

**Reclassification Petition for Metal/Metal
Semiconstrained Hip Joint Prostheses with
Cemented or Uncemented Acetabular
Components 21 CFR 888.3320 and 888.3330
Docket Number 2005P-0405**

**OSMA
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Documents Management Branch
(HFA-305)
Food and Drug Administration
5630 Fishers Lane
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Re: Reclassification Petition for Metal/Metal Semiconstrained Hip Joint Prostheses
with Cemented or Uncemented Acetabular Components 21 CFR 888.3320 and 888.3330
Docket Number 2005P-0405

Dear Sir:

Enclosed are five copies of our response to your deficiency letter dated June 29, 2006. A CD-ROM with identical content to the paper submission is also included for your convenience. Our original petition seeking to reclassify Metal/Metal Semiconstrained Hip Joint Prostheses with Cemented or Uncemented Acetabular Components from Class III 510(k) status to Class II 510(k) status was received by the agency on August 10, 2005 and amended on September 22, 2005.

To facilitate your review we have listed our reply in bold face following the question.

Device Characteristics:

1. You suggest a conventional metal-on-metal bearing would be defined as one whose composition and design parameters fall within the range of those presently in use. You then provide a table on page 28 outlining the main characteristics of several cleared metal-on-metal devices. We believe this table is incomplete and does not provide sufficient detail in some areas. Therefore:
 - a. Please complete the attached table (Attachment 1), so that we will have all information necessary to characterize metal-on-metal semi-constrained hip systems.

Enclosed in Attachment 1, are the tables which characterize the metal-on-metal devices sold by Biomet, DePuy and Zimmer.

ORTHOPEDIC SURGICAL MANUFACTURERS ASSOCIATION

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- b. In order to identify the appropriate devices for downclassification, we need to distinguish the design differences of the current generation of clinically successful metal-on-metal devices from the first generation of metal-on-metal hip systems that were determined to be failures. To assist us in distinguishing these design differences, please first complete the attached table for the first generation metal-on-metal hip systems that were previously determined to be failures. Please include all metal-on-metal designs that have been legally marketed even if they are not currently marketed (i.e., both pre-amendments devices and devices cleared through 510(k)) including designs that have equatorial bearings, threaded acetabular cups, devices made of inferior materials or manufacturing methods, etc. Using this information, please identify the key design characteristics which are thought to have been responsible for the failure of the first generation devices and then differentiate between the devices currently being considered for downclassification and those devices with characteristics suggesting they should remain as Class III.

Enclosed as Attachment 2, is the table for the Ring and McKee Farrar Devices we were able to obtain. We have also provided an early paper (Amstutz HC et al: Motion studies for total hip replacements, Clin Orth Rel Res, 1975, 111:124-130) that describes the range of motion and neck-socket contact angles for the McKee Farrar device (see Attachment 3). The authors note that neck socket impingement has been causally implicated in the loosening of the McKee Farrar and other all metal total hip replacements. As we stated in our petition, first generation devices (McKee Farrar, Ring, Stanmore, Sivash, Mueller) were often characterized by problematic outcomes including equatorial contact caused by low or negative head-cup clearances and deformation of thin shell acetabular cups, both of which resulted in high frictional torques, component seizing, and implant loosening. Clinical success was impacted by suboptimal implant design and manufacture. Fluid film lubrication was another factor. Surface geometry of retrieved McKee Farrar devices indicated that while the devices had been designed with friction considerations, the manufacturers failed to consider the effect of fluid film lubrication on clinical performance. (Kothari M et al: Surface geometry of retrieved McKee Farrar total hip replacements. Clin Orth Rel Res 1996 329S:S141-147) (see Attachment 4).

Section VI in our petition discussed each of the design issues related to optimal performance. First generation devices varied in clearance, several references report on early failures due to equatorial bearing where clearances were too small or negative. Second generation devices have been strictly controlled for

tolerances, using quality control methods (coordinate measuring machines) that are accurate to within a few micrometers. Thus equatorial bearing is eliminated. Sphericity control has also markedly improved. First generation devices were hand polished leading to sphericity deviations up to 40 µm. Modern automated polishing reduces the deviation to less than 10µm. Tolerancing based on lambda ratios are currently considered by rigorously enforced inspection criteria. All of these considerations apply to the devices recommended for downclassification.

- c. From the information collected, please propose the specific parameters that may be considered for special controls.

We have enclosed in Attachment 5, a redacted protocol for measuring Torsional Friction Moments for the agency to consider as one of the Special Controls. Other special controls including labeling, metallurgy, surface finish and fluid film thickness are discussed throughout this response and summarized in the concluding paragraph.

- d. In addition, it is our understanding that resurfacing devices are not for consideration in this petition, yet information on a resurfacing device was included in the table submitted. Therefore, please remove all references to resurfacing components as hip joint metal/metal semi-constrained resurfacing prostheses are post-amendments Class III devices requiring Premarket Approval Applications (PMA).

We agree that resurfacing devices are not to be included in the petition and thus are not the subject of downclassification. All references to resurfacing devices will be removed from the petition.

2. In modern metal-on-metal hip implants a fluid film lubrication may occur where a thin microscopic layer of lubricant completely separates the head and cup bearing surfaces thus protecting the articulating surfaces during relative motion. By protecting these surfaces, the fluid film lubrication plays a role in reducing the wear of metal-on-metal bearings. There are several factors which may affect the thickness of the fluid film (e.g. surface finish, sphericity, clearance, diameter, material and elastic modulus). Please evaluate and describe how each of these factors affects fluid film thickness. Then identify any key differences that may affect the fluid film thickness in current metal-on-metal designs in comparison to the first generation of metal-on-metal hip systems that were determined to be failures. This information may help in the development of special controls to evaluate different metal-on-metal hip systems.

With regard to your question regarding fluid film thickness and differences between first and current generation devices, our response is as follows:

1. Effects of design parameters on the thickness of the fluid film and key differences between 1st generation and current metal on metal hip bearings.

- Fluid film thickness may be calculated using the Reynolds equation. For spherical contacts, the steady-state minimum film thickness h_0 is given by (reference: A Cameron, 1983: “Basic Lubrication Theory, 3rd edition”, John Wiley and Sons):

$$h_0 = \frac{28.43U^2\eta^2R^3}{W^2}$$

where U = surface speed

η = dynamic viscosity

R = effective radius given by $R = R_cR_h/(R_c-R_h)$, where R_c = cup radius and R_h = head radius, hence it is a function of the radial clearance, with larger clearances giving smaller values of effective radius and smaller film thickness

W = applied load

- The above equation does not take into account elastic deformation of the surfaces (ElastoHydrodynamic Lubrication – EHL). There is no exact analytical EHL solution for spheres, but approximate solutions have been given in the literature (e.g. Cameron, 1983):

$$\frac{h_0}{R} = 1.15 \left(\frac{U\eta\alpha}{R} \right)^{0.744} \left(\frac{ER^2}{W} \right)^{0.078}$$

using the same notation and additionally introducing:

α = the pressure-viscosity coefficient of the lubricant defined by

$\eta_p = \eta_0 \exp(\alpha p)$ (note that this parameter has not been measured for typical serum-derived lubricants used in hip simulator studies)

E = effective elastic modulus given by

$$\frac{1}{E} = \frac{1}{\pi} \left(\frac{(1-\nu_c^2)}{E_c} + \frac{(1-\nu_h^2)}{E_h} \right)$$

where E_c = elastic modulus of cup, ν_c = Poisson’s ratio of cup, etc

- The lubrication regime is defined by the ratio of fluid film thickness to surface roughness – the lambda ratio, given by

$$\lambda = \frac{h}{\sigma} = \frac{h}{\sqrt{\sigma_c^2 + \sigma_h^2}}$$

where σ_c = RMS roughness (R_q) of the cup, etc

Where $\lambda > 3$, the surface asperities do not contact, and the lubrication is described as fully hydrodynamic. For $\lambda < 1.5$, substantial asperity contact occurs, and the lubrication regime is boundary. Intermediate values of λ give 'mixed film' lubrication.

- From the above equations, the testing parameters that influence the fluid film thickness (hence λ ratio) are load, speed and serum viscosity. These values are held constant and can be made worst case by controlling the test cycle and the protein concentration of the serum.
- From the above equations, the material properties that influence the fluid film thickness (hence λ ratio) are elastic modulus and Poisson's ratio. These values are not greatly affected by the metallurgical condition or carbon content of the CoCrMo alloy.
- From the above equations, the design parameters that influence the fluid film thickness (hence λ ratio) are: bearing radius (but only weakly), radial clearance and surface finish.
- 1st generation metal-on-metal hips were variable in clearance but tended to be bigger in diameter (34 – 41mm). Some lasted decades although larger clearances may have led to large amounts of running-in wear. Several papers have reported on early failures due to equatorial bearing where the clearances were too small/negative. Impingement was also an issue with McKee-Farrars.
- Modern MOM hips have strict control over tolerances and, critically, quality control methods (such as co-ordinate measuring machines) that are accurate to within a few micrometres. Therefore it is now impossible for a modern MOM hip to have clearances below the minimum defined by the manufacturers. This quality control eliminates equatorial bearing contact.
- Sphericity control has also markedly improved in the last 15 years. 1st generation devices were hand polished which can lead to sphericity deviations up to 40 μ m. Modern automated polishing reduces this sphericity deviation to below 10 μ m. Obviously a combination of poor sphericity control and very small clearance could have led to equatorial bearing in 1st generation devices.

3. In your January 10, 2003 letter to Mr. Phil Phillips, Deputy Director, Science and Regulatory Policy of the Office of Device Evaluation, you proposed a preclinical test protocol to evaluate device components having suboptimum articular geometries serving as “negative controls.” We later provided feedback to you regarding the proposed protocol. In Section VI: Summary of Testing II. D. Negative Clearance and Frictional Torque of this petition, you indicate “Tribologists at Biomet, DePuy and Zimmer have recently used hip simulator tests to verify that negative clearance also causes severe frictional torque and wear of 2nd generation metal-metal hips.” As a result of this, only positive clearances were used. You also indicate “state of the art coordinate measuring machines can detect eccentricities on the order of one micron, ensuring that the clearance exceeds the eccentricity in all positions for a given design of a metal-metal hip is essentially a quality assurance issue, and does not need to be routinely verified though hip simulator testing.” No further information is provided regarding the wear evaluation completed by these manufacturers. Please provide a full test report and protocol for the analysis comparing designs with positive and negative clearances.

In Attachment 6, we have enclosed Paper no. 0503, “Effects of negative clearance on the wear performance of a modern metal-on-metal implant in a hip simulator study” written by Liao, Y-S and Hanes, M. from DePuy Orthopaedics. The wear tests compared two groups, four sets of each. The first group, Group A, represented devices with a negative diametrical clearance of $-8.0 \pm 2.5\mu\text{m}$, in Group B, the positive clearance measured $80.5 \pm 8.2\mu\text{m}$. The initial motion for the negative clearance group was erratic during each cycle due to the equatorial contact for the heads and inserts. The erratic motion resulted in a different wear surface. The negative clearance group had more than 100 times the wear than the positive group. Diametric clearance is one of the critical factors in metal on metal implant design. Equatorial contact bearings will occur if the diameter of the head is slightly larger than the inner diameter of the insert which occurred in some of the failed first generation implants due to poor manufacturing techniques. This study demonstrates that wear simulation using an 8-station hip joint simulator can distinguish between good and suboptimal designs.

4. The petition indicates that you believe pooling the data from the four IDE studies included in this petition is justified based on the similarities in the materials used to manufacture these devices and on the design specifications of the metal-on-metal articulations. To justify pooling the data from four different IDE studies, which were conducted by three different manufacturers using different metal-on-metal prostheses, we believe supporting technical evidence, clinical evidence, and statistical evidence need to be presented. Technical evidence should show that the different metal-on-metal hip prostheses devices are comparable in the materials, diameter, clearances and tolerances as well as other relevant and important aspects of the devices. Clinical evidence should show that the safety and effectiveness characteristics of these metal-on-metal hip devices are similar at

baseline and other postoperative time points. Statistical evidence should show that the study cohorts in these IDE investigations are comparable with respect to important baseline characteristics, such as age, sex, weight, height, daily exercise level, inclusion/exclusion criteria, etc. To obtain the statistical evidence, subject level data are required from the study investigators, and appropriate statistical methods need to be used. Please provide the supporting technical, clinical and statistical evidence to justify pooling the data from these four different IDE studies. Otherwise, please report the results and analyses of each study individually.

Clinical Justification of Pooling Data

Pooling data from a number of studies with different inclusion and exclusion criteria enhances statistical power and makes conclusions about the performance of metal/metal hips in the general population, without extrapolation.

The fact that the demographics of these studies differ with respect to mean age, weight, height, gender distribution, and other factors is an advantage. Moreover, the significant differences in gender would account for significant differences in weight and height. This allows us to cover the population domain that we wish to provide an inference. Tables 1 to 8 (Attachment 7) show that the studies differ with respect to demographics, but that there is overlap between any two studies with respect to each of the demographic variables examined. Pooling these studies creates a composite of patients that covers the population that will be treated by metal/metal hips. Thus, inferences may be made without extrapolation.

Although these studies differ, the performance of metal/metal hips is comparable between studies with respect to implant survival (see the answer to question 5). The similarity between studies with respect to the most important variable associated with the success of a prosthesis—survival—provides evidence that we are combining results from subpopulations that came from a contiguous population that was artificially segmented by inclusion and exclusion criteria within each study. This enhances evidence of continuity within the pooled dataset that is evident when demographic variables are examined. Looking at the studies individually is certainly informative, and we have done this (see the answer to question 5); but to refrain from pooling the data seems inadvisable. Neglecting the collective picture of the pooled data would omit the clearest picture of survival outcomes that can be expected in the future across the population that will receive metal/metal hips.

Attachment 1 demonstrates the comparability in materials, diameters, clearances, and tolerances as well as other important aspects of the devices. The response in our answer to question 6 which refers to the four IDE studies provides clinical evidence of safety and efficacy for metal-on-metal prostheses. We feel that pooling the data from the studies is the best method available to provide the agency with the clearest picture of implant performance in standard practice.

5. Regarding the survivorship analyses of metal-on-metal hip devices, please address the following items:

- a. On page 39, you stated that, “A 7.6 year survival estimate of 97.4% is entirely consistent with a 10-year revision rate that is substantially less than 10%.” However, you did not explain how this conclusion was reached and why the data was extrapolated. Therefore, please provide information to support your statement including details regarding statistical models used for the prediction and comment on missing data, loss to follow-up issues, and informative/non-informative censoring. Otherwise, you may remove this 10-year analysis from the petition, revise your survivorship analysis accordingly, and base conclusions on the 7.6-year survival data.

The 10-year survival estimate is now valid with the incorporation of additional data (see Attachment 8).

- b. You provided two Kaplan-Meier survival estimate plots with post-operative data out to seven years. In the Kaplan-Meier survival estimate plots, please modify the scale of the y-axis and the color of the curves to make the plots easier to read.

The scale of the y-axis and curve colors have been changed to make plots easier to read (see Attachment 9).

- c. The Kaplan-Meier survival estimate plots include survival of the devices and 95% upper and lower confidence limits. It may be more informative to compare the survivorship results on metal-on-metal hip devices with those of metal-on-polyethylene hip devices, if such controls are readily available in these four IDE studies. Please provide a Kaplan-Meier survival plot comparing survival of metal-on-metal hip devices to the survival of a control.

The Kaplan-Meier survival estimate plots have been amended to include a plot showing all randomized metal/metal hips that have randomized polyethylene hip controls (Attachment 10); only the Biomet and DePuy studies included polyethylene controls. The

probability of a difference in these curves is $p = 0.59$, log rank test (see Attachment 9).

- d. You claim that pooling the data from these four IDE studies was justified based on the similarities in the materials used to manufacture these devices and on the design specifications of the metal-on-metal articulations. In addition to pooling the data for these four IDE studies, it may be helpful to look at the survivorship of each device to determine if there are significant differences in survivorship across manufacturers. Please provide a separate Kaplan-Meier survival estimate plot for each metal-on-metal device. If possible, compare the survivorship of the metal-on-metal devices to the survivorship of the control devices used in the studies.

Survivorship has been provided in separate Kaplan-Meier curves for the metal/metal hips in each study individually, and 95% confidence intervals have been included (see Attachment 10). In addition, a graph showing metal/metal results simultaneously from all four studies is provided. The y-axis scales and colors have been modified to make these plots easier to read (see Attachment 11). Considering only the metal/metal hips in all four studies, a log-rank test was performed to determine whether differences in the four survival curves exist ($p = 0.13$). Therefore, with a 95 % confidence interval, there is no statistically significant difference seen. In addition, metal/metal hips with matching polyethylene controls have been pooled to determine whether a difference exists between metal/metal hips and polyethylene hips from the same studies. Because the two Zimmer studies did not include polyethylene controls, the Kaplan-Meier survival plots have been furnished omitting metal/metal hips from these two Zimmer studies and including only metal/metal and metal/polyethylene hips from the Biomet and DePuy studies (see Attachment 9). The probability of a difference in these curves is $p = 0.59$, log rank test.

6. You provided no information besides device survivorship regarding the metal-on-metal total hip prostheses clinical studies. Please provide a complete summary of the clinical and radiographic data and patient accounting information over the course of the studies (e.g., pre-op, post-op, 6 months, 12 months, 24 months, 5 years, etc.). The information will allow us to adequately analyze primary clinical and radiographic endpoints and patient accountability of your four unpublished studies. Please provide all clinical and radiographic data and patient accountability for all four clinical studies, as well as their investigational protocols, and please format all data as described per our guidance document "Guidance for Industry and FDA Staff—Clinical Data Presentations for Orthopedic Device Applications" at <http://fda.gov/cdrh/ode/guidance/1542.pdf>

Please note that the agency had indicated in a discussion at a meeting with officials on January 23, 2002 and subsequent teleconferences held on April 25 and September 4, 2002 that we were to present a device survivorship analysis of metal on metal hip devices from clinical studies from member companies. (See pages 13 and 14 in our original submission.) Accordingly, the sensitive task of sharing information between competing companies was aimed at providing only the essential data. We have summarized the critical information including demographics, Harris Hip Scores, radiographic data and anticipated/unanticipated adverse effects from each of IDE's used as a basis for this petition.

We included data from four unpublished IDE studies in our original downclassification petition. The investigational protocols were provided in the following submissions: (1) IDE G940106 Multicenter Trial of the Cementless Metasul System When Used with the Cemented APR II-T Non-Porous Femoral Stem in Total Joint Arthroplasty (Study #110) (Final Report submitted by Zimmer on February 28, 2005), (2) IDE G 940106 Multicenter Trial of the Cementless Metasul System When Used with the APR Acetabular Shell and Natural-Hip Porous Femoral Stem in Cementless Total Hip Arthroplasty (Study #111) (Final Report submitted by Zimmer on February 28, 2005), (3) IDE G 960262 Ultima Metal-on-Metal Total Hip S-ROM and PFC Femoral Stems (Final Report submitted by DePuy on July 1, 2002), and (4) IDE G950011 Metal-on-Metal Acetabular Study (Final Report submitted by Biomet on September 27, 2002). The Final Reports contain all of the requested information in a format similar to that described in your guidance document. The Indications for use in each of the studies are identical.

The following information is a summary of the Final Reports and identified as Company A through D.

Company A

Description of patient enrollment:

Three hundred fifty five devices implanted (175 control and 180 experimental) in one arm of the study and 168 devices (79 control and 89 experimental) in the second arm. Thus, there were a total of 523 devices (254 control and 269 experimental). Patient accountability, demographic data and follow-up information is included in IDE G960262.

Summary of results:

Mean Total Harris Hip Scores: the means results differed between experimental and control groups. The mean Harris Hip score for the experimental group was 95.7 versus 93.9 for the control group (p= 0.0410.)

Harris Pain Score Results: Mean results for pain scores differed between the experimental and control groups, favoring the experimental treatment group. The mean for the experimental group was 42.7 versus 41.5 for the control group ($p=0.0166$).

Harris Function Score Results: No statistically significant difference was observed between the experimental group mean (31.2) and the control group mean (31.1) ($p=0.7870$).

Harris Activity Score Results: The mean Harris Activity Score for the experimental group (12.2) was slightly higher than the mean for the control group (11.9), but this difference was not statistically significant ($p=0.0607$).

Conclusion: There is no clinically meaningful difference between experimental and control groups with respect to Harris Hip score results. Differences where statistically significant results were observed were small, and favored the experimental group.

Radiographic data: There were 10 radiolucencies noted in AP views of experimental patients in radiographs of 213 patients (4.7%). There were no statistically significant differences between this rate and the frequency observed in the control group (15 of 207, 7.2%). These distributions were evaluated with a two-tailed Fisher's exact test ($p=0.3065$). Similar results were obtained where lateral radiographs were evaluated. Nine of 213 experimental radiographs exhibited radiolucencies (4.2%), versus 15 of 207 control radiographs (7.2%). This difference is not statistically significant (two tailed Fisher's exact test, $p=0.2106$).

Conclusion: The proportion of radiographs in the experimental and control groups that exhibit evidence of radiolucency at 24+ months is similar.

Cup Evaluation: Three different aspects of cup migration were evaluated at 24+ months to determine whether a difference exists between experimental and control patients with respect to this factor. Superior-inferior, medial-lateral, and inclination migration were evaluated. Patients were categorized in each of these types of migration into two classes: those with migration $> 5\text{mm}$ and those with migration $=$ or $< 5\text{mm}$.

Superior-inferior migration: Fifty one of 214 experimental patients had superior-inferior migration $> 5\text{mm}$ (23.8%). This compares to 43 of 206 control patients (21.2%). This difference is not statistically significant (two tailed Fisher's exact test, $p=0.4844$).

Medial-lateral migration: Fifty six of 214 experimental patients had medial-lateral $> 5\text{mm}$ noted at 24+ months (26.2%). No statistically significant

difference was observed in this rate compared to the control group (43 of 206, 20.9%, two-tailed Fisher's exact test, $p=0.2082$).

Inclination migration: The experimental group had inclination migration at a rate of 31 of 214 (14.5%). There was no statistically significant difference between this rate and the rate observed in the control group (30 of 207m 14.5%).

Conclusion: No statistically significant differences between the experimental and control groups were observed at 24+ months with respect to cup migration. There are significant proportions of experimental hip cases with cup migration greater than 5 mm with each of the follow-up time points. However, since this also occurs with the control hip cases, it is likely a result of the methods used for obtaining this measurement rather than factors attributable to the experimental hips

Anticipated/Unanticipated Adverse Effects: A total of four subjects were withdrawn from the study, two cases of acetabular cup revision (both control devices) and one death occurred in a bilateral patient. The bilateral patient died from a cerebral vascular accident. The death was not related to the implant. One experimental case had a revision of the femoral stem due to a fracture of the femur; the acetabular cup was not revised or removed. Overall complications reported are considered typical sequelae of total hip joint replacement surgery.

Note: The IDE study was terminated as 82% of all subjects enrolled returned for their 24+ month clinical evaluation and the experimental device had been cleared for marketing under premarket notification.

Company B

Description of patient enrollment:

A total of 302 devices were implanted in 279 patients (23 patients were bilateral). One hundred fifty three were experimental cases and 149 controls. Of the 23 bilateral patients, 4 received the test device on both sides, 5 received a control device on both sides, and 14 received both a test device and a control device. The average age at surgery of patients receiving the test device was 68.9 years, 68.2 for men and 69.5 for women. The youngest patient receiving the test device was 27 years, the oldest was 89. The average age of patients receiving the control device was 68.6 years, 67.7 years for men and 69.2 for women. Ages for the control device patients ranged from 38 to 84 years. Patient accountability and follow-up information is contained in IDE G940106.

Harris Hip Scores: Mean Total Harris Hip Scores during the last follow-up were 96.0 for the test device and 90.5 for the control.

Radiographic data: Radiographic assessment of the hip was made from anteroposterior (AP) and lateral X-rays of the pelvis and operative femur. Data on component orientation and movement (i.e., subsidence), radiolucencies and osteolysis were recorded by an independent third party reviewer to determine prosthetic fixation and potential loosening. At the last follow-up, subsidence was observed for the femoral components of four control implants and one investigational implant. At the 3 year evaluation two control femoral components had 3 mm of subsidence. One control femoral stem had 3 mm of subsidence of the femoral component at the 4 year evaluation. The other control femoral component had subsidence of 1.5 mm at one and two years respectively. The test femoral component was observed to have 1 mm of subsidence at 2-year evaluation. The trend of radiolucency incidence is the same for both the control and investigational devices. Femoral radiolucencies > 2mm are extremely rare and were not observed for either the control or investigational devices until the 3 year evaluations. Femoral osteolysis has been observed in 80 implants (43 test, 37 control). Osteolysis usually involves Zone seven or to a lesser degree, Zone one. Sixty nine (39 test, 30 control) of the 80 implants with femoral osteolysis have a single zone involved. Eight of the 39 test stems and 3 of the 30 control stems with a single stem zone osteolysis also have osteolysis in one or more of the three acetabular zones. Twenty eight implants (13 test, 15 control) were reported with the size of femoral osteolysis > 5mm. Acetabular osteolysis has been observed in 22 implants (13 test, 9 control). Eighteen (11 test, 7 control) of the 22 have a single acetabular zone involved. Two test and 2 controls each have two acetabular zones involved. One control has all three acetabular zones involved (> 3mm). Eleven implants (7 test and 4 control), reported acetabular osteolysis > 5 mm.

Anticipated/Unanticipated Adverse Events: No unanticipated adverse events have been reported. Overall, there have been 342 adverse events reported (197 test, 145 control) by a study population of 153 test and 149 control patients. The study population also reported 531 concomitant medical events (256 test, 275 control). All adverse events are classified as either pertaining to the operative site or as systemic problems. One hundred twenty four of the adverse events (60 test, 64 control) were classified as operative site and 181 were considered systemic (109 test, 72 control). Twelve deaths have been reported for patients with the control device and 9 for the test device. One test device patient had bilateral hip replacement. Two test device and 3 control device patients had unknown causes of death. All other deaths were attributed to heart failure, respiratory failure, ruptured spleen, cancer, cerebral hemorrhage, influenza, myocardial infarction and gastrointestinal hemorrhage. Eight test implants and 7 control devices have been revised. Progressive osteolysis, femoral stem tip osteolysis, hip pain, and deep infection were the causes stated. Three test device patients have been revised because of hip pain and chronic dislocations.

Company C

Description of patient enrollment:

A total of 313 devices were implanted in 282 patients (31 patients received bilateral implants). Of the 31 bilateral patients, nine received the test device on both sides, six received a control device on both sides, and 16 received both a test device and a control device. One hundred fifty seven were experimental cases and 156 were controls. The average age at surgery of patients receiving the test device was 50.9 years, 50.5 for men and 51.7 for women. The youngest patient receiving the test device was 18, the oldest was 76. The average age of patients receiving the control device was 52.3 years, 51.2 for men and 54.3 for women. Ages for the test device patients ranged from 19 to 86 years. Patient accountability and follow-up information is included in IDE G940106.

Harris Hip Scores: Total Harris Hip Scores at the last follow-up were 98.6 for the test device and 98.0 for the controls.

Radiographic Data: Radiographic assessment of the hip was made from anteroposterior (AP) and lateral X-rays of the pelvis and operative femur. Data on component orientation and movement (i.e., subsidence), radiolucencies, and osteolysis were recorded by an independent third party reviewer to determine prosthetic fixation and potential loosening. At the last follow-up, subsidence was observed for the femoral components of 2 control implants (1.5 mm at 1 year of follow-up and 2 mm at 3 year follow-up) and 1 test implant (2 mm at 6 month). Data at final follow-up confirmed no change in subsidence for any of these femoral components and no acetabular subsidence has been observed. The trend of radiolucency incidence is the same for both devices, i.e., a small but gradual increase over time. The trend is seen only for the sizes categorized as < 1 mm and 1-2 mm, the majority being in the < 1 mm category and located most often in Zones 2 through 6. Femoral radiolucencies > 2 mm are rare and observed infrequently and inconsistently for both the control and test devices beginning (and disappearing) at the operative evaluation. Acetabular control device radiolucencies in the category < 1 mm were observed in all Zones 1 with a similar fluctuating that appears to slightly favor Zone 1.

Anticipated/Unanticipated Adverse Events: No unanticipated adverse events have been reported. Overall, there have been 261 adverse events reported (119 test devices in 79 patients, 142 control devices in 82 patients) and 280 concomitant medical events (141 test devices in 77 patients, 139 control devices in 74 patients) reported. All events are classified as either pertaining to the operative site or as systemic problems. One hundred eighteen of the adverse events (50 test, 68 control) were classified as operative site and 143 were considered systemic (69 test, 74 control). The most frequently received operative site adverse events were hip/trochanteric pain. Then test device implants and 14 control device implants had hip/trochanteric pain. There

were 6 dislocations in the test device group and 11 dislocations in the control device group. Eleven cases of trochanteric bursitis were reported (5 test, 6 control). Six cases of groin pain, 5 of subluxation and 2 intra-operative fractures were reported for patients with control devices. Five cases of proximal femoral fracture and 5 with superficial infection occurred in the test device group. Seven deaths were reported for patients with the test device and 3 deaths reported for patients with the controls. Of the deaths in test device patients, 1 died from a self inflicted gunshot wound, 3 were killed in motor vehicle accidents, 1 died intra-operatively and the other 2 died from myocardial infarction and cardiac arrest. One control device patient died from severe emphysema and heart failure, 1 from amyloidosis and the last as a result of an injury while operating heavy machinery.

Company D

Description of patient enrollment:

One hundred ninety four total cases were enrolled in the two year study, 97 received the test device, a metal on metal liner and 97 received the control, a polyethylene liner. Seventy one males and 26 female patients received the test device and 72 males and 25 females received the control. The mean age in years for test devices was 50, with a range of 26.7 to 78.7. The mean age in years for the control was 51, with the range from 18.6 to 82.3. Nineteen patients were lost to follow-up. Patient accountability and percent follow-up was included in the final report for IDE G950011.

Harris Hip Scores:

Five year data for total Harris Hip scores for the metal liner indicated that 79.2% of the 19 patients had excellent results, 8.3 % (2 patients) were good, and 12.5% (3 patients) had fair results. For the controls, 88.9% (16 patients) had excellent results, 5.6% (1 patient) had good results, and 5.6% (1 patient) had a poor result.

Radiographic data: A comprehensive listing of femoral and acetabular radiographic results are included in the IDE.

Anticipated/Unanticipated adverse events: No unanticipated adverse effects were reported. Non-device related adverse effects included myocardial infarction (2), thrombophlebitis, left iliopsoas bursitis, hip dislocation (4), thigh and groin pain (2), pulmonary embolism (3), chronic lymphocytic leukemia (not device related), superficial wound infection, femoral fracture, wound dehiscence, falls (2), and hematoma (2). Five deaths were reported, two due to cardiovascular complications, one from a cerebral aneurysm, and two from unknown causes.

7. In Section VIII you provide a summary of fifty nine adverse events made available through Medical Device Reporting (MDR) regulations. The analysis included reports made from January 1, 1992 to March 31, 2005. A more recent search of our manufacturer User Facility and Distributor Experience (MAUDE) database revealed 137 adverse events associated with the metal-on-metal product code “KWA” from 2004 through March 31, 2006, if not later. Of the 137 adverse events listed through this time period, at least 70 adverse events were reported since your database closure of March 31, 2005. Please update your adverse event analysis to include adverse events through at least March 31, 2006, if not later. When evaluating these adverse events please analyze them in tables according to the type of failure, manufacturer, etc. When developing your special controls, please consider the risks illustrated by these adverse events and address how you believe these risks can be mitigated.

We have updated our adverse events analysis for product code KWA in a table format and have included the information in Attachment 12. The risks identified in the analysis included infection, disassociation or loosening of components, dislocations, revisions, pain, osteolysis, component malalignment and breakage. The most frequent adverse effects resulting in revision surgery were due to disassociation or loosening of components, dislocations, unexplained pain, and infection. These risks often were related to surgical technique and can be minimized or mitigated with specific training programs for physicians and comprehensive instructions for use. Labeling, therefore, should be included in the special controls.

8. You provided recommendations for special controls for metal-on-metal hip prostheses. You then propose a two-tiered program dividing components into the categories of “Conventional” and “Experimental” bearings. “A conventional metal-on-metal bearing would be defined as one who composition and design parameters fall within the range of those presently in use, such that it may be assumed with reasonable reliability that its tribological performance in vivo will be comparable as well.” If the relevant regulations are downclassified from Class III to Class II, all previously cleared components will be downclassified including those that may not be presently in use. Therefore, special controls do not need to be defined for the “Experimental Bearings” and any data may be requested to support substantial equivalence to a legally marketed predicate device. Please remove the “Experimental Bearings” section from the special controls. Additional preclinical testing and/or clinical data will be requested as necessary for “Experimental Bearings.”

We agree with your rationale, and will remove the “Experimental Bearings” section from our recommendations for special controls

9. Under the “Wear Testing” section of the proposed special controls, you indicate the worst-case (highest wear) combinations should be evaluated. You suggest combinations of smallest and largest clearance or roughest initial surface finish to

be considered in worst-case selections. Wear properties are also related to fluid film thickness. Please include fluid film thickness as a suggestion for worst-case selection.

Fluid film thickness will be added to the worst- case (highest wear) combinations tested as part of the proposed special control for metal-on-metal hip prostheses.

In advance of testing, lambda ratios will be calculated to determine the worst-case (highest wear) combination(s) as part of the proposed special control for metal-on-metal hip prostheses. For the range of components in the system under consideration, lambda ratios will be calculated using the following equation for fluid film thickness (see discussion for response 2):

$$h_0 = 3.55 \times 10^{-7} \frac{R_c^{1.42} R_h^{0.77}}{(R_c - R_h)^{0.77}} W^{-0.21}$$

This assumes an orbital motion test running at 1 Hz with CoCrMo heads and cups (E = 229.3 GPa) and with $\eta = 0.001$ Pas (viscosity of water). A mean load value (W) of 1 kN may be used for this calculation, corresponding to a Paul cycle with 2.4kN peak load. Since this analysis is comparative, the exact load value is unimportant in this context.

The lambda ratio will then be calculated for each combination of head and cup/liner, using the following equation:

$$\lambda = \frac{h_0}{\sigma} = \frac{h_0}{\sqrt{\sigma_c^2 + \sigma_h^2}}$$

where σ_c = worst-case RMS roughness (R_q) of the cup, σ_h = worst-case RMS roughness (R_q) of the head

10. You listed frictional torque measurement as a special control for Experimental Bearings. Frictional effects are known to cause seizing and loosening in metal-on-metal hip systems. Therefore, we believe the friction between the insert and the cup is an important parameter in assessing the safety and effectiveness of a metal-on-metal hip systems. Please include interfacial rotational and flexion/extension frictional torque data on the system both before and after the devices undergo wear testing as a special control for "Conventional Bearings."

We agree, and will include interfacial rotational and flexion/extension frictional torque data as special controls for metal-on-metal hip systems before and after the devices undergo wear testing. Our recommendation is as follows:

Frictional Torque Special Control

Measure the frictional torque generated between the ball and socket of the hip prosthesis during loading and motion typical of human gait. Specifically, measure the frictional torque under the same loading and motion patterns used for hip simulator wear testing. Frictional torque should be measured prior to wear testing, after an initial wear-in period (if one is apparent) and after five million cycles of wear. If the wear simulator has suitable instrumentation, the frictional torque should be measured about three orthogonal axes, including about the load axis, about the flexion extension axis and about the abduction-adduction axis, during a typical wear cycle (i.e., that includes simultaneous motions about each of these axes.) If this is not possible, the frictional torque can be measured during uniaxial motions about the flexion, extension and rotational axes (which may involve cycling on a separate frictional test apparatus). If such uniaxial motion is applied to a metal-metal bearing, care should be taken that substantial galling wear of the metal surfaces does not occur that could result in artificially high frictional torques (i.e., that would not occur under more physiological, multi-axis motion.)

11. To certify that a device fits the definition of a conventional bearing you indicate the bearing should include at least one surface of high carbon alloy. It is unclear what is considered to be a high carbon alloy. Please define what is meant by a high-carbon or a low-carbon alloy and please specify a standard that must be met to certify the material is high-carbon. Also, when completing the attached table, please ensure that the definition provided in response to this item is applied to each entry for each head and cup material.

ASTM F 1537 Alloy 2 specifies the carbon content for high carbon wrought material as 0.15 to 0.35 % by weight. ASTM F 75 specifies the carbon content for cast material as 0.35 % maximum, with no minimum requirement. In practice, the minimum carbon content is defined by the internal specifications of each manufacturer. As a broad definition, high carbon alloy would contain 0.15 to 0.35%, carbon. Low carbon alloy contains less than that percentage. According to one of our petitioners, most manufacturers would generally not accept any alloy with less than 0.2 % carbon. A table with the chemical composition of alloys used in metal-on-metal bearings is included as Attachment 13. We have complied with your request to include the definition in each entry for head and cup materials in Attachment 1.

12. In Appendix 2, Unpublished Reports (pg. 158) there is an analysis by Jim Nevelős, Ph.D., that looks at 1st Generation Metal-on-Metal Hip Replacements (pg. 165). In Method 2 you evaluate retrieved components. Of the five sets of retrieved components, only one patient had a short term failure at 1 year with two of the failed components surviving for 20 years. Again, you conclude variability of manufacturing and tolerancing can have a significant impact on the clinical results and this data is supportive of modern metal-on-metal hips. Based on

the current follow-up data and proposed design parameters for metal-on-metal systems, it is difficult to differentiate why the current designs will be more successful than the first generation metal-on-metal systems. Please incorporate these manufacturing and tolerancing considerations into your special controls.

As previously mentioned, early failures of 1st generation devices were often due to poor dimensional controls during manufacturing which would allow for heads fractionally larger than the cups to be implanted. This led to equatorial bearing, high friction and loosening with wear patterns discussed by Kothari et al, CORR 1996; 329S:S141-147. (Copy enclosed in Attachment 4.) These problems were often due to lack of accurate measuring technologies which would allow for tolerancing such that equatorial bearing was not possible. An example would be outside diameters for heads (27.9 to 27.95 mm) and cups inside diameters measuring 28 to 28.05 mm which would provide a minimal diametrical clearance of 0.05 mm (50 microns) and a maximum diametrical clearance of 150 microns. These tolerances are limited by whether the components can be accurately measured to a precision less than the minimum clearance so that equatorial bearing is impossible. Tolerancing is now more carefully carried out based on lubrication analyses such as that reported in the literature by Jin ZM et al: Analysis of fluid film lubrication in artificial hip joint replacements with surfaces of high elastic modulus. Proc Inst Mech Eng 1997;211 (3):247-56 (see Attachment 14). These analyses, coupled with the clinical experience learned from 1st generation devices have led to the establishment of rigorously enforced inspection criteria and tolerance bands. Accurate quality control using coordinate measuring machines (CMM) means that minimum specified tolerance will be the actual minimum tolerance. Typical accuracy of a CMM is 1 micron in each axis, leading to radial measurements accurate to less than 2 microns. Therefore, equatorial bearing is no longer a clinical issue. Diametrical clearances and tolerances for each manufacturer are listed in Attachment 1. They can be used to develop special controls. Measurements of all components are part of the information included in the device master and history records.

13. You provided an Unpublished Report by Jim Nevelós, Ph. D., analyzing "Metal Ion Release from Metal on Metal Hip Replacement Implants." You conclude that "there is no causal link between joint replacement and cancer" and the clinical effects of chromosomal abnormalities is yet to be established. While the full effects of metal ions have not been established, there is much scrutiny regarding what the long term effects on patients will be. Therefore, the proposed special controls should clearly identify labeling measures that will ensure patient safety such as contraindications or warnings against the use of metal-on-metal devices in females of child bearing age, patients with renal insufficiency, patients with metal sensitivity, patients on medications (such as high dose or chronic aminoglycoside treatment) or with co-morbidities (such as diabetes) that increase the risk of future renal impairment, etc.

We agree that the recommended contraindications and warnings are warranted and can be included in the special controls. Our suggestions on labeling are as follows:

LABELING

The following indications for use, relative contraindications, warnings, precautions and potential adverse effects were identified by a previous panel and by the agency for devices to be reclassified:

Indications for Use

The metal-on-metal total hip replacement prosthesis is indicated for use in patients requiring hip replacement due to the following conditions:

- a) Non-inflammatory, degenerative joint disease including avascular necrosis, diastrophic variant, fracture of the pelvis, fused hip, Legg-Calve-Perthes disease, osteoarthritis, slipped capital epiphysis, subcapital fractures, and traumatic arthritis;**
- b) Rheumatoid arthritis**
- c) Correction of functional deformity**
- d) Treatment of non-union, femoral neck fracture, and trochanteric fractures of the proximal femur with head involvement, unmanageable using other techniques**

2. Failed previous surgery including: joint reconstruction, internal fixation, arthrodesis, surface replacement arthroplasty, hemi-arthroplasty or previous hip replacement.

Relative Contraindications

Bone or musculature compromised by disease, prior infection, or prior implantation that cannot provide adequate support or fixation of the prosthesis, any active or suspected infection in or about the hip, skeletal immaturity, metal sensitivity, and females of child bearing age.

Warnings

Patients with kidney disease or compromised renal function may not be candidates for implantation with metal-on-metal hip prostheses.

Patients on medications (such as high dose or chronic aminoglycoside treatment or with co-morbidities (such as diabetes) that increase the risk of future renal impairment may not be candidates for implantation with metal-on-metal devices.

Patients should be warned about the impact of excessive loading that can result if the patient is involved in an occupation or activity that includes substantial

walking, running, lifting, or excessive muscle loading due to patient weight that place extreme demands on the hip and can result in device failure.

Precaution

Do not combine components from different manufacturers. This may lead to premature wear or failure of the device.

Potential Adverse Effects

1. Infection
2. Pain
3. Loosening, wear or mechanical failure of prosthetic components
4. Dislocation of the hip prosthesis requiring additional surgery
5. Localized progressive bone resorption (osteolysis)
6. Nerve impingement or damage, vascular disorders (including thrombus)
7. Heterotopic bone formation
8. Sensitivity to implant materials*
9. Gastrointestinal and/or genitourinary complications
10. Pulmonary embolism
11. Death
12. Myocardial infarction
13. Effusion
14. Bursitis
15. Special Note: Although there is no conclusive evidence of the relationship between orthopedic implants and malignant tumors, any condition that causes chronic damage to tissues may be oncogenic.

* A low incidence of metal sensitivity has been reported with failed metal-on-metal implants. The clinical relevance of these findings is unclear, and it not known whether metal hypersensitivity causes implant failure.

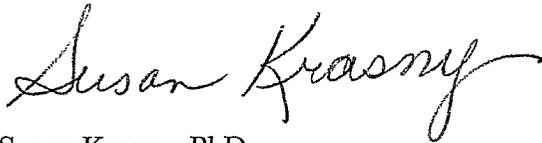
Special Controls Summary

As noted above, we recognize that in order to change the classification of metal-on-metal hip prostheses it is necessary to have sufficient regulatory controls to provide reasonable assurance of the safety and effectiveness of the device for its intended use. We believe such information is contained in our initial petition and with this submission. Attachment 6 addresses the issue of diametrical clearance and demonstrates that wear simulation using an 8-station hip joint simulator can distinguish between good and suboptimal designs. Fluid film thickness can be calculated using the formula provided in question 9. Surface roughness is incorporated in the equation as a means of providing a special control. We have included a suggested protocol for frictional torque in question 10. ASTM standards F 1537 and F 75 can be used to ensure the metal composition for metal-on-metal

devices. We agreed that the labeling supplied in question 13 are warranted and should be part of the special controls.

If you require additional information or have any questions, please contact the undersigned by telephone at 201 760-8150 or by email susan.krasny@stryker.com.

Sincerely yours,

A handwritten signature in cursive script that reads "Susan Krasny". The signature is written in black ink and is positioned above the typed name and address.

Susan Krasny, PhD
OSMA President
2 Pearl Court
Allendale, NJ 07430

Enclosures