1 mm in **all three** zones
b) Femoral component
Subsidence<5mm **and** tilting<1 degree in varus/valgus
No new complete radiolucencies>2mm in **all three** zones

Based on this information:

a) Please discuss the appropriateness of changing the study radiographic measurement techniques and success/failure criteria after the study completion.
b) Please comment on how the final proposed endpoints impact our ability to interpret the patient outcomes and whether they are able to predict the success/failure of this resurfacing hip system.

The Panel Members abstained or had no comment in three cases and in two of three cases expressed concern over the changing of the wording of the documentation of radiolucencies from "progressive radiolucencies" to "complete radiolucencies." Dr. Skinner pointed out that the new criteria may have been more realistic. The Panel as a whole believed the changes would have some effect on the final results. Mr. Melkerson asked the surgeons what they would want to see in the labeling of this device. The surgeons on the Panel said they would like to see additional wording on the packaging relating to progressive radiolucencies, though radiolucencies in only one zone or in the cup may not be appropriate. Cups can be difficult to seat, and some radiolucencies are not clinically significant.

3) The applicant provided post-hoc analyses of the learning curve and explored patient preoperative risk factors that may help explain the revision rates observed for the Cormet 2000 Hip Resurfacing System. The Kaplan-Meier Estimates of Revision Rates at 24+ Months were 8.1% for the Pivotal Study Unilateral Cohort and 7.2% for the All-Enrolled Cohort.

a) Please discuss the significance of these revision rates and any safety concerns they raise, such as femoral neck fractures.
b) The applicant's analysis of patient selection criteria demonstrates the device revision rate is higher than average for females, patients requiring use of smaller device components, patients requiring use of smaller device components, patients with diagnoses other than osteoarthritis, patients with low function HHS scores and patients with leg length discrepancies $\geq$ 1 cm. Please comment on the clinical significance of these risk factors, given the applicant's proposed indications for use:

"The Cormet 2000 Hip Resurfacing System is intended for use in resurfacing hip arthoplasty for reduction or relief of pain and/or improved hip function in skeletally mature patients having the following conditions:
1. Non-inflammatory degenerative arthritis such as osteoarthritis, and avascular necrosis (AVN));
2. Inflammatory arthritis such as rheumatoid arthritis.

> Hip resurfacing arthoplasty is intended as a primary join replacement for patients who are at risk of requiring more than one hip joint replacement over their lifetime. While it is not possible to predict if a patient will require a future hip revision, several factors such as gender, age, weight, and activity level may increase the risk of the need for revision."

The Panel was concerned about the risk factors. The failure rate was high, compared to the gold standard, total hip replacement, and the Panel said the indications needed to be clearer, especially in delineation of both relevant and absolute contraindications.

4) Based on a new surgical technique for hip resurfacing procedures, the Sponsor proposes a four-tiered training curriculum to introduce the Cormet 2000 Hip Resurfacing System. Please comment on the adequacy of the proposed training program to ensure sufficient surgeon preparation and knowledge of the surgical procedure.

The Panel was in agreement that the training system proposed by the Sponsor was adequate and sufficient for training future surgeons in the procedure.

5) Under CFR 860.7(e)(1) effectiveness is defined as reasonable assurance that, in a significant portion of the population, the use of the device for its intended uses and conditions for use, when accompanied by adequate directions for use and warnings against unsafe use, will provide clinically significant results. Considering the study design and endpoints discussed today, please discuss whether the clinical data in the PMA provide reasonable assurance that the device is effective.

The Panel's general opinion was that the device was effective.

6) Under CFR 860(d)(1), safety is defined as reasonable assurance, 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 revision rates and the femoral neck fractures for the subject device, please discuss whether the clinical data in the PMA provide reasonable assurance that the device is safe.

The Panel generally believed that the device was safe. However, the Panel expressed concerns about the higher revision rate compared to total hip replacement.

OPEN PUBLIC HEARING

Ms. Benson-Gyles clarified her position from the morning's open public hearing. She was in favor of hip resurfacing and came to speak about the heat treatment that caused failure in her device. She expressed disappointment that the Sponsor did not address the issue.

FDA AND SPONSOR SUMMATIONS

The FDA had no further comment. For the Sponsor, **Dr. Trier** clarified that 85 percent of the subjects in the pivotal group had complete composite clinical success, so there was a complete set of radiographs made. **Dr. Collins** thanked the FDA and the Panel.

PANEL VOTE

Executive Secretary Jean read the voting statement to the Panel, defining safety and effectiveness as well as describing the voting options. **Dr. Mayor moved** that the PMA be judged approvable with conditions. **Drs. Skinner and Naidu seconded** the motion simultaneously. **Chairman Mabrey** opened the floor to conditions.

Dr. Mayor moved that the first condition be a 10-year post-approval study, following the cadre of 1,100 patients for 10 years to determine the long-term durability of the device. **Dr. Propert seconded** the motion, and **Chairman Mabrey** asked the Sponsor to present its proposed post-approval study protocol.

Dr. Trier described Corin's proposed post-PMA approval study protocol to monitor clinical performance out to 10 years post-operative, measuring device by HHS. The single-arm study would follow operations performed at the five largest sites (377 procedures, 291 unilateral) through post-approval surveillance. The primary endpoint would be good clinical status to 10 years, measured by HHS of 80 or better. The eligibility criteria would be to be subjects enrolled in the Cormet IDE pivotal study at one of the five largest sites. Of the 291 possible subjects, 250 was the target. The subjects would be tracked both by monitoring and periodic evaluations. No concurrent control was proposed.

For the FDA, **Dr. Kaczmarek** said that a post-approval study was needed to show long-term device safety and effectiveness at 5 and 10 years, which would help in post-market management. Medical device reporting would be insufficient, since adverse events are generally underreported to directories. In the proposed study, the primary endpoint was a CCS defined as the absence of revision, replacement, or removal of the device and HHS of 80 or above. There would also be film studies in the first five years. FDA complaints were that the proposed study was descriptive, not hypothesis-driven, that it lacked a control, and that it probably underestimated the loss to follow-up over 10 years. Since the protocol did not include any new enrollment of doctors, patients, or sites, the study would not study actual conditions of use and might not meet sample size requirements. FDA wanted to see film studies throughout the trial, as well as serum ion level monitoring. The FDA asked for further refinement of the Sponsor's protocol.

Dr. Mayor proposed modifying his motion to address the FDA concerns, suggesting that the Panel should help in devising the study. **Dr. Naidu seconded** the amendment. **Ms. Adams**, expressed concern about bias introduced into the process by the FDA presentation on post-approval studies. **Dr. Normand** asked for clarification of the motion. **Dr. Mayor** said his modified motion was to include some elements of the Sponsor's plan to pursue post-market surveillance of 442 procedures at the predicate centers with attention to details of follow-up, which should be included beyond those outlined in the study protocol presented, at least semi-annual radiographic evaluations and serum cobalt and chromium determinations. **Dr. Naidu** said it would be impossible

to devise a protocol at the meeting and suggested negotiation between the FDA and Sponsor to develop a study protocol. **Chairman Mabrey** agreed on the x-ray and serum ion follow-ups. **Dr. Normand** said she favored certain protocol features, such as a control arm, but she stressed that the protocol should be made in negotiation between the Sponsor and FDA and that it would not make sense to develop the protocol in committee. **Dr. Skinner** said that the proposed studies didn't seem designed to provide useful information. He wanted to see ion levels at 10 years but saw little other benefit to the designs offered. **Ms. Whittington** stressed the importance of the cumulative revision rate. **Chairman Mabrey called the question**, summarizing the condition as a 10-year follow-up with radiographic and ion determinations every two years following 442 patients from the multi-center study. **The motion failed, 3 to 2**.

Dr. Propert moved the condition of a post-market surveillance study of at least 424 patients with a protocol to be determined outside of the Panel. **Dr. Normand seconded the motion. Dr. Propert** said the study should last 10 years. **Ms. Whittington** was concerned about excluding the smaller sites. **Dr. Normand** said the 10-year duration came after she seconded the motion, and she did not agree with it. **Chairman Mabrey** called for a second to replace Dr. Normand's. **Dr. Mayor seconded the motion**. **Dr. Normand** said negotiations between the FDA and the Sponsor would involve trade-offs and that the 10-year duration was not more important that other possible matters. **Dr. Skinner agreed**, saying that the actual information being sought and its usefulness was more important. **Dr. Propert re-amended his motion,** withdrawing the requirement of 10 years. **Dr. Mayor accepted the modification. Chairman Mabrey** summarized the motion as being for a post-market approval study to be worked out between the Sponsor and the FDA. **Mr. Melkerson** pointed out that the FDA would consider the Panel's discussion in devising the protocols. He said he had heard the Panel's concerns and that the FDA would take those concerns as advice. **Dr. Skinner** said that he would like to see what the Kaplan Meier curve for revision looked like after 10 years. **Ms. Adams** noted that there were no indications of danger from ions in the study and questioned their value as a key area of concern in the follow-up. **Dr. Mayor** supported the comments on the Kaplan-Meier curve and noted that it is important to get long-term data in order to get valid consent from patients. **The amended motion carried unanimously.**

Dr. Skinner moved that the post-market, four-tiered training programs for surgeons be made mandatory. **Dr. Naidu seconded the motion**. **Mr. Melkerson** said the training requirement could be a condition of approval and that details could be worked out between the Sponsor and the FDA. **The motion carried unanimously**.

Dr. Naidu moved that the labeling reflect the device-related complications compared to total hip replacement be reflected in the labeling. Mr. Melkerson noted that labeling typically includes an adverse event profile for device and control on a table. **Chairman Mabrey** called for a second. **The motion died for lack of a second**.

Dr. Propert moved as a condition of approval that there be clarification of risk groups clearly outlined in the labeling. **Dr. Mayor seconded** the motion. **Ms. Whittington** suggested that the information be in both surgeon and patient labeling. **Drs. Propert and Mayor accepted** it as a friendly amendment. **Mr. Melkerson** noted that using the term "labeling" would cover both, plus other categories of labeling. **Dr.**

Propert so amended, and Dr. Mayor accepted the amendment. The Chairman called the question, and **the motion carried unanimously**.

Chairman Mabrey called for other conditions. Hearing none, **he called for a vote on the main motion, to recommend approvable with the conditions voted upon. The motion carried 4-1** with Dr. Normand in the minority. Chairman Mabrey asked the members to state the reasons for their votes. **Dr. Mayor** said the data presented demonstrated adequate safety and effectiveness. **Dr. Propert** expressed frustration with the control group but saw compelling data for short-term efficacy and thought surveillance would give data for long-term efficacy. **Dr. Naidu** agreed with Drs. Mayor and Propert and hoped post-market study would clarify the early complications. **Dr. Normand** voted against the motion because she did not find the control group comparable to the device. She disagreed with many analytical considerations. She saw an effectiveness endpoint reached, but not effectiveness itself, and she did not think the question of safety should be deferred to a post-approval study. **Dr. Skinner** agreed with Dr. Mayor. **Ms. Adams** said the study had been a difficult situation with a new technology. **Ms. Whittington** said the device would open new opportunities for young, active patients needing the procedure. **Dr. Mabrey** noted that randomizing prospective clinical trials will become more difficult as patients gain more information. **Mr. Melkerson** suggested that future Panels discuss the questions they want answered by post-approval studies.

ADJOURNMENT

Chairman Mabrey thanked the participants and **closed the meeting at 3:55 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

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