DEPARTMENT OF H. .LTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

JUN 29 2006

0034 7 SEP 24 A10:23

Ms. Sally L. Maher
President
Orthopedic Surgical Manufacturers Association
325 Corporate Drive
Mahwah, New Jersey 07430

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
Received: August 10, 2005
Amended: September 22, 2005

Dear Ms. Maher:

The Food and Drug Administration has reviewed the above referenced petition for reclassification pursuant to section 513(e) of the Federal Food, Drug, and Cosmetic Act (Act). Metal/Metal semiconstrained hip joint prostheses are currently Class III 510(k) devices. This petition seeks reclassification of Metal/Metal Semiconstrained Hip Joint Prostheses with Cemented or Uncemented Acetabular Components from Class III 510(k) status to Class II 510(k) status.

As you are aware, when Metal/Metal Semiconstrained Hip Joint Prostheses with Cemented or Uncemented Acetabular Components (21 CFR 888.3320 and 888.3330) were originally classified as Class III. The classification panel identified risks to health which became the basis for classifying this device type as Class III. The basis for the classification was that the Panel believed these risks could not be controlled by either general controls (e.g., Registration and Listing, adherence to Good Manufacturing Practices (GMPs)) or special controls (e.g., performance standards, FDA Guidance Documents, postmarket surveillance, and patient registries).

The purpose of a reclassification petition is to demonstrate that the risks previously identified for a preamendments Class III device, in light of new information, can be adequately addressed/minimized by either special controls, along with general controls, and, therefore, should be reclassified as Class II devices.

Based on review of the data submitted in your petition, we are unable to further consider reclassification of these devices until the following concerns have been adequately addressed. In particular, we continue to have questions regarding the differences between the designs of the recently cleared metal-on-metal hip systems that are clinically successful versus the first generation of devices that were unsuccessful. We must identify these key characteristics in order

2005P-0405

LET 3

to determine if all metal-on-metal hip systems may be downclassified or if some devices should remain Class III.

Device Characterization:

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 pg. 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.

    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.

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

    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).

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.

Preclinical Testing:

3. In your January 10, 2003 letter to Mr. Phil Phillips, Deputy Director, Science & 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, DuPuy 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 are 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 through hip simulator testing." No further information is provided regarding the wear evaluation completed by these manufacturers. Please provide the full test report and protocol for the analysis completed comparing designs with positive and negative clearances.

Unpublished Clinical Studies:

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 hip 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 later post-operative 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.

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

    a. On pg. 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.

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

    c. The Kaplan-Meier survival estimates plots include survival of the devices and 95% upper and lower confidence limits. It may be more informative to compare the survivorship results of 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.

    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.

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 yrs, etc.). This 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://www.fda.gov/cdrh/ode/guidance/1542.pdf.

Adverse Events:

7. In Section VIII you provided a summary of fifty nine adverse events made available through Medical Device Reporting (MDR) regulations. The analysis includes 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. 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.

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 whose 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."

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.

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 system and should be evaluated for all 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."

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.

Analysis of First Generation Devices:

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.

Biological Studies:

13. You provided an Unpublished Report by Jim Nevelős, 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.

If you submit information correcting these deficiencies, we will reevaluate your reclassification petition. Please provide five (5) copies of your response to this letter. The information should reference the above docket number (2005P-0405) and be submitted to:

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

If you have any questions related to reclassification, please contact Ms. Marjorie Shulman at (301) 594-1190, extension 132. For scientific and technical assistance, please contact Ms. Elizabeth Frank by phone at (301) 594-2036, extension 115 or by email at elizabeth.frank@fda.hhs.gov.

Sincerely yours,

Donna-Bea Tillman, Ph.D.
Director
Office of Device Evaluation
Center for Devices and
Radiological Health

Attachment 1: Device Comparison Table

Device	Example				
510(k) Number	**K060000**				
Femoral Heads:					
Material	Cast High Carbon CoCrMo (ASTM F-75)*				
Diameter	28 & 32mm				
Sphericity	<5 microns				
Surface Finish	0.005 microns				
Taper Sleeve Adapters Taper Geometry	Femoral Heads: 12/14 internal taper Cast High Carbon CoCrMo alloy (ASTM F-75)				
Taper/Neck Lengths	12/14 taper; -3.5, 0, +3.5mm offset necks				
Acetabular Component	**Metal Liner**				
Material	Cast High Carbon CoCrMo (ASTM F-75)*				
Method of Fixation (Coating Type)	Porous Coating (Sintered beads)				
Outer Diameter	44-64mm (in 2 mm increments)				
Inner Diameter	28 & 32mm				
Sphericity	<5 microns				
Surface Finish	0.005 microns				
Diametrical Clearances and Tolerances**	28mm: nominal 100μm ± 20μm (min: 80μm, max: 120μm) 32mm: nominal 120μm ± 20μm (min: 100μm, max: 140μm)				
Range of Motion	28 mm – 126° 32mm – 132°				
Wear Rates	28mm – 0.73 $mm^3/10^6$ cycles 32mm – 0.15$mm^3/10^6$ cycles				

Attachment 1 Continued: Device Comparison Table

Rotational Frictional Torque Measurements	32mm – 2.6Nm				
Flexion/Extension Frictional Torque Measurements	32mm – 7.7Nm				

* Per definition identified in response to item 11.

**For the diametrical clearances please include the least and most tolerances for both the head and liner. In addition, please do not group all sizes together. Please list each size and each minimum and maximum clearance range for each diameter separately.