
Reclassification Memorandum

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Subject: Reclassification Petition for Metal/Metal Semi-Constrained Hip Joint Prosthesis
To: File

Through: Celia Witten, Division Director of General and Restorative Devices

Date of Petition: September 25, 2000
Amended: November 28, 2000, June 4, 2001

Overall Summary:

This petition seeks reclassification of the Metal/Metal Semi-Constrained Hip Joint Prosthesis with cemented and uncemented Acetabular Components from Class III premarket approval (888.3320 and 888.3330) to Class II allowing for premarket notification, 510(k) clearance. The petitioner has provided a the summary and results of three unpublished studies comparing the metal/metal semi-constrained hip joint prosthesis to metal/polymer semi-constrained hip joint prosthesis. The petitioner also provided a tabular summary of clinical results of several significant published clinical studies. The risks stated in the petition are all similar risks endured by the metal/polymer semi-constrained hip joint prosthesis. In order to control these risks, the petitioner has identified special controls (labeling, pre-clinical test methods, standards, and general 510(k) controls). Lastly, the petition provided a literature summary of old and new designs for hip joint prostheses.

Petition Basis

This document is a petition for reclassification of metal/metal, semi-constrained total hip prostheses, cemented or uncemented, from class III to class II. Sufficient evidence now exists that addresses the risks cited in the July 2, 1982 Proposed Rule (Ref 47 FR 29052) that originally led to placement of these devices into class III. In the Proposed Rule, FDA commented that insufficient clinical experience existed to fully establish the persons for whose use the devices are intended and proper conditions of use. The petitioner believes that published and unpublished information, both in the U.S. and Europe, since the original classification of these devices by FDA now provides sufficient proof of the safety and efficacy these designs to the degree that risks to patients can be adequately controlled by class II controls. This reclassification petition consists of a summary report of the testing of metal/metal hip designs from the medical and scientific literature, a summary report of the data from regulated prospective multi-center clinical trials of metal/metal semi- constrained total hip prostheses conducted in the U.S. and Europe and a summary of the published clinical outcomes. Also included is a summary of the adverse events reported to the U.S. and European regulatory authorities and reported in the published literature. Another section assesses the known risks to patients by these devices and how these risks can be adequately controlled via the pre-clinical testing, labeling and other regulatory requirements imposed on class II devices.

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The petition satisfies all administrative requirement for filing. See attachment 4.

Recommendation: I recommend that this reclassification petition for the metal/metal hip joint prosthesis be placed on hold for further review and panel input.

1. Device Description

The following describes the devices for which reclassification is being sought.

A. General Device Description

Total hip prostheses are orthopaedic reconstructive devices intended to replace the principal articulating surfaces of the hip joint where these surfaces are not present or have been severely damaged by inflammatory or degenerative joint disease or by traumatic injury. The main objectives of this surgery are relief of pain and restoration of function.

Total hip prostheses generally consist of two components, a femoral component and an acetabular component. Either of these components can be modular in design (e.g. a taper-fit femoral head and a metal acetabular shell with an insert liner). The femoral component is intended to replace the head of the femur, and its stem is inserted into the medullary canal of the femur to anchor it. Femoral components are manufactured from alloys such as cobalt-chromium-molybdenum or titanium-aluminum-vanadium. Femoral components may be fabricated as a single piece (head-stem) or they may be modular with separate head and stem components having a variety of head diameters/neck lengths that can be fitted to a stem of a chosen size. Modular femoral components are generally fitted together by Morse taper connections. Femoral stems may be cemented or press-fit into the medullary canal of the femur. The spherical femoral head is designed to articulate with the acetabular component that is fixed into the prepared acetabulum.

The metal/metal acetabular component can either be a one-piece design or a modular design. For one-piece metal designs, the entire component can be fabricated from a single piece or it may have a metal insert that is permanently welded to the metal outer shell. One-piece metal and polyethylene component designs have a polyethylene outer shell that is molded to the metal insert.

The modular acetabular designs consist of either a metal insert component that is secured to the metal outer shell by means of a Morse taper, or a polyethylene component that is molded to a metal insert which is then secured to the metal outer shell by means of a mechanical interlock. The acetabular components are manufactured in a variety of sizes and inner diameters to meet the anatomical needs of patients. They are secured to the prepared acetabulae employing different fixation methods including bone screws, spikes, fins, threads, bone cement, and/or porous coatings for biological fixation. (Porous coated, semi-constrained hip prostheses intended for use without bone cement were reclassified from class III to class II by the FDA in 1994)

FDA comments: The petitioners device description is very similar to the currently approved metal/metal semi-constrained hip joint prosthesis. The petitioner did not identify the individual metal/metal semi-constrained hip joint prosthesis that is intended to be reclassified. Also, they identified that geometry and surface finish of the femoral head and acetabular component as being two major design issues facing metal/metal semi-constrained

hip joint prosthesis, but did not provide any specific values for these design issues. Some of these issues such as sphericity, clearance, and surface roughness play an important role in the success of a metal/metal hip prosthesis

Response: After several conference calls with the petitioner, it was concluded that they are trying to reclassify all metal/metal hips, except those with screw in acetabular cups. This is reflected in their proposed CFR classification wording. Also they plan on submitting a range of values for the specific design parameters. They are going to submit a range of values for clearances between the femoral head and the metal bearing insert, surface roughness of the femoral heads and metal bearing surfaces, femoral head sphericities, grain size for the femoral heads and bearing inserts, and metal alloys for the femoral head and bearing inserts, and diameters of the heads and bearing inserts. See above for the specific range of values.

2. CFR Classification

CFR CLASSIFICATION OF METAL/METAL SEMI-CONSTRAINED HIPS

A. Current CFR Classifications of Metal/Metal Semi-Constrained Hip Prostheses

888.3320 Hip joint, metal/metal semi-constrained, with a cemented acetabular component, prosthesis.

(a) *Identification.* A hip joint metal/metal semi-constrained, with a cemented acetabular component, prosthesis is a two-part device intended to be implanted to replace a hip joint. The device limits translation and rotation in one or more planes via the geometry of its articulating surfaces. It has no linkage across-the-joint. This generic type of device includes prostheses that consist of a femoral and an acetabular component, both made of alloys, such as cobalt-chromium-molybdenum. This generic type of device is limited to those prostheses intended for use with bone cement. (888.3027).

(b) *Classification.* Class III.

888.3330 Hip joint, metal/metal semi-constrained, with an uncemented acetabular component, prosthesis.

(a) *Identification.* A hip joint metal/metal semi-constrained, with an uncemented acetabular component, prosthesis is a two-part device intended to be implanted to replace a hip joint. The device limits translation and rotation in one or more planes via the geometry of its articulating surfaces. It has no linkage across-the-joint. This generic type of device includes prostheses that consist of a femoral and an acetabular component, both made of alloys, such as cobalt-chromium-molybdenum. The femoral component is intended to be fixed with bone cement. The acetabular component is intended for use without bone cement (888.3027).

(b) *Classification.* Class III.

Requested Classification

Based upon the information contained in this petition, the sponsor proposes the following changes to the descriptions and identifications under the device classification codes listed in 21 CFR 888.3320 and 888.3330 for total hip prostheses. Please note that all proposed changes appear in bold face type.

888.3320 Hip joint, metal/metal semi-constrained, with a cemented acetabular component, prosthesis.

(a) *Identification.* A hip joint metal/metal semi-constrained, with a cemented acetabular component, prosthesis is a two-part device intended to be implanted to replace a hip joint. The device limits translation and rotation in one or more planes via the geometry of its articulating surfaces. It has no linkage across-the-joint. This generic type of device includes prostheses that consist of a femoral and an acetabular component, both made of alloys,

such as cobalt-chromium-molybdenum. This generic type of device is limited to those prostheses intended for use with bone cement (888.3027).

(b) *Classification Class II.*

888.3330 Hip joint, metal/metal semi-constrained, with a porous coated, uncemented acetabular prosthesis.

Identification. A hip joint metal/metal semi-constrained, porous-coated uncemented acetabular prosthesis is a device intended to be implanted to replace a hip joint. The device limits translation and rotation in one or more planes via the geometry of its articulating surfaces. It has no linkage across-the-joint. This generic type of device has a femoral component made of a cobalt-chromium-molybdenum (Co-Cr-Mo) alloy or a titanium-aluminum-vanadium (Ti-6Al-4V) alloy and an acetabular component composed of a metal articulating bearing surface in a metal shell made of Co-Cr-Mo or Ti-6Al-4V. The acetabular shell has a porous coating made of, in the case of Co-Cr-Mo substrates, beads of the same alloy, and in the case of Ti-6Al-4V substrates, fibers of commercially pure titanium or Ti-6Al-4V alloy. The porous coating has a volume porosity between 30 and 70 percent, and average pore size between 100 and 1,000 microns, interconnecting porosity, and a porous coating thickness between 500 and 1,500 microns. The generic type of device has a design to achieve biological fixation to bone without the use of bone cement. The femoral component is intended to be fixed with or without bone cement.

Classification. Class II.

Identification. A hip joint metal/metal semi-constrained, uncemented acetabular prosthesis is a device intended to be implanted to replace a hip joint. The device limits translation and rotation in one or more planes via the geometry of its articulating surfaces. It has no linkage across-the-joint. This generic type of device has a femoral component made of cobalt-chromium-molybdenum (Co-Cr-Mo) alloy or a titanium-aluminum-vanadium (Ti-6Al-4V) alloy and an acetabular component composed of a metal articulating bearing surface in a metal shell made of Co-Cr-Mo or Ti-6Al-4V. The acetabular shell has no porous coating and fixation is achieved by means of threads on the metal shell, or by other uncemented means. The femoral component is intended to be fixed with or without bone cement.

Classification. Class II – This device as described in the above *Identification* will be subject to the availability of clinical data in support of substantial equivalence in addition to the other special controls listed in this regulation.

Changes to the CFR definition:

The only changes made in the CFR definition 888.3320 were changing the device from a Class III to a Class II. The changes made to the CFR definition 888.3330 are the following:

- The title of the regulation was changed by adding the phrase “with a porous coated” between the “semi-constrained” and “uncemented”. This change narrows down the field of devices to only porous coated when being cemented. Other changes that were made were the addition of “made of a cobalt-chromium-molybdenum (Co-Cr-Mo) alloy or a titanium-aluminum-vanadium (Ti-6Al-4V) alloy and an acetabular component composed of a metal articulating bearing surface in a metal shell made of Co-Cr-Mo or Ti-6Al-4V. The acetabular shell has a porous coating made of, in the case of Co-Cr-Mo substrates, beads of the same alloy, and in the case of Ti-6Al-4V substrates, fibers of commercially pure titanium or Ti-6Al-4V alloy. The porous coating has a volume porosity between 30 and 70 percent, and average pore size between 100 and 1,000 microns, interconnecting porosity, and a porous coating thickness between 500 and 1,500 microns. The generic type of device has a design to achieve biological fixation to bone without the use of bone cement.” to the end of the definition. These changes limit the device material to Ti-6Al-4V and Co-Cr. These changes also limit the porosity, pore size, and coating thickness of the porous coating on the implant.

- A third identification was added to identify threaded acetabular components, which will be supported by clinical data.

3. Indications for Use, Contraindications, Warnings, Precautions, and Adverse Events

The following indications for use, relative contraindications, warnings, and precautions were identified by a previous panel for the 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.
- e) Failed previous surgery including: Joint reconstruction, internal fixation, arthrodesis, surface replacement arthroplasty, hemi-arthroplasty or previous total hip replacement.

Relative Contraindications

1. Bone or musculature compromised by disease, infection, or prior implantation that cannot provide adequate support or fixation for the prosthesis.
2. Any active or suspected infection in or about the hip
3. Skeletal immaturity

Warnings

1. Patients should be warned on 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 causing extreme demands on the hip that can result in the failure of the device. Extreme demands on the device may also cause loosening of the prosthetic components.
2. Bending, contouring, or modifying the device may adversely affect the implant potentially leading to early implant failure.
3. 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

Summary

The above risks to health have been identified for metal/metal semi-constrained hip joint prosthesis. This information is found in currently approved for metal/metal semi-constrained hip joint prosthesis. Are the proposed indications for use, contraindications for use, warnings, precautions, and adverse events adequate for metal/metal semi-constrained hip joint prosthesis. If not, please identify additional information for the indications for use, contraindications for use, warnings, precautions, and adverse events.

FDA comments: The intended uses, relative contradictions, warnings, and adverse events are identical to those of previously cleared metal/metal hip joint prosthesis.

4. Summary of Pre-Clinical Testing

The pre-clinical testing provided in the reclassification petition was based solely on literature reviews.

Introduction

Metal/metal femoral head-acetabular cup combinations were originally introduced in the 1960s with implants such as the McKee-Farrar, Ring, Stanmore, Sivash, and Muller prostheses. These first generation metal/metal devices 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.^{139,185,189,192}

It is clear, however, that the problems undermining the clinical success of the first generation metal/metal joints resulted primarily from suboptimum implant design and manufacture. It is important to note that these problems were not related to the wear performance of the metal/metal bearing combination itself. Indeed, many of the early metal/metal implants have survived in situ for over two decades,^{139,189} and there have been only few documented reports of associated problems with peri-implant osteolysis (which were deemed to be related to polymethylmethacrylate particles, not metal^{24,58,71}). Furthermore, analyses of retrieved metal/metal components after long service periods typically indicate highly polished surfaces with minimal scratches, near maintenance of the original surface finish,^{34,39,40,59,61,75,138,185} and relatively low linear and volumetric wear.^{34,132,138,139,189,190,191}

Much of the recent work published in the orthopaedic literature has focused on the design parameters that control the wear of metal/metal hip implants with the following major conclusions.

Design Issues

I. Material

Metal-metal implants have been traditionally fabricated from surgical grade cobalt-chromium-molybdenum (CoCrMo) alloys because of their corrosion and wear resistance. They are generally well-suited as self-bearing materials and are known for a specific self-healing capacity where visible surface scratches are typically polished out rather than made progressively worse with continued cycles in service.^{122,124,141,142} This is an essential property in light of the possibility of entrapment of third body wear particles (metal or acrylic) or release of hard carbide phases of certain CoCrMo alloys into the articulating interface during service.^{141,142}

Both cast and wrought forms of CoCrMo have been used clinically with reasonable success.^{69,185} Although many engineering details about first generation metal-metal hip implants were largely undocumented (or undisclosed), it is known that the original McKee-Farrar implants were made from the cast material. The wrought alloy, on the other hand, is available with varying levels of carbon with nominal levels of < 0.05 % and > 0.25 % carbon for low and high carbon alloys, respectively. With differing levels of carbon content, the relative wear resistance of either wrought CoCrMo has been the subject of experimental scrutiny.^{69,89,91,133-135} Wrought alloys in general have also been shown to exhibit lower friction in pendulum studies.^{69,133-135} Streicher et al^{69,135} have suggested

that high carbon wrought rather than cast CoCrMo alloys has superior wear performance based on pin-on-disc wear testing with a very high contact stress. This behavior may have resulted from the presence of small, finely distributed carbides at the component surface rather than the coarse, more widely spaced carbides of the cast alloy.^{69,133-135} The smaller carbides and smaller grain sizes of the wrought material generally result in reduced surface roughness and increased hardness thus enhancing mechanical properties. Because the low carbon grade of wrought CoCrMo alloy does not have pronounced carbides at the surface, even lower surface roughness can be achieved. In terms of wear performance, however, the benefits of decreased surface roughness may be compromised by the slight decrease in bulk hardness of the low carbon wrought material.^{69,133-135} However, recent laboratory evaluations using sophisticated hip material simulators have indicated that both cast and wrought forms of CoCrMo, with the wrought material in both low and high carbon formats, exhibit similar wear properties.^{19,91} It is important to note that this was the case when other design variables (to be discussed) were held relatively constant, suggesting that wear performance is less sensitive to the particular grade of CoCrMo alloy when other specific engineering parameters are well-controlled within specific limits. **See below for explanation of exact material standards.**

2. Clearance

To avoid problems related to high frictional torques and equatorial seizing associated with first generation metal/metal implants from the 1960s, the current approach is to provide a small gap or clearance between the femoral head and acetabular cup components. This ensures a polar contact, where the head-cup contact area is necessarily placed away from the equator.^{136,139}

Suggestions have been made that an optimal range of clearance values (mismatch between the major head and cup diameters) exists for metal/metal articulations with lower clearances favorable for improved wear performance.^{61,69,133,135} This has been confirmed in recent studies where head-cup clearance was identified as an independent parameter affecting metal/metal wear performance.^{84-91,93,94,97-100,107,130} In spite of this work, the optimum clearance may not be the lowest possible mismatch that can be manufactured. Extremely small clearances can result in off-the-shelf parts to be matched with an excessively tight fit, thus resulting in congruent head-cup components and potentially resulting in the equatorial contact that plagued the original first generation designs. Furthermore, tight clearances can also prevent the ingress of lubricant and egress of wear particles. Therefore, the optimum design clearances must be a combination of low clearance to achieve low wear and high enough clearance to meet design safety.^{84-91,93,94,97-100} **See below for exact clearance parameters.**

3. Form and Finish

With the availability of both improved manufacturing processes and sophisticated metrology devices used for quality assurance, head and cup components can be manufactured with high quality surfaces and form (sphericity). Much of the recent metal/metal testing has been performed on parts that have been finished on several commercially-available final-stage grinding units that can achieve extremely good sphericity and low surface roughness values.

Form has not been specifically quantified as a parameter affecting metal/metal wear. However, it has been suggested that the initial period of slightly accelerated wear (often referred to as the wear-in or bedding-in phase) is the correction of initial asphericity between the head and cup components. Better sphericity may therefore result in a gentler wear-in phase and thus a lower amount of total wear.^{89,90,100}

Surface roughness, however, has been identified as a variable that can modulate the wear performance of metal/metal parts. Simulator studies have shown that wear decreases with lower starting surface roughness values.^{84-91,93,94,97-100} This is particularly important as femoral head surface roughness has not been identified in the literature as a critical design parameter affecting metal/polyethylene wear. Manufacturers, therefore, must try to achieve lower surface roughness for both the head and cup components of a metal/metal bearing through advanced grinding and polishing technologies. **See below for exact surface roughness parameters.**

4. Lubrication

In first generation metal/metal implants, a type of lubrication referred to as boundary lubrication was thought to have occurred where molecular components of the lubricant would bond chemically to the metal head and cup surfaces. The adherent lubricant layer would shear in preference to the surfaces themselves, thus providing some degree of surface protection during articulation.¹³⁶⁻¹³⁸

While it would be difficult to achieve full fluid film lubrication where a microscopic layer of lubricant would completely separate the head and cup surfaces in relative motion, some degree of lubrication may be expected. Theoretical studies employing advanced lubrication theory have indicated that strict control over design and manufacturing can, in fact, produce conditions favorable for fluid film lubrication to occur.^{92,100,109} Specifically, low clearance values can result in larger head-cup contact areas and the corresponding generation of thicker lubricant film layers at the articulating interface.^{92,100} Furthermore, lower surface roughness values have also been shown theoretically to result in a more effective lubricant layer (because rough counterface surfaces would require a thicker lubricant layer for complete separation compared with smooth surfaces which can be separated by thinner lubricant layers), thus enhancing the state of lubrication between the articulating surfaces.^{92,100} In fact, a time-varying lubrication model was developed that suggested that sufficiently low clearance and low surface roughness can result in good fluid film lubrication of metal/metal implants even under the varying loads experienced in service due to normal gait.^{92,100} It should be emphasized that these studies were theoretical analyses based on established lubrication theories that have been proven for other engineering fields. However, of note is a recent study which provided direct experimental evidence of lubrication for metal/metal hip implants tested on a hip simulator.¹⁰³ This work is important because it corroborates the previous theoretical studies indicating that the protection of metal/metal articulating surfaces is possible through an interposed fluid layer and that lubrication is a major mechanism in the wear reduction of metal/metal bearings. Coupled with theoretical lubrication studies and the extensive database of published wear test results for metal/metal hips, low wear can be achieved when specific major design parameters are properly controlled.

Simulator Issues

All modern evaluations of metal/metal implants have been performed using simulators that subject the test specimens to close-to physiological load levels and motion. Because these tests are simulations, it is important to determine how closely they represent in vivo wear morphology. For metal/metal implants, Park et al¹²² compared the morphology of wear produced in several types of hip simulators from different laboratories to what has been observed on retrieved metal/metal implants. Allowing for differences in the location of the wear zones, a result of specific kinematics unique to each machine, the types of wear appeared very similar amongst the machines. Perhaps of greater importance is that the types of wear were also found to be very similar to what was seen on the retrieved modern metal/metal hip bearings examined in the same study.

From a wear particle standpoint, Campbell et al¹⁵⁰ examined the histological appearance of tissue around retrieved metal/metal hip implants to characterize metal wear particles. They found that particles were relatively small (<200 =) with the majority of particles described as amorphous with undefined edges (i.e. oval or round). The particle morphology from Campbell et al¹⁵⁰ so was confirmed in a similar study by Catelas et al¹⁵² in which the majority of particles extracted from the serum of simulator-tested metal/metal hip implants was identified as either round or oval and less than approximately 233nm in size. It is encouraging, therefore, that existing metal/metal simulator studies have produced results that correlate well with clinical data, indicating that hip wear simulators are viable tools for evaluating wear performance. **See below for wear testing protocol.**

Biological Issues

A significant amount of research has been performed using animal and biologic models to assess the biological response to metal implants. These articles explain the level of metal particles/ions released, the nature of any

reactions, where these particles eventually reside, how they are able to move within the system, and long term effects.

1. Particles and Inflammatory Response

Doom et al¹⁵⁵ and Amstutz et al¹⁸³ presented reviews of histologic reaction to metal versus polyethylene wear in total hip replacements. Polyethylene particles were found to generate a cellular response consisting of mononuclear histiocytes and multinucleate foreign body cells; metal wear particles generated a reaction of mononuclear histiocytes with rare giant cells.

Doorn et al¹⁵⁷ analyzed four long term McKee-Farrar (21-25 years) implants and five short term metal/metal implants (<2.5 years) of various designs. Metal particle sizes ranged from submicrometre to 1-4 μm . Generally, the metal debris did not invoke production of multinucleate giant cells as had been previously seen with polyethylene implants, most likely due to differences in size and number of particles. The lower volumetric wear (10-40 times less) with metal/metal as compared with metal/polyethylene is significant with respect to the lower amount of histiocytic reaction seen. Doorn reported that the distribution of the histiocytes reflected the initial pathway of the metal particles. After being ingested along the synovial surface, particles were transported to lymph or deeper soft tissues. These findings were also supported by Brodner et al¹⁴⁸ and Jacobs et al¹⁶⁵ who found elevated levels of serum cobalt and serum chromium. If transport of particles via the lymph system was less than the locally produced amount, histiocytes should eventually fill the periprosthetic tissue. If an excess amount of metal particles is generated, local tissue buildup could occur with possible harmful response to the bone/implant interfaces. However, if wear generation was not excessive, equilibrium and histiocytic activity could be maintained within the periprosthetic tissue.

Campbell et al¹⁵⁰ examined the histological appearance of tissue around retrieved metal/metal hip implants and determined the biological response to particles. They found that there were fewer macrophages and wear particles in these tissues compared with typical samples from metal/polyethylene hips. In general, the macrophage and giant cell response to particles from metal/metal articulations was described as "mild".

Willert et al¹⁸² evaluated 19 retrieved metal/metal devices as well as the surrounding tissues. Chromium was found in the greatest proportion followed by cobalt, nickel and molybdenum. Although the ratio of chromium to cobalt in the initial material was reported to be 0.5 to 1, tissue analysis revealed a significant shift (10 to 18 times higher) towards chromium. Tissues surrounding the retrievals were not dominated histologically by metal particles as very little particulate wear was found. Similar to the work of Doorn et al¹⁵⁷, particle size ranged from 0.5 to 5 μm . Even more similar is the fact that particles were also found around blood vessels, indicating transport via the perivascular lymphatics, which has also been suggested by Doorn¹⁵⁷.

Langkamer¹⁶⁸, like Willert¹⁸² and Doorn¹⁵⁷, presented a review of systemic wear debris in two total hip retrieval cases (titanium hip implant, Charnley stainless steel hip implant). Tissue analysis revealed that chromium levels increased to a ten fold level in the synovium, bursa and lymph nodes. Although widespread particle dissemination was found in the nodes, spleen and liver, concentrations were highest in the synovium and tapered off into these more distant organs. This report confirmed that particles move via the lymphatic system.

2. Toxicity

Merritt et al¹⁷¹ reported on the distribution of metal products and the associated biologic reactions. The majority of materials from which orthopedic devices are manufactured (cobalt, nickel, molybdenum) were rapidly cleared from the body in urine. Chromium⁴³ (the same valence as nutritional supplements) was less toxic to cells while the Cr⁴⁶ state was shown to become cell-associated and highly toxic. This form is unlikely to occur in the use of metallic implants. Studies involving CoCr injections have shown that there is initial cell toxicity as corrosion begins, but that normalization occurs once the particles are completely corroded to the ionic state and removed.

Howie et al¹⁶⁴ noted that cellular models showed that once phagocytosed, the metal oxides of CoCr particles were disrupted by the reduction in pH, causing release of cobalt ions. These CO^{+2} ions, which were more stable at neutral pH, were suggested to be toxic to cells. Chromium in the Cr^{+3} form, on the other hand, was more stable at neutral pH because it could not cross cell membranes as could Cr^{+6} ions (highly toxic). Studies to date have shown no formation of the Cr^{+6} ions from solid implant materials. Howie also reported that intra-articular injection studies in rats revealed that exocytosed cobalt (from digested CoCr) at cell death seemed to lessen particle toxicity to other cells. This was confirmed by presence of early macrophage cell death followed by the appearance of healthy macrophages containing endocytosed material. Howie warned that animal models may not be fully representative of human responses since single bolus delivery is often used (instead of over time) and animal sensitivity may be at question.

3. Hypersensitivity

Evans et al¹⁵⁸ analyzed 39 patients with uninfected CoCr components, and suggested an association between loosening and sensitivity to the metal alloy. Metal sensitivity tests revealed that in cases in which the component was loose, nine showed metal sensitivity whilst five did not. Of 24 cases in which there was no loosening, no metal sensitivity was detected. The correlation between loosening and sensitivity was not statistically relevant and there have been no additional studies to date expressing this relationship.

4. Carcinogenicity

Howie et al¹⁶⁴ reported that particulate CoCr in animal models, whilst still associated with macrophages, had shown a doubtful link to tumor formation. Chromium in the Cr^{+3} form, which is more stable at neutral pH, is not able to cross cell membranes as is the case with Cr^{+6} , the extremely toxic Cr^{+6} ions. Studies to date have shown no formation of the Cr^{+6} ions from solid implant materials.

Lewis et al¹⁶⁹ presented results of rats injected intra-articularly with wear particles 1.5 to 50 μm in size and examined over a two year period. CoCr particles were generated in a wear simulator. Positive (nickel subsulfide) and negative (manganese) controls were also used. Those rats receiving CoCr particles had no local tumors. Particles were identified in the subsynovium with minimal fibrosis. The author offered that a significantly larger group (500 rats) would be needed to substantiate a 1% tumor incidence.

Swanson et al¹⁷⁵ pointed out that although his wear and laboratory studies in rats did tend to indicate that CoCr particles constitute a risk of carcinogenesis, the risk is extremely small and not calculable. Additionally, the probable induction period is longer than the life expectation of many patients who could potentially benefit from such operations. As an interesting comparison, Swanson noted that earlier rat studies on larger particle polyethylene generated this same conclusion (carcinogenesis).

Case et al¹⁵³ analyzed the genetic aberration (chromatid breaks, gaps, etc.) in the marrow samples of 71 revision arthroplasty patients and 30 primary arthroplasty patients. Revisions included 27 Charnley devices, 17 D-series, 5 Howse, 6 Thompson, 1 each of Harris-Galante, Wagner, Stanmore, and Exeter, 3 unknown, and 2 each of McKee-Farrar and Ring prostheses. Case found that aberration was higher (statistically significant) in marrow cells adjacent to stems in revision cases than in marrow of the iliac crest of the same patient or in patients undergoing primary arthroplasty. These findings are significant since the majority of the revision cases were "standard" arthroplasty devices and not metal/metal devices.

Visuri et al¹⁷⁸ reported on 433 cemented McKee-Farrar patients (511 devices) operated on from 1967 to 1973 representing 5729 person years. Average follow-up was 9.2 years for males and 9.8 years for females. Using the Finnish cancer registry, it was found that the risk of total cancer of THR patients did not increase. However, the incidence of site specific cancers did vary. A decreased risk of breast cancer was found. A slightly increased risk of leukemia and lymphoma was also found. The author cited other published reports supporting the fact that while cobalt has carcinogenic properties, there was inadequate evidence to show that it is a human carcinogen.

Cobalt has reportedly been used for more than 20 years as an anemia treatment since it stimulates erythropoiesis; no cases of cancer have been reported. Longer term studies with more patients were recommended to allow further analysis.

As a follow-up to his prior work focusing on McKee-Farrar implants¹⁷⁸, Visuri¹⁷⁹ compared the incidence of cancer in both metal-on-metal and metal-on-polyethylene devices to that of the general population in Finland. Again using the registries available, a significant amount of follow-up (over 28,000 person years) over a long period of time (12.5 years for metal/polyethylene, 15.7 years for metal/metal) was assessed. Both groups were found to have significantly less occurrence of lung cancer and no variation in the rate of other cancers when compared to the general population. Metal-on-metal patients had an insignificantly (i.e., not statistically significant) increased risk of leukemia and lymphoma. No local sarcomas were noted in either group. The overall cancer rate for metal/metal patients was lower than that of the general population in all but the 1e year (examined over a 15 year period). Based on the information, it is suggested that factors other than the total hip arthroplasty played a major role in the origin of cancer. In a more recent study describing a longer follow-up, Visuri¹⁷⁷ was unable to confirm the previously described increased risk of leukemia and lymphoma. Furthermore, lung cancer and the risk for cancer mortality were reduced and the risk of local sarcoma was insignificant.

Tharani et al¹⁷⁶ concluded in their analysis that there was no causal link between total hip replacement and cancer, and that there was only one study in which there appeared to be an increased risk of cancer following metal/metal total hip replacement but that this was small in comparison with other studies. Their review also showed no increase in bilateral patients which is another observation against cancer induction by total hip arthroplasty.

Gillespie et al¹⁵⁹ presented results from an analysis of 1358 total hip patients (representing 14256 person years) in New Zealand from 1966 to 1973. Mean follow-up was 10.52 years (6 months to 17 years). Similar to the works of Visuri¹⁷⁷⁻¹⁷⁹, cancer and death registries were searched for this same time period; 164 cancers were recorded. Overall incidence of cancer following THR was significantly decreased through 10 years. Overall incidence significantly increased for patients followed beyond 10 years. Breast, colon and rectal cancer was significantly diminished in THR patient to 10 years. Lymphatic and hematopoietic cancers were found to be significantly increased overall in THR patients. The author notes that these associations may be purely mathematical chance or related to other underlying factors such as concomitant disease treatment or social/occupational factors (e.g., pesticides in agrarian New Zealand).

Mathiesen et al¹⁷⁰ presented an analysis of 10785 total hip patients in Sweden (representing 58437 patient years) implanted from 1974 to 1988. Use of the Swedish cancer registry and death registry allowed evaluation of tumor incidence. The overall actual incidence of malignancy (881) was lower than expected (917.7). Incidence of leukemia and lymphoma was slightly higher in the first year of follow-up but had a corresponding decrease the second year of follow-up. When year 1 and 2 are analyzed together, this incidence is not significant. Patients followed for greater than 10 years had a slightly higher incidence of total cancer, but a decreased risk of leukemia and lymphoma. Bilateral and revision patients were analyzed as a subset in order to evaluate potential for increased malignancy due to increased exposure. The overall cancer incidence in this subset was found to be less than expected for bilateral patients and slightly increased for revision cases; leukemias and lymphomas were less frequent than the entire series. Possible selection bias is cited as THR patients are generally more healthy with a longer life expectancy. The author notes that an association between THR and increased incidence of cancer during the first 10 postoperative years was unable to be made, possibly due to the long latency period for metal associated cancers.

5. Summary

- Metallic wear particles result in a cellular reaction consisting mostly of mononuclear histiocytes, which differs from that seen with polymer particles (mononuclear histiocytes and multinucleate giant cells).

- Metal/metal bearings can result in increased serum and urine metal (cobalt chromium) ion levels
- Cobalt ions are initially toxic to cell tissues but may be normalized after clearance. Chromium ions appear to be toxic only in the hexavalent state which has not been shown to occur with metal implants.
- Wear particles from metal/metal couples tend to be extremely small (submicrometre to 5 Mm).
- Concentrations of metallic wear particles are typically highest in the immediate surrounding tissue (e.g., synovium) with concentrations tapering off at more distant organs supplied by the lymphatic system and blood. Organs which perform a processing/filtration function (e.g., liver, lymph nodes) experience increases in metal levels over the normal.
- Cancer/tumor studies have shown no correlation or extremely small and unmeasurable correlation with the presence of CoCr wear particles.
- Analyses of massive patient registries in three countries (New Zealand, Finland, Sweden) have been unable to make a strong statistically significant link between cancer incidence and total joint arthroplasty. Although several articles have shown a slight increase in risk of leukemia and lymphoma for total hip replacement patients, many also report that incidence of other cancers have shown a decrease when correlated to total joint replacement. These authors suggest that factors other than total joint replacement may play a role in cancer formation.

FDA Comments: In the testing, the petitioner did not describe exact values for the clearance, sphericity, and other design issues. They described that these design issues played an important role in the successfulness of these devices, but failed to give any acceptable values. The FDA asked the petitioner for a table of values for the sphericity, clearance, and surface roughness for each metal/metal semi-constrained hip joint prosthesis identified in the published literature and unpublished clinical data contained in this petition.

Response: See above explanation concerning this deficiency.

Response and FDA comments: The sponsor sent a proposal to the FDA citing ranges of values thought to represent of well performing devices. The design ranges the petitioner sent us were the ranges of the nonpublished clinical literature. These values will be used as descriptive information for the nonpublished clinical studies, and as comparison information.

Parameter	Range
Diametrical Clearance	30 to 200 μm
Sphericity	$\leq 7 \mu\text{m}$
Surface Roughness (R_a)	$\leq 30 \text{ nm}$
Material and material properties/characterization	ASTM F75-98, F799-96, F1537-94

The petitioner also wanted to use The American Society for Testing and Materials (ASTM) standard F1714-96 entitled Gravimetric Wear Assessment of Prosthetic Hip Designs in Simulator Devices. This would provide information related to the in vitro simulator wear assessment of bearing surfaces for total hip arthroplasty.

Rather than the use of absolute wear quantities (e.g. run-in wear, total wear, or wear rate), the petitioner proposed that the performance benchmark would be 28 mm metal-metal devices (control group) tested concurrently with the candidate devices (experimental group). The articulating surfaces of the control devices would necessarily satisfy the ranges set forth for a series of parameter ranges (see above).

See below for wear proposal response.

5. Summary of the Published Clinical Studies

The reclassification petition divides published and unpublished clinical data.

The following is a summation of several significant articles found in published literature using a search of various medical databases. A tabular presentation of the clinical results is below also.

Albrecht-Olsen et al.¹ reviewed 238 Ring prostheses implanted during the period 1968-1979. Of those cases, 127 with a median follow-up of 9 years were available for evaluation with 90% of those patients demonstrating excellent/good results upon self assessment. Using the Charnley scale, 87% had a pain score of 4 or greater (score of 6 = no pain), 76% had a motion score of 4 or greater, and 57% had a walking score of 4 or greater. The author cites an infection rate of 2.5% (6 deep infections, 16 superficial infections). Four dislocations were also encountered. At the time of this evaluation, 17% (n=40) of the patients had been revised, mainly due to pain. Overall results predicted an 81% survival rate at 12 years, comparable to outcomes seen with metal-on-polyethylene articulation

Aimby² reported on 93 patients receiving the Muller device, 57% of which had been followed for more than 10 years. Using the Charnley scale (6 possible points in each category), 90% had pain rating of 4 or better or a range of motion greater than 100°. Nine deep infections were reported. Thirty patients died (26 unrelated to device, 1 embolus, 1 ileus, 1 renal failure, 1 septic). Twenty-nine patients were revised (19 aseptically loose, 7 septicallly loose, 4 stern fractures, 1 fracture). Twenty-three acetabular and 16 femoral components showed signs of loosening. Femoral loosening was secondary to calcar resorption and cement settling in most cases. Survivorship in this series was calculated to be approximately 80% at 5 years and 57% at 10 years.

Andrew³ presented his results of 116 Ring patients followed for 8 years. Using the Harris scoring system (100 points possible), 33% of the patients had 80 points or greater with another 13% exhibiting total scores of 70-80. Using the Ring evaluation, 49% of the patients rated excellent or good. Two deep infections and 4 dislocations were encountered. Other complications included grade IV heterotopic ossification (5), fracture (4), embolic event (7), and sciatic palsy (1).

Results of 175 patients with the McKee-Farrar device at an average 13.9 years of follow-up are presented by **Auguste**. Using the Harris evaluation, the average total score was 76.4, with 48.9% having excellent/good outcomes. On self assessment, 90% of the patients rated themselves as having a satisfactory outcome. Sixty-four patients were revised, mainly for loosening, stem fracture and bone fracture. Over 50% of the stems and cups showed signs of looseness radiographically. Additionally, the cup showed signs of protrusion in 62.5% of rheumatoid patients. Heterotopic ossification (grade IV was reported in 2.7% of the cases. August calculated survival at 84.3% at 14 years and 27.5% at 20 years.

Djerf⁴ presents results on 107 McKee-Farrar and 70 Charnley devices with 5 years follow-up. Analysis revealed 94% of patients to have no pain and 78% to have improved flexion. Unrelated death occurred in 12% of the patients. Six infections (3.4%) and 4 dislocations (2.3%) were reported. Other complications included trochanteric problems (2.8%), nerve injury (1.7%), deep venous thrombosis (1.7%), pulmonary embolus (0.60%), fracture (0.6%), and ossification (0.6%). Loosening was evident in 32% of the cases. Analyses showed no significant difference in the outcomes of either implant.

A comparison was performed by **Jacobsson et al²⁴** on a series of McKee-Farrar metal-on-metal patients and a series of Charnley metal-on-polyethylene patients. No major differences were observed between the two groups with regard to radiographs, Harris Hip Scores or walking ability. At 12 years, average Harris hip scores for the McKee-Farrar and Charnley were 82 and 83, respectively. At 20 years, average Harris hip scores were 75 and 77. Sixteen McKee-Farrar and eight Charnley devices were removed. No debris was noted in the McKee-Farrar retrievals. The infection rate is 2.8% for McKee-Farrar and 4.3% for the Charnley. The dislocation rate is 2.8% for the McKee-Farrar and 1.4% for the Charnley. Loosening of the McKee-Farrar was noted in 5 cups and 6 stems; 4 cups and 4 stems were loose in patients receiving the Charnley device. Extensive scalloping was observed in 5111 Charnley devices. Nerve damage (1.9%) and femoral fracture (0.9%) were also reported with

the McKee-Farrar device. Trochanteric pain (7.1%), deep venous thrombosis (4.3%), nerve damage (1.5%), pulmonary embolus (1.4%) and ectopic bone (1.4%) were experienced in the Charnley patients. This study determined that there was no statistically significant difference in survivorship at more than 11 years: 82% for the McKee-Farrar patients compared to 89% for the Charnley patients.

Jantsch²⁵ analyzed follow-up at 14 years in a series of 248 patients with 330 McKee-Farrar devices. Only 56% of the patients were followed clinically to this period (24% died, 17% untraceable, 3% refused participation). Using the Mayo rating system, **48% of the patients were found to have excellent/good ratings (62% if revisions are excluded)**. Based on radiographs available, **34% of the cups and 26% of the stems were unstable. There were 36 retrievals (22 cup and stem, 7 cup, 7 stem)**.

McKee³⁵ reports on four series of patients treated with the various iterations of the McKee-Farrar device from 1956-1971. As shown in the attached tables, postoperative outcome improved through each design iteration, with **approximately 89% achieving excellent or good outcomes in the 1965-69 series (4-7 year follow-up) and 97% achieving excellent or good outcomes in the 1971 series (2 year or less follow-up)**. Retrievals have occurred in 4% of the 1965-69 series and 0% of the 1971 series. Fifteen (15) deaths were reported in the 1965-69 series; two were reported in the 1971 series. The reported rate of infection was 4% in the 1965 series and 0% in the 1971 series. Two dislocations (2%) were also reported in each of these series. Other complications include pulmonary embolus, deep venous thrombosis, shaft perforation, hematoma and heterotopic ossification.

Ring⁵² presents results on 106 metal-metal Ring prostheses with 7-17 years follow-up. Postoperatively, 83% were assessed as excellent/good clinically. Outcomes of the various design iterations are again presented in this article. Thirteen retrievals have occurred (7 femoral failures, 2 pelvic failures, 3 combination failures, 1 ankylosis). **Survivorship of patients implanted from 1968-73 was 81% at 18 years; survivorship was 95% at 16 years for those implanted from 1972-79.**

Thirteen McKee-Farrar patients (15 devices) with an average follow-up of 23.7 years are presented by **Schmalzried⁵⁸**. **The average Harris hip score of these patients was 86 with 11 patients having an excellent/good rating.** These patients outscored a matched metal-on-poly control population on the SF-36 Health Status questionnaire. Activity levels were also reported to exceed the averages for this age population. The only complication reported is that of lysis in three femurs and one acetabulum.

Zaoussis⁷⁹ presents results on 38 McKee-Farrar patients followed for 12-20 years, with 26 having greater than 15 years follow-up. At the time of this evaluation, **45% were found to have very good outcomes. Fifty-three percent (53%) of the patients were pain free and 79% had 60-90° range of motion.** Three infected components and four loose components were retrieved. There have been five dislocations (all in one patient). Nine components show looseness. Other complications include five peroneal nerve palsies, one cortical perforation and one ossification.

FDA Comments: The review of the published literature suggests that mediocre long term results comparable to current metal-on-polyethylene prostheses can be achieved with well designed metal-on-metal devices. As outlined, the complications encountered with metal-on-metal devices are common to current total hip arthroplasty. Most of the metal-on-metal articles show very low survivorship at fairly early timepoints. It is noted, though, that many of the causes for failure were due to other issues besides the metal/metal couple. This review further highlights the importance of preventive therapies and proper surgical technique in good clinical outcomes.

Published reports by Dorr, et al. (1996), (2000), Hilton, et al. (1996), Wagner and Wagner (1996) and Weber (1996) of the clinical experience with the Metasul® (Sulzer Orthopedics, Austin, TX) metal/metal semi-constrained hip designs lend further support to the conclusions drawn from the results reported here.

It is unclear to what extent the petitioner wants to use the articles. Most of the articles cite low survivorship at long term dates. Some of the revisions were caused by loosening, fracture, and dislocations among others. The petitioner does not state in the petition how some of these risks are to be minimized by controls, and the controls they do propose will not take into account the long term. These articles were reviewed to look at some of the problems associated with the early designs, and what the petitioner proposed to limit or minimize these risks. In conclusion for the published clinical articles, they showed fair results, and poor results for long term analysis.

Table 8. Clinical Outcomes

<i>Author/Ref No.</i>	<i>-Device -Patients/Devices -Age (Range)</i>	<i>Diagnoses</i>	<i>Follow-up</i>	<i>Pre-Op Score</i>	<i>Post-Op Score</i>	<i>Other Clinical Outcomes</i>	<i>Other Comments</i>
Albrecht-Olsen, 1	-Ring -238 devices only 127 followed to 9 years -67 (20-82) for all 238 hips	205 Primary OA 33 Sec OA or post trauma OA	9 yrs (6-17) (for 127 hips followed)	Charnley: Pain: 98% with $\leq 3/6$ Motion: 83% with $\leq 3/6$ Walking: 69% with $\leq 3/6$	Charnley: Pain: 87% with $\geq 4/6$ Motion: 76% with $\geq 4/6$ Walking: 57% with $\geq 4/6$	Charnley rating post-op 38% exc./good 62% fair/poor	Pt. Assessment post-op: 90% exc./good 10% fair/poor Of original 238 hips, 17 pts. Were unwilling to participate, 51 pts. Died (nondevice), and 23 were revised (131 devices)
Almby, 2	-Muller -93 pts./106 dev. (only 63 pts. Followed -64 (36-83)	68% -OA 12% -RA 17% Post. Trauma 3% -CDH	57% with >10yrs.		Charnley rating (for 38 pts): Pain: >90% with $\geq 4/6$ >90% with >100° ROM	Of original 93 pts., 30 died over 10 yrs (80% of these survived 5 yrs). 38/63 pts. Retained device @16yrs. Survivors hip: ~80% @5 yrs. ~57% @10 yrs.	

Andrew, 3	-Ring -179 pts. (only 116 pts. /154 hips were followed long term -63 (21-83)	138-OA 6-RA 6-Pagets 2-CDH 1-Ankyl. Spond. 1-Avasc. Nec.	8 yrs.		Harris: 33% with 80 pts. or greater 13% with 70-80 points	Ring rating: 75(49%)-exc./good 67(44%) fair/poor 12(&%) -no class	Post-op Charnley range of movement for most hips was 101-160 degrees Of original 179, 55 dies (nondevice related). Of remaining 124, only 116 were able to be followed clinically
August, 4	-McKee-Farrar -175 pts/ 230 dev. -60.3 (24-78)	87.5%-OA 6.5%-RA 2.0%-CDH 2.0%-Post trauma 2.0%-Other	13.9 years (10-22)		76.4 (Harris)	48.9%-exc/good 78%-Occ. Pain or o. pain 90%-pts satisfied per self assessment	Survival: 84.3% at 14 yrs. 27.5% at 20 years
Baldursson, 5	-McKee-Farrar -78 pts/ 105 dev. -56 (20-75)	RA	47 mos. (9-85)	d'Aub.: Pain-1.8/6 Walking: 1.7/6 Mobility 3.2/6	d'Aub.: Pain-5.5/6 Walking: 2.4/6 Mobility: 4.6/6		14 pts. Considered failures
Bentley, 6	-McKee-Farrar (M/F) Charnley (Ch) -85 pts./101 dev. (M?F) 112 pts./128 dev.(Ch) -51-80 (M?F) 38-84 (Ch)	155-OA 32-RA	1-4yrs.	Charnley: Pain: ≤3/6 95%-M/F 92%-Ch Motion: ≤3/6 94%-M/F 89%-Ch ROM ≤100: 82%-M/F 88%-Ch	Charnley: No Pain: 83%-M/F 96%-Ch Disability ≥4/6: 85%-M/F 97%-Ch ROM ≥100: 88%-M/F 88%-Ch		

Breck, 9	-Urist -46 pts./ 47 dev. -59.4 (23-84)	17-unknown 6-RA 6-Injury w/o fracture 5-Fracture 3-Primary 2-Protrusio 2-Congenital 1-Dysplasia 1-Brain tumor 1-Cerebal Palsy 1-Asept. Necr. 1-Prior Failure 1-fract. Disloc	2.1 yrs. (6m-4yrs.)		21-excellent 18-good		
Briant, 10	-Ring -214 pts./253 dev	96% -OA					Survival: 70.6% at 10 years 60.4% at 20 years
Debeyre, 13	-Urist -54 pts./63 dev. -majority >60	"crippling coxarthrosi s"	33>2 yrs 17> 3 yr		d'Aub.: Pain: 74% w/ ≥5/6 Mobility: 65% w/ ≥ 5/6		
Djerf, 14	-McKee-Farrar (M/F) Charnley (Ch) -177 dev. 107 M/F 70 Ch. -66.9	80%-OA 11%-Neck Fract 9%-RA	5 yrs.		94% with no pain 78% with improved flexion		Analysis of results showed no significant difference in McKee-Farrar and Charnley components
Dorr, 15	-Weber Metasul Cup/ APR Stem -70 pts. (only 54 followed)		2.7 yrs. (2yr-4yr)	49 (Harris)	93 (Harris)	98% rated good or excellent 94% pts. Had good or excellent self-assessmen t	Hip aspirates taken on metal/metal group and metal/poly control group: Metal/Metal: 10/22 w/metal particulate 6/22 w/poly particulate Metal/Poly: 7/14 w/metal particulate 11/14 w/poly particulate

Evarts, 18	-Ring -32 pts./34 dev. -67 (43-83)	16-Deg Arthr. 5- RA 4- CDH 1- SCFE 1- Protusio 1- Paget 1- Ank. Spond. 1- Cup	2.5-3 yrs.	Iowa score: 33.5/100 Avg. ROM: 90	Iowa score: 64.9/100 Avg ROM: 150	36% had exc./good outcome at 3 yrs. Compared to 72% at 1 yr.	Major loss of rating at 3 yrs. Was due to pain and function category. Deep persistent groin pain was common complaint
Freeman, 20	-Howse McKee- Farrar -297 pts./ 360 dev. -OA pts: 65.7 (14- 85) Polyarth Pts: 56.6 (24-80)	191-OA 106- Polyarthr.	OA pts: 20.9 mos (6-72) Polyarthr. Pts: 28.8 mos (6- 72)		d'Aub.: 86% very good/good	OA pts: 91% Very good/good Polyarthr. Pts: 77% very good/good	Author cites difficulty in assessing polyarthrits pts. Due to overall condition and involvement of disease
Hilton, 23	-Weber Metasul Cup/ APR Stem -74 pts.		2.2 yrs. (6m-4yr)	48 (Harris)	91 (Harris)	99% rated good or excellent 95% pts. Had good or excellent self- assessmen t	
Jacobson, 24	-McKee-Farrar (M/F) Charnley (Ch) -107 (M/F) 70(Ch) 66(M/F) 68(Ch)	OA-76%- M/F 85%- Ch. Rheumatoi d 11%-M/F 6%-Ch.	29 M/F @ 20 yrs. 11 Ch. @ 20 yrs.		Harris score @ 12 years 82 M/F 83 Ch 20 years 75-M/F 77- Ch		Survivorship Analysis: @12 yrs. 82%-M/F 89%-Ch. @20yrs. 77%-M/F 73%- Ch No statistically significant difference
Jantsch, 25	-McKee-Farrar -248 pts./330 dev. (Only 56% able to be followed long term) -70	56%-Idio. Coxa. 31%- Dysplasia 5.2%-RA 3.9%-Post Trauma	14 yrs.		Mayo rating: Revisions excluded: 62% with exc./good Revisions included: 48% with exc./good		Of original population: 24% died over long term 17% were untraceable 3% refused to participate (leaving 56% able to be followed)

Kreusch-Brinker, 28	-McKee-Farrar -531 pts./ 617 dev. -61.8 (28-80)	Coxarthrosis 66% Post-Trauma 16.5% Nutritional disorders and inflammatory processes 16.5%	13.2 yrs. (11-18)				Of original 5331 pts., there were 153 deaths and 81 pts. Lost to follow-up leaving 297 pts./335 dev. Available
Langenskoild, 30	-McKee-Farrar -116 dev -63 (41-82)					Charnley rating: Pain: 99% with $\geq 5/6$ Walking: 97% with $\geq 4/6$ ROM: 99% with $\geq 3/6$	
Leinbach, 31	-Muller (Mull), McKee-Farrar (M/F), Ring (R), Charnley (Ch), Huggler (H) -612 pts./700 dev. 427 Mull, 120 M/F, 40 R, 30 Ch, 16 H -72 (22-89)	58%- deg. Arth. 7.5%-RA 12% Revision 12% Nonunion of femoral neck 4.5% Idiop. Aseptic Necr. 3.5% Sec. Arth. 2.5%-Other	126@ 4yrs 194@ 3yrs 186@2yrs 107@1yrs 87@6mos			d'Aub. Rating: 46% exc. 45% good	
Lindholm, 32	-Ring -37pts./40 dev -61 (44-74)	36-OA 1-RA	3 yrs (1-6)	d'Aub.: Pain-39/40 @ $\leq 2/6$ Mobility: 33/40 @ $\leq 2/6$ Gait: 40/40@ $\leq 3/6$		57.6% fair/good/excellent ('56-'60 series) 80% exc./good ('61-'64) 89% exc./good ('exc./good ('65-'69) 97% exc./good ('71-)	
McKee, 36-37	-McKee-Farrar -50 dev.	Chronic arthritis				94% (47 pts.) had exc./good result	

McMinn, 41	-McMinn -235 devices (70 press fit, 6 HA, 43 cement, 109 hybrid) -48.7	OA-73.6% Inflamm-8.5% Sec Arthr. 10.6% Avasc Necr. 7.2%	Pressfit 50.2 mos., HA 40.2 mos, Cement 33.2 mos. Hybrid 8.3 mos	Charnley score: Press Fit-9/18 HA-9/18 Cement 9.5/18 Hybrid-9.5/18	Charnley Score: Pressfit-16.5/18 HA-17.3/18 Cement-16.5/18 Hybrid-16.5/18		Hybrids (current practice) consist of HA coated M/M acetabular component with cemented femoral component
Morris, 42	-McKee-Farrar (M/F) Charnley (Ch) -313 pts./399 dev. (97 M/F, 302 Ch)			89% w/disabling pain 98% w/restricted function 72% w/restricted Movement Markedly reduced	Slight or no pain: 86% M/F 92% Ch Function of $\geq 5/6$: 59% M/F 56% Ch Movement of $\geq 5/6$: 66% M/F 83% Ch	Post-op results represent 180 devices/131 pts. Followed (125 Ch, 55 M/F)	
Nicholson, 43	-McKee-Farrar (M/F) Charnley (Ch) -86 M/F, 939 Ch. -73.4% ≥ 61	63%-OA 10%-RA 27% Failures, misc. diagnoses	to -6yrs.	Charnley score: Pain: 2.79/6 Walking 2.41/6 Movement: 3.10/6			Loosening of M/F led to preference for and long term follow-up of Charnley.
Patterson, 44	-McKee-Farrar -403 dev. (368 followed) -70% were ≥ 60 yrs	241 Idio. OA 42-Post. Trauma 39-RA 16-Dysplasia 7-Ank. Spond. 23-Other	1.4 yrs (3 mos -4yrs) 87 > 2yrs			Charnley rating: 85% pain improvement 76%-ROM improvement 69%-ability to walk improved	20.1% of population has a previous operation of hip
Postel, 45	-Low Friction band -100 dev. -67	"variety of indications but the usual proportions"	6yrs				
Postel, 46	-McKee-Farrar -113 dev. -64	53% -Prim. OA 26%-Sec. OA	9 yrs (33% with 15 years)		Rating: 56% very good/good 44% Poor/Very poor	For 91 nonrevised hips with 9 yrs follow-up, average pain/motion/stability score is 14.8/18	

Ring, 52	-Ring (Metal/Metal = M/M Metal/Poly = M/P) -172 dev. 106 M/M, 66M/P) -13<30 29@31-40 130@41-50	"Young hips with primary or secondary degenerativ e changes"	7-17 yrs (M/M) 1- 7 yrs (M/P)		Rating: 83% exc./good (M/M) 95.5% exc./good (M/P)		Survivorship: Patients implanted 1968- 1973 is 81% @ 18 yrs Patients implanted 1972- 1979 is 95% @16 yrs.
Ring, 50	-Ring -128 pts./ 158 dev. -69 (40-79)	114 - Deg. Arthr. 3- Cup Arthr. 2-Judet rev. 3-Osteot. 5-RA 1-Ank. Spond.	Up to 4 yrs.		Rating: 53.5%- excellent 42.5%-good	82% no pain, 18% min. weight bearing pain 86- >90 ROM 51-60-90 ROM	
Ring, 51	-Ring, 3 types (M/M, ploy-head, Metal-Poly -1598 pts./1808 dev. M/M_649 devices, poly- head-1159 dev.		5-14 yrs.	M/M only: 75% exc. 18% good			Metal/Metal results comparable to Metal/Poly results 78%-exc. 18%- good
Ring, 53	-Ring -1000 dev. 3 design modif. 193 Early, 569 Mid, 238 Current -majority @ > 60	890-OA 62-Misc. 37-RA 7-CDH 4-Ank. Spond	Early: 5-8 yrs. Mid.: 1-5 yrs. Current: <1 yr.		Early: 74%- exc/good Mid/Current: 90% exc./good		
Ruszkow ski, 54	-Ring -59 pts./63 dev. -majority 60-70	69.8%-OA 11.2% - CDH 6.4%-RA 6.4%-Ank. Spond. 4.7%- Necrosis 1.5%- Injury	36.8%-4-5 yrs. 9.5%- 3-4yrs. 31.8%-2-3 yrs. 26.9%-<2 yrs.		33.3% exc. 50.8% good		
Salenius, 55	-McKee-Farrar -126 pts./143 dev. -20-76 (110 @<50)	OA, RA			d'Aub rating 78%- exc/good 9%-fair	Post-op, 103/139 reached ROM of 60-100 degrees	
Scharm alried, 56	-McMinn (MM), Wagner (W) -19 pts./21 dev. (17 MM, 4 W) -42 (22-64)	7-OA 3-Dysplasia 2-PTA 2-Juv. Rheum. 2-SCFE 5-Other	16 mos. (10-25)	UCLA score: 20/40	UCLA score : 34/40	Range of motion/fu nction increased to better than that of a standard THR	All patients underwent trochanteric osteotomy

Schmalzried, 57	-McKee-Farrar (M/F) Sivash (s) -6 dev. (5 M/F, 1 S) -40.8 (21-57)	2-Legg Perthes 2-OA 1-Tuberculosis 1-Avasc. Necr.	21.3 yrs. (19-24.5)				All were removals. Estimated wear was 4.2 um/yr.
Schmalzried, 58	-McKee-Farrar (M/F) -13 pts./ 15 dev. -58.3 (41-67)	11-OA 2-Juv. Rheum. 2-Dysplasia	23.7 yrs. (21-26)		Harrisscore: 86 (71-95)	11/13 pts. Had exc./good rating	Patient outscored matched control pop. On SF36. The average levels also exceeded the average for this age.
Shorbe, 63	-McBride -92 pts./ 103 dev. -83 pts. >50	52-Coxarthr. 17-Avasc. Necr.	13-RA			58-Good 22-Fair 6-Poor	
Sivash, 66	-Sivash -164 pts./200 dev.	107-Ank. Spond. 56-Tuber Cox. 24-Bilat. Arthr. 10-Pseudoarthr. 3-Injury	1-9 yrs.			105/107 Ankylosing Spond. Pts. Has excellent results	
Smith, 67	-Gaenslin cup with Austin Moore or Leinbach stem -36 pts./40 hips -40-87 (20 >60 yrs)	19-Degen. Arthr 7- Prior Surgery 4-RA 3-CDH	to 8yrs.		75%-exc 12.5%-v. good		
Smith, 68	-Gaenslin cup with Austin Moore stem -92 pts./112 dev. -33-87	71-Deg Arthr. 15-RA 13-Painful cup/system	56@ 2-5 yrs 26@5+ years 30@<2 yrs	d'Aub.: 106 dev. ≤7/18	d'Aub.: 95 dev ≥14/18		
Wagner, 73	-Metasul -105 dev. (70 thr, 35 resurf) -49.5(thr) 36.2(resurf)	47-Dysplasia 25-OA	34.3 mos.(thr) 20 mos. (resurf)	Harris: 36(thr) 32(res.) d'Aub.:9.3(thr) 8.3(res.)	Harris: 96(thr) 94(res.) d'Aub.:17.6(thr) 17(res.)	No thigh pain reported	
Weber, 75	-Weber Metasul -110 dev. (100 followed) -59 (22-78)	48-OA 23-Dysplasia 18-Slip Epip. 7-RA 4-Idio. Necr.	3.5 yrs. (2-7)	Harris: 98%-fair/poor (70 points or less)	Harris: 98%-good/exc. (80 points or more)		Retrievals @ 4,5,6 years showed signs of wear of 4.7, 4.5 5.9 um

Wilson, 76	-Stanmore 3 groups based on design modif. -101 pts/ 108 dev. Gr I: 14 dev. Gr II: 36 dev. Gr III 43 dev. -21-81	55-Prim OA 21-Failures 9-Tumor 6-RA 5-Other Arthr. 4-Post Trauma 1-Ankyl. Spond.	1.5-9 yrs. Gr I: 6-9 yrs. Gr II: 5-6 yrs. Gr III: 1.5-4 yrs.		d'Aub.: Pain free: Gr I: 57% Gr II: 72% Gr III: 93% ROM >60: Gr I: 86% Gr II: 83% Gr III 95%	d'Aub. Function, hips with minor to no restriction : 64%-GrI 61%-GrII 100%-Gr III	Clinical evaluations exclude tumor patients
Wilson, 77	-McKee-Farrar -86 pts/ 100 dev. -61 pts. >60 yrs	38 Bilateral Degen. Disease 15- Unilateral Degen. Disease 16-Failed Dev. 12-RA 2-Ank. Spondy. 3-Post-Trauma	2 years on all pts. (16 @ 3yr)	Harris, Pain: 79≤4/10 Walking: 65≤4/10 Motion: 64≤4/10 Function: 67≤4/10	Harris, Pain: 75≥6/10 Walking: 63≥6/10 Motion: 66≥6/10 Function: 52 ≥6/10		21 failures not included in clinical evaluation
Zaoussis, 79	-McKee-Farrar -38 pts. 43 dev.	25-OA 7-RA 5-Ank. Spond. 6-CDH	12-20 yrs (26 pts w/>15 yrs)		Rating: 45%-very good 36%-fair	23 (53%)-pain free 34 (79%)-ROM of 60-90	

FDA Comments: In the tables that presents the clinical outcomes of published literature and the adverse events of the published literature, the petitioner provided follow-up, pre-op score, post-op score, and several other categories for analyzing the published literature. However, they did not provided copies of the literature articles upon your summaries were based.

Also, in the reclassification petition, the petitioner summarized several published articles but did not identified how the literature search was performed including:

- Name(s) of the databases;
- Search terms (i.e. keywords);
- Range of years; or
- Acceptance and rejection criteria for each journal article.

These items were requested in a deficiency letter sent to the petitioner.

Response and FDA comments: The petitioner responded with the following:

- Name(s) of the databases: Medline, Embase, Biosis
- Search terms (i.e. keywords): "metal on metal hips", "hip prosthesis", "acetabular", "McKee-Farrar", "Ring", "Sivash", "Metasul"
- Range of years: 1966-1998
- Acceptance and rejection criteria for each journal article: Only English language articles were searched.

The petitioner pooled together early metal/metal design and contemporary metal/metal designs. The early metal/metal designs were pooled together by length of follow-up, diagnoses, and prostheses design.

1. Follow-up greater than 5 years, follow-up not reported, or results not stratified by follow-up categories: 1, 2, 3, 4, 10, 12, 14, 24, 25, 28, 30, 31, 35, 36, 37, 42, 43, 45, 46, 51, 52, 53, 57, 58, 63, 66, 67, 76, 79.
2. Surface replacement: 41, 56
3. Diagnosis completely RA: 5
4. Contemporary design, 15, 23, 75
5. Contemporary design and results not stratified by design category: 73

Due to multiple clinical outcomes utilized (Harris Hip, Charnley, Iowa, d'Aubigne) and inconsistent reporting of patient demographics, the analysis of results was restricted to post operative loosening.

The overall loosening rates for the literature controls (147/1624, 8.94%) was significantly greater ($p < 0.001$, Fisher's Exact 2-sided) than the reported for the pooled results in the unpublished studies A, B, and C (1/403, 0.25%)

The dislocation rates for the literature controls were (37/1624, 2.25%) was not significantly different ($p = 0.439$, Fisher's exact 2-sided) than the reported for the pooled results for the unpublished studies A, B, C, (6/403, 1.49%).

The petitioner also pooled together the contemporary metal/metal designs, which were references 15, 23, 75 based on length of follow-up, diagnosis, and design. The results for loosening and dislocations were similar to the unpublished clinical studies A, B, C.

The most pertinent articles are contained in the original petition under Appendix 3.

All of these articles were done on the Sulzer Metasul hip. One article had long term follow-up data out to 4-7 years. They reported very positive results compared to metal/poly hips. This article will be viewed as very important because it is one of the only articles that actually has long term data on a second generation hip.

6. Summary of Unpublished Clinical Data

Study A:

The investigation was a prospective, multi-center, randomized controlled clinical trial performed in the U.S. The diagnostic indication was non-inflammatory degenerative joint disease (NIDJD), which included osteoarthritis, avascular necrosis, developmental hip dysplasia, protrusio acetabula, crystalline arthropathy, slipped capital femoral epiphysis, and traumatic arthritis. The investigation had two treatment arms: cemented and uncemented femoral components. The patients were randomly selected to receive either the metal acetabular liner or the UHMWPE liner.

There were 219 patients in the investigational group and 206 patients in the control group. There were 115 men and 104 women, with a mean age of 55.7 years in the investigational group and 127 men and 79 women, with a mean age of 57.0 years in the control group. The diagnostic indications for the investigational and control groups, respectively, were osteoarthritis 164 and 152, avascular necrosis 29 and 33, post-traumatic arthritis 11 and 10, DDH 8 and 8, and other 7 and 3.

Study B:

This investigation was a prospective, multi-center, open clinical trial performed in Europe. The diagnostic indication was non-inflammatory degenerative joint disease (NIDJD), which included osteoarthritis, avascular necrosis, developmental hip dysplasia, Legg-Calve-Perthes disease, and traumatic arthritis. All patients enrolled received the metal acetabular liner. All acetabular shells were uncemented. Both cemented and uncemented femoral components were included. There was a historical literature-based control for this study.

There were 87 patients in the investigational group. There were 52 men and 35 women, with a mean age of 57.4

years. The diagnostic indications were osteoarthritis 74, post-traumatic arthritis 1, DDH 6, and other 6.

Study C:

The investigation was a prospective, multi-center, randomized controlled clinical trial performed in the U.S. The diagnostic indication was non-inflammatory degenerative joint disease (NIDJD), which included osteoarthritis, diastrophic variants, pelvis fractures, fused hips, avascular necrosis, Legg-Calve-Perthes disease, slipped capital femoral epiphysis, and traumatic arthritis. The patients were randomly selected to receive either the metal acetabular liner or the UHMWPE liner. The acetabular shells were implanted without cement, but both cemented and uncemented femoral prostheses were used.

There were 97 patients in the investigational group and 97 patients in the control group. There were 71 men and 26 women, with a mean age of 49.8 years in the investigational group, and 72 men and 25 women, with a mean age of 50.3 years in the control group. The diagnostic indications for the investigational and control groups, respectively, were osteoarthritis 75 and 72, avascular necrosis 12 and 14, post-traumatic arthritis 6 and 7, and other 4 and 4.

Study D:

The investigation was a prospective, multi-center, historically controlled clinical trial performed in the U.S. The diagnostic indication was non-inflammatory degenerative joint disease (NIDJD), which included osteoarthritis, avascular necrosis, developmental hip dysplasia, and traumatic arthritis. All patients received the metal acetabular liner. The acetabular shells were implanted without cement, but both cemented and uncemented femoral prostheses were used.

There were 221 patients in the investigational group. There were 133 men and 88 women, with a mean age of 54.0 years. The diagnostic indications were osteoarthritis 174, avascular necrosis 34, DDH 4, and other 2.

With the study pooled together, the numbers are increased to the total study population having 624 total patients in the metal/metal group, and 303 patients in the metal/poly group. Most of these were diagnosed with OA. Of the patients, there were 97 patients at 24 months for metal/metal hips, and 66 patients for metal/poly. At 36 months the patient population was 30 and 20 for metal/metal and metal/poly, respectively. At 48 months the pooled study had 2 patients in each group. The average follow-up time for the studies combined was 27.1 months for metal/metal and 27.3 months for metal/poly.

The HHS score was taken for 598 metal/metal patients and 289 metal/poly patients in pre-op, and the sponsor had 96 metal/metal HHS scores, while having 73 metal/poly scores. The mean score for metal/metal at 24 months was 95.5 and for metal/poly was 92.5. The radiographic observations for each group was pretty even throughout. There was a total of 8 revisions for the metal/metal group, while there was only 1 revision for the metal/poly group.

FDA Comments: In the reclassification petition the petitioner described four unpublished clinical studies (Study A, B, C, and D). They presented clinical data from 4 non-published studies, but they did not provided a complete summary of the clinical data or patient accounting information (e.g. Harris Hip Score levels: Excellent, Good, Fair, and Poor) over the course of the studies (e.g. pre-op, post-op, 6 months, 12 months, 24 months). This information would allow us to adequately analyze primary clinical endpoints and patient accountability information for these four unpublished clinical studies.

Also, the petitioner did not provided complete radiographic data for the patients in the four unpublished clinical studies. For example, in Studies A, B, C they did not provide any radiographic data on acetabular cup migration, radiolucencies, or other signs of acetabular loosening. In addition, there was no radiographic information on the presence of heterotopic ossification. Also in Study D, the petitioner did not provide any

radiographic data. Although Study D contained clinical data, radiographs provide essential information, including early signs of loosening.

When describing the device used in the unpublished clinical studies, the petitioner provided a picture of the device and device materials, but did not provide the name and specifications of the device (e.g. femoral head size, acetabular cup size, type of cup).

When describing the data of the unpublished clinical studies, they compared the data of metal/metal hip joint prosthesis to data of metal/polyethylene hip joint prosthesis. We asked the petitioner for some type of an analysis of the results based on the study protocol, and individual patient success, based on clinical and radiographic parameters. We also asked them to provide a comparison of the results of the study individually, if this type of analyses was not described in the protocol, and the study pooled together.

For some of the clinical studies the petitioner provided the number of revisions and removals of the device in Study A, B, D but did not provide this data for Study C.

All of these deficiencies were addressed in a letter to the petitioner.

Response and FDA comments: Because Study D is lacking in pertinent information, it will not be used in evaluating this petition, and will only be used as adjunctive data.

The important information concerning each device was recommended instead of the name of the device. This deficiency was addressed in the design issues of the hip and cup (see above).

After several conversations with the petitioners, they said that combining the data and doing a statistical analysis would not generate enough power to make an adequate conclusion. The FDA responded that we would provide some guidance on how to analyze the data compared to past products. I consulted with Ted Stevens on a previous PDP, which the sponsor compared means of Harris Hip Scores, and with Mel Siedman who was the statistical consult for that PDP. It was concluded that the petitioner try to compare the results of the metal/metal devices with the metal/poly devices in each of the studies. Also it was asked for the petitioner try to statistically compare the results of the unpublished clinical studies with the published clinical studies (with modern devices).

Amendment: The sponsor responded to our deficiencies concerning the information provided for the clinical trials.

Description of device used in the three unpublished clinical trials.

	Study A	Study B	Study C
Acetabular Component			
Modularity (Y/N)	Y	Y	Y
Material			
a. Bearing Insert	ASTM F-1537 CoCrMo	ASTM F-1537 CoCrMo	ASTM F-1537 CoCrMo
b. Outer shell	ASTM F-136 Ti6Al4V	ASTM F-136 Ti6Al4V	ASTM F-136 Ti6Al4V
Grain Size	ASTM 10-12	ASTM 10-12	ASTM 10-12
Femoral Head/Bearing Insert Clearance	20-40 microns	20-40 microns	25-75 microns
Surface Roughness	0.01 microns max	0.01 microns max	0.05 microns
Sphericity	5 microns	5 microns	2 microns
Inner Diameter (mm)	28	28	28
Femoral Head Component			
Modularity (Y/N)	Y	Y	Y

Material	ASTM F-1537 CoCrMo	ASTM F-1537 CoCrMo	ASTM F-799 CoCrMo
Grain Size	ASTM 10-12	ASTM 10-12	ASTM 10-12
Surface Roughness	0.01 microns max	0.01 microns max	0.09 microns
Sphericity	12.5 microns	12.5 microns	<5 microns
Head Diameter (mm)	28	28	28
Femoral Stem Components			
Brand Name	S-ROM Femoral Prosthesis	S-ROM Femoral Prosthesis	Mallory/Head K853259
Material	ASTM F-620 or F-136	ASTM F-620 or F-136	ASTM F-620 or F-136
Brand Name		ULTIMA Femoral Prosthesis	Bimetric K921224
Material		ASTM F-799 CoCrMo	ASTM F-620 or F-136
Brand Name		ULTIMA LX Femoral Prosthesis	Taperloc K830313
Material		ASTM F-799 CoCrMo	ASTM F-620 or F-136
Brand Name		ULTIMA TPS Femoral Prosthesis	Integral K921225
Material		ASTM F-799 CoCrMo	ASTM F-620 or F-136
		PFC Femoral Prosthesis	Ranawat/Burnstein K921277
		ASTM F-620	ASTM F-799 CoCrMo

Some of these values for the devices are different from what the parameters that are given in the 510(k) submission.

The study protocols are as follows:

Study A

Study A is from the DePuy ULTIMA M/M IDE number G960262. The study compared metal/metal hip with a metal/poly hip. The primary control was survival at 2 years, meaning failures are revisions or a HHS score of below 70.

This protocol for this study calls for a sample size of 300 patients (150 in each study group). From the patient accounting tables provided in the Amendment 2 (pg.18,19) they 24 month patient total was 86 (40 for M/M hips, 46 for M/PE hips). It is also noted in the protocol (pg.79) that 125 patients are needed for a 95% power to determine whether the two groups are equivalent. The patient numbers are well below this number, therefore it seems that no determination of equivalence can be made.

Besides the very low follow-up rate, the HHS score for the M/M was equivalent to the M/PE hips. The radiolucencies showed a 2.6% radiolucency rate of the femur and 5.1% rate of cup radiolucencies for M/M, but the number were slightly higher for the M/PE at 24 months.

Study B

Study B is from also DePuy ULTIMA M/M but this protocol is not from a FDA regulated study, but was a study in Europe and to look at the short term survivorship of M/M hips. The study was an open, prospective clinical investigation with survivorship as the primary endpoint. The protocol does not outline any success/failure criteria or directly specify a control. The study protocol did not discuss any sample size justification either. The study was for only 50 patients. The protocol the provided is not complete. The patient accounting is not provided for the control patients.

This study did not have a control, so it was hard to compare the results to anything. The HHS score showed drastic improvements over the 24 month time period. The radiographic observations showed an 8.6% rate of femoral radiolucencies and 11.1% rate of cup radiolucencies.

Study C

Study C is from a Biomet study for the Metal on Metal Articulating Acetabular system with a control being a metal/PE hip. The study looked at comparison of function and pain of the two devices, radiographic data, and safety data. A total of 196 patients were to be enrolled (98 for both groups).

This study had 34 patients on the M/M hip at 24 months and 37 for the M/PE hips at 24 months out of 97 in each group. They had 28% and 23% missing at 24 months for M/M and M/PE hips, respectively. In addition, the Amendment 1 (pg.44) shows that 18 and 20 patients were at 24 months for M/M and M/PE hips, respectively. The HHS score looked equivalent to the M/PE control at 24 months. There was a high rate of radiolucencies for this study in both the M/M hips and the M/PE hips.

For a more complete review of the unpublished clinical studies, please see attached clinical memo.

The information they provided in their Amendment 2, provided some clarification to issues such as study protocols, devices used for the unpublished clinical studies. The unpublished clinical studies showed a very low follow-up rate. As noted in the clinical review, for Study A, the follow-up rates are 36.7% and 46.0% for the Metal-Metal and Metal-Poly groups, respectively. For Study B, the follow-up rates are 42.5% for the Metal-Metal. For Study C, the follow-up rates are 47.2% and 56.1% for the Metal-Metal and Metal-Poly groups, respectively. The protocol for Study specifically states that in order to come to a conclusion for the success of the study, the sample size must be a certain size, and the follow-up rate ended up being much lower than the success sample size determination. So technically, based on the study protocol, the success of this study cannot be determined. The issue concerning the follow-up rates will be proposed to the panel, and their input will be noted.

Also from the information the petitioner provided, you cannot determine the patients progress throughout the duration of the study. The petitioner does provide the HHS score for the pre-op, 12 month, and 24 month timepoints. The petitioner also provides the HHS score broken up by the different timepoints, but the studies are pooled together. It would be very useful to have the progression of the patients as the study progresses. This will also be asked the panel for input.

As pointed out in the unpublished clinical studies, there is pretty high rate of radiolucencies especially dealing with the acetabular cup. With all four studies pooled together there was an incidence of 12.6% radiolucencies in the acetabular cup. Radiolucencies are a sign of possible loosening. It is unclear, though, rather these radiolucencies were progressive or not. The literature articles that the petitioner presented state high rates of loosening, which was the main reason for revisions. There have been dramatic improvements in fixation for hip stems and acetabular cups, but not significantly enough to reduce the rates that much. A big concern could be the hard on hard loading conditions, and the detrimental effect that has on the surrounding acetabular bone. There are different loading conditions for metal/poly hips because the polyethylene is so much softer than the metal. The petitioner did not address any special controls to minimize the potential for loosening or did not address any performance standards looking at this. Once again, like the wear, this loosening effect is a long term event, and cannot be determined with the unpublished clinical data they have provided. This will brought up as a concern for the panel.

On July 11, 2001, the sponsor provided new patient accounting tables. These patient accounting tables looked at a later database closure. The numbers had improved to 87%, 54% and 76% for the metal/metal groups in studies A, B, C respectively.

Please see the clinical review for a complete review of the petition.

7. Special Control of Risks

Complications can be distinguished between those related to surgery in general, and those that are specific to the device. Broken components requiring revision surgery would be considered a failure of the device. Loosening may involve device design, but it also depends on surgical technique, as well as uncontrollable patient factors. The complications specific to the metal-on-metal device are similar to those specific to class II hip joint replacement prostheses. Complications such as infection, pulmonary embolism, gastrointestinal and genitourinary problems are not generally device specific, but are risks associated with most major surgical procedures.

The primary difference between the metal-on-metal total hip prosthesis (class III) and the metal/polymer total hip prosthesis is the wear of articulating surfaces. The metal-on-metal articulating surfaces wear on both the metal ball and the acetabular cup, but at a much slower rate than metal/polymer articulating surfaces. The metal/polymer hip generally wears primarily in the polymer acetabular cup. The surfaces of the prosthetic components that are in apposition to bone (fixation surfaces) are the same in both the metal-on-metal and the metal/polymer devices. Moreover, the fixation methods to bone are the same for both devices.

Based upon the above considerations, this petition recommends that the approach to regulatory control of risks should be the same for a metal-on-metal hip prosthesis as for a metal/polymer hip prosthesis. Regulatory control of the device can be simple and straightforward. Device risks can be handled through material standards, with substantial equivalence determinations serving to control device design. Patient and surgical risks can be minimized through device labeling, and device quality through Good Manufacturing Practices (GMP) Quality System Regulation (QSR). FDA has authority through the 510(k) process, as well as its general authority over misbranding and adulteration, to impose controls along these lines. FDA guidance documents are available to provide specific guidance regarding materials, testing, and labeling. The risks defined by clinical experience are well suited to controls of these types, and this petition's specific recommendation of the appropriate controls follows in this section.

RISKS AND CONTROLS FOR METAL ON METAL HIP ARTHROPLASTY	
<i>Risks/Complications Identified in this Petition</i>	<i>Means to Control/Minimize risks</i>
Loosening/Migration of Components	510(k) Requirement - Sterility Adulteration Authority - GMP, QSR Sterility Misbranding Authority - Labeling Indications/contraindications/warnings/precautions
Revision of Components Dislocation of the Hip prosthesis	510(k) Requirement - Substantially Equivalent Design 510(k) Requirement - Laboratory Testing Wear/fatigue/liner torque-out/liner push-out/lever-out 510(k) Requirement - Conformance to Material Stds. Misbranding Authority - Labeling Indications/contraindications/warnings/precautions
Implant Failure Fracture/Wear Osteolysis Sensitivity to Materials	510(k) Requirement - Substantially Equivalent Design 510(k) Requirement - Conformance to Material Stds. 510(k) Requirement - Conformance to FDA guidance for acetabular & hip femoral components OMP/QSR - Design Controls/Quality Systems Misbranding Authority - Labeling Indications/contraindications/warnings/precautions

Infection	510(k) Requirement - Sterility Adulteration Authority - GMP/QSR Sterility Misbranding Authority - Labeling Indications/contraindications/warnings/precautions
Nerve Impingement/Damage, Pain, Vascular Disorders, Pulmonary Embolism, Gastrointestinal/Genito-urinary Complications	Misbranding Authority - Labeling Warnings/precautions/potential adverse effects

Device related risks associated with metal on metal hips are similar to those reported in the reclassification petition for constrained hip prostheses, which the Panel recommended be classified into class II. Those risks, as these, are grouped into three major categories, as follows:

RISKS TO HEALTH IDENTIFIED BY THE PETITIONER (grouped into three major categories)

1. Loss Or Reduction Of Joint Function

Loosening, Revision of Components, Implant Failure/Fracture/Wear/Dislocation

Special Controls to Minimize Risks

ASTM Material Standards - F67, F75, F136, F1377, F1580

ASTM Test Methods - F1044, F1147, F1612, F1714, F1814, F1820, F1875, F1978

FDA Guidance Documents

Guidance Document for Testing Orthopedic Implants with Modified Metallic Surfaces Opposing Bone or Bone Cement. (Facts-on-Demand #827)

Guidance Document for Femoral Stem Prostheses (Facts-on-Demand # 1 87)

Guidance Document for Testing Acetabular Cup Prostheses (Facts-on-Demand #453)

Guidance Document for Testing Non-Articulating, "Mechanically Locked" Modular Implant Components (Facts-on-Demand #916)

Draft Guidance Document for the Preparation of Premarket Notification 510(k) Applications for Orthopedic Devices - The Basic Elements (Facts-on-Demand #832)

Guidance for Industry on the Testing of Metallic Plasma Sprayed Coatings on Orthopedic Implants to Support Reconsideration of Postmarket Surveillance Requirements (Facts-on-Demand #946)

2. Adverse Tissue Reaction

Osteolysis, Sensitivity to Metal Implants

Special Controls to Minimize Risks

ASTM Material Standards - F67, F75, F136, F1377, F1580

FDA Guidance Documents

Use of International Standard ISO-10993, Biological Evaluation of Medical Devices Part 1: Evaluation and Testing

3. Infection

Special Controls to Minimize Risk

510(k) Sterility Review Guidance

Additional Risks

Nerve Impingement/Damage, Pain, Vascular Disorders, Pulmonary Embolism,
Gastrointestinal/Genitourinary Complications

These additional identified risks are associated with orthopedic surgery in general, and are not unique to constrained hip surgery.

LIST OF SPECIAL CONTROLS

Following is a listing of special controls available to minimize the risks to health identified by the petitioner and confirmed by a previous panel. These special controls are in addition to the general controls applicable to all orthopedic implants. These special controls include 18 ASTM standards for materials and test methods, and 8 FDA Guidance Documents. In addition, the FDA may require certain mechanical testing as part of a 510(k) premarket notification. These tests could include wear testing of the articulating surfaces as described in this petition.

The ASTM standards define implant material specifications and testing methods applicable to the metal-on-metal hip prosthesis. Adherence to these standards and comparison of the results from these standard tests can control the risks to health of adverse tissue reaction, pain and/or loss of function, and revision by having the manufacturer use surgical implant quality materials, prudent design assurance and good manufacturing practices.

ASTM Standards

1. ASTM F67-95 Standard Specification for Unalloyed Titanium for Surgical Implant Applications. This specification covers the chemical, mechanical, and metallurgical requirements for four grades of unalloyed titanium used for the manufacture of surgical implants.
2. ASTM F75-98 Standard Specification for Cobalt-28 Chromium-6 Molybdenum Casting Alloy and Cast Products for Surgical Implants (UNS R30075). This specification covers the requirements for Cast cobalt-chromium molybdenum alloy, shot, bar, or ingot for surgical implant applications.
3. ASTM F86-91 Standard Practice for Surface Preparation and Marking of Metallic Surgical Implants
4. ASTM F136-98 Standard Specification for Wrought Titanium-6 Aluminum-4 Vanadium ELI (Extra Low Interstitial) Alloy (RS6401) for Surgical Implant Applications. This specification covers the chemical, mechanical, and metallurgical requirements for wrought annealed Titanium-6 Aluminum-4 Vanadium ELI (extra low interstitial alloy (RS6401) to be used in the manufacture of surgical implants.
5. ASTM F648-98 Standard Specification for Ultra-High-Molecular-Weight Polyethylene Powder and Fabricated Form for Surgical Implants. This specification covers ultra-high-molecular-weight polyethylene powder (UHMWPE) intended for use in surgical implants.
6. ASTM F983-86 Standard Practice for Permanent Marking of Orthopaedic Implant Components. The purpose of this standard is to (1) recommend that orthopedic implants be permanently marked, and (2) recommend practical amounts of information that should be included in the marking.
7. ASTM F1044-99 Standard Test Method for Shear Testing of Calcium Phosphate and Metal Coatings. This test method covers "lap shear" testing of porous and non-porous coatings adhering to dense metal substrates.

8. ASTM F1147-99 Standard Test Method for Tension Testing of Calcium Phosphate Porous Metal Coatings. This test method covers tension testing of porous and nonporous metal coatings adhering to dense metal substrates at ambient temperatures and determination of the degree of adhesion of coatings to substrates, or the internal cohesion of a coating in tension normal to the surface plane.
9. ASTM F1377-98a Standard Specification for Cobalt-28 Chromium-6 Molybdenum Powder for Coating of Orthopedic Implants (UNS-R30075). This specification covers requirements for cobalt-chromium-molybdenum alloy powders for use in fabricating coatings on cobalt-chromium-molybdenum alloy orthopedic implants.
10. ASTM F1472-99 Standard Specification for Wrought Titanium-6Aluminum- 4 Vanadium Alloy for Surgical Implant Applications (UNS R56400).
11. ASTM F1612-95 Standard Practice for Cyclic Fatigue Testing of Metallic Stemmed Hip Arthroplasty Femoral Components with Torsion. This practice covers a method for the fatigue testing for evaluation in comparisons of various designs and materials used for stemmed femoral components.
12. ASTM F163 6-95e1 Standard Specification for Bores and Cones for Modular Femoral Heads. This specification covers the functional dimensions and tolerances for tapered cones of proximal femoral stems and the bores of mating ceramic and metal heads.
13. ASTM F1714- 96 Standard Guide for Gravimetric Wear Assessment of Prosthetic Hip-Designs in Simulator Devices. This guide describes a laboratory method using weight-loss technique for evaluating the wear properties of materials or devices, or both, which are being considered for use as bearing surfaces of human-hip-joint replacement prostheses. The hip prostheses are evaluated in a device intended to simulate the tribological conditions encountered in the human hip joint, for example, use of a fluid such as bovine serum, or equivalent pseudosynovial fluid shown to simulate wear mechanisms and debris generation as found in vivo, and test frequencies of 1 Hz or less.
14. ASTM F1814-97a Standard Guide for Evaluating Modular Hip and Knee Joint Components. This guide covers a procedure to assist the developer of a modular joint replacement implant in the choice of appropriate tests and evaluations to determine device safety.
15. ASTM F1820-97 Standard Test Method for Determining the Axial Disassembly force of a Modular Acetabular Device. This test method covers a standard methodology by which to measure the attachment strength between the modular acetabular shell and liner. Although the methodology described does not replicate physiological loading conditions, it has been described as means of comparing integrity of various locking mechanisms.
16. ASTM F18 75-98 Standard Practice for Fretting Corrosion Testing of Modular Implant Interfaces: Hip Femoral Head-Bore and Cone Taper Interface. This practice describes the testing, analytical, and characterization methods for evaluating the mechanical stability of the bore and cone interface of the head and stem junction of modular hip implants subjected to cyclic loading by measurements of fretting corrosion.
17. ASTM F19 78-99 Standard Test Method for Measuring Abrasion Resistance of Metallic Thermal Spray Coatings by Using the Taber™ Abraser. This test method quantifies the abrasion resistance of metallic coatings produced by thermal spray processes on flat metallic surfaces. It is intended as a means of characterizing coatings used on surgical implants.
18. ASTM F1978-99 Standard Test Method for Measuring Abrasion Resistance of Metallic Thermal Spray Coatings by Using the Taber™ Abraser. This test method quantifies the abrasion resistance of metallic coatings

produced by thermal spray processes on flat metallic surfaces. It is intended as a means of characterizing coatings used on surgical implants.

FDA Guidance Documents

1. Guidance Document for Testing Orthopedic Implants with Modified Metallic Surfaces Apposing Bone or Bone Cement. (Facts-on-Demand #827)
2. Guidance Document for Femoral Stem Prostheses (Facts-on-Demand # 1 87)
3. Guidance Document for Testing Acetabular Cup Prostheses (Facts-on-Demand #453)
4. Guidance Document for Testing Non-Articulating, "Mechanically Locked" Modular Implant Components (Facts-on-Demand #916)
5. Draft Guidance Document for the Preparation of Premarket Notification 510(k) Applications for Orthopedic Devices - The Basic Elements (Facts-on-Demand #832)
6. Guidance for Industry on the Testing of Metallic Plasma Sprayed Coatings on Orthopedic Implants to Support Reconsideration of Postmarket Surveillance Requirements (Facts-on-Demand #946)
7. Use of International Standard ISO-10993, Biological Evaluation of Medical Devices Part 1: Evaluation and Testing (Facts-on-Demand #361)
8. 510(k) Sterility Review Guidance ... and Revisions of I 1/1 8/94 and ORDB 7/3/97 (K90-1) (Facts-on-Demand #361)

FDA guidance documents provide guidance on how to meet general orthopedic device premarket notification (510(k)) requirements, including biocompatibility testing, sterility testing, mechanical testing, and physician and patient labeling. Use of the preclinical section of the FDA guidance documents can control the risks to health of adverse tissue reaction, infection, pain, and/or loss of function, and revision by having manufacturers use surgical quality implant materials, adequately test and sterilize their devices, and provide adequate directions for use, including recommended surgical techniques and patient information.

LABELING

The following indications for use, relative contraindications, warnings, and precautions were identified by a previous panel for the 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.
- e) Failed previous surgery including: Joint reconstruction, internal fixation, arthrodesis, surface replacement arthroplasty, hemi-arthroplasty or previous total hip replacement.

Relative Contraindications

1. Bone or musculature compromised by disease, infection, or prior implantation that cannot provide adequate support or fixation for the prosthesis.
2. Any active or suspected infection in or about the hip
3. Skeletal immaturity

Warnings

1. Patients should be warned on 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 causing extreme demands on the hip that can result in the failure of the device. Extreme demands on the device may also cause loosening of the prosthetic components.
2. Bending, contouring, or modifying the device may adversely affect the implant potentially leading to early implant failure.
3. 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

SUGGESTED LABELING FORMAT FOR TOTAL HIP REPLACEMENT PROSTHESIS INFORMATION FOR PRESCRIBERS DEVICE DESCRIPTION

The metal/metal total hip replacement prosthesis is intended for use as a permanent replacement of the hip joint to restore hip function in patients suffering from certain pathologies of their hip joint. (See INDICATIONS FOR USE section)

<insert compatible cup shells and liners>

<insert compatible femoral head sizes/neck lengths>

Material: <insert applicable ASTM standard for metal>

<insert a description of the components and how they function> INDICATIONS FOR USE

The metal/metal total hip prosthesis is intended for the replacement of the severely painful and/or disabled hip joint resulting from inflammatory arthritis, noninflammatory degenerative joint disease, acute traumatic fracture of the femoral head or neck, traumatic arthritis, diastrophic variant and failed previous surgery including: Joint reconstruction, internal fixation, arthrodesis, hemiarthroplasty, surface replacement arthroplasty, or previous total hip replacement.

CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, and POTENTIAL ADVERSE EFFECTS

CONTRAINDICATIONS

Absolute Contraindications Include:

1. overt infection;
2. distant foci of infections (which may cause hematogenous spread to the implant site);
3. rapid disease progression as manifested by joint destruction or bone absorption apparent on roentgenogram;
4. skeletally immature patients;
5. cases where there is inadequate neuromuscular status (e.g., prior paralysis, fusion and/or inadequate abductor strength), poor bone stock, poor skin coverage around hip joint which would make the procedure unjustifiable;

Conditions presenting increased risk of failure include:

1. uncooperative patient or patient with neurologic disorders, incapable of following instructions;
2. marked bone loss or severe osteoporosis;
3. metabolic disorders which may impair bone formation;
4. osteomalacia; and
5. poor prognosis for good wound healing (e.g., decubitus ulcer, end-stage diabetes, severe protein deficiency and/or malnutrition).

Warnings

1. Use of the metal/metal total hip prosthesis is a technically demanding surgical procedure. Familiarity with and attention to the surgical technique utilized with this device is imperative for optimal results.
2. It is essential to obtain correct vertical alignment and version alignment and of the device components. Incorrect alignment may result in suboptimal contact between the femoral head and acetabular prosthesis articulating surfaces resulting in the potential for increased wear.
3. The success of the hip joint reconstruction is heavily dependent upon the conformity of the articulating surfaces of the femoral and acetabular components, therefore it is imperative that the acetabular components not be interchanged between manufacturers.
4. Patients should be warned on 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 patient weight causing extreme demands on the prosthesis that can result in its failure.
5. Bending, contouring, or modifying the device may adversely affect the implant potentially leading to early implant failure.

Proper surgical procedures and techniques are the responsibility of the medical professional. Each surgeon must evaluate the appropriateness of the procedure used based on personal medical training and experience. A detailed surgical technique is available for surgeon reference. Medical procedures for optimal utilization of the prosthesis should be determined by the physician. However, the physician is advised that there is recent evidence that the potential for deep sepsis following total hip arthroplasty may be reduced by:

1. Consistent use of prophylactic antibiotics.
2. Utilizing a laminar flow clean air system.
3. Having all operating room personnel, including observers, properly attired.
4. Protecting instruments from airborne contamination.
5. Impermeable draping.

Metal Components. Some of the alloys used to produce orthopedic prostheses may contain some elements that may be carcinogenic in tissue cultures or intact organisms. Questions have been raised in the scientific literature as to whether or not these alloys may be carcinogenic to actual prosthetic recipients. Studies conducted to date to evaluate these questions have not produced convincing evidence of such phenomenon.

Cemented Application. Care is to be taken to assure complete support of all parts of the device imbedded in bone cement to prevent stress concentrations which may lead to failure of the procedure. Complete cleaning prior to closure (complete removal of bone chips, bone cement fragments, and metallic debris) of the implant site is critical to prevent accelerated wear of the articular surfaces of the implant.

PRECAUTIONS

1. Careful selection of components and familiarity with all aspects of the surgical technique are important to the success of the surgery.
2. An implant should be handled carefully to avoid damage that could compromise the mechanical integrity of the device and cause failure of the implant.
3. Inspect implants for nicks, scratches, or other defects that may cause failure of the implant.
4. To prevent contamination of the prosthesis, keep free of lint and powders. Do not open the package until surgery. Do not place the implant in contact with prepared bone surfaces before the final decision to implant has been made.
5. An implant should never be reused. Any implant once assembled and disassembled should be discarded. Even though it appears undamaged, it may have small defects and internal stress patterns that may lead to failure.
6. The wear rate of prosthetic surfaces is greatly accelerated if loose fragments of bone cement become detached and act as an abrasive in the bearing surfaces. When using bone cement, care should be taken to remove all excess from the periphery of the implant.

POTENTIAL ADVERSE EFFECTS

1. Early and/or long term increased serum, urine, and tissue levels of metal ions.
2. Inadequate or lack of physiological lubrication of the prosthesis articulating surfaces.
3. Infection
4. Pain
5. Loosening, wear, or mechanical failure of prosthetic components
6. Dislocation of the hip prosthesis requiring additional surgery
7. Localized progressive bone resorption (osteolysis)
8. Nerve impingement or damage, vascular disorders (including thrombus)
9. Heterotopic bone formation
10. Sensitivity to implant materials
11. Gastrointestinal and/or genitourinary complications
12. Pulmonary embolism
13. Death
14. Myocardial infarction

Important Physician Information.

Bone resorption is a natural consequence of total joint arthroplasty due to changes in bone remodeling patterns. Bone remodeling is mediated by the changes in stress distribution caused by implantation. Extensive resorption around the prosthesis may lead to implant loosening and failure. It is generally agreed that osteolysis is the result of localized foreign-body reaction to particulate debris generated by cement, metal, and ultra-high molecular-weight polyethylene (UHMWPe). Regarding the etiology, it has been hypothesized that particulate debris generated by the components of a prosthesis migrate into the synovial cavity and the bone-implant interface,

where they recruit macrophages and stimulate phagocytic action. The degree of recruitment is determined by the size, distribution, and amount of particulate debris (rate of debris generation). The phagocytic action results in the release of cytokines and intercellular mediators (IL-1, 2, PE2) which encourage osteoclastic bone resorption. Clinical and basic research is continuing in order to provide scientific basis for the causes of this phenomenon and potential ways to reduce its occurrence.

Osteolysis can be asymptomatic and therefore routine periodic radiographic examination is vital to prevent any serious future complication. Presence of focal lesions which are progressive may necessitate replacement of the prosthetic component(s).

ANALYSIS OF PERTINENT CLINICAL STUDIES

<insert bibliography>

PATIENT COUNSELING INFORMATION

In addition to the patient related information contained in the Warnings and Potential

Adverse Effects sections, the following information should be conveyed to the patient.

1. Joint prostheses will not restore function to the level expected with a normal healthy joint, and the patient should be instructed as to the limitations of the device.
2. Wear of the components can occur and potentially lead to future complications, including bone resorption and loosening, necessitating the removal and replacement of the prosthetic components.
3. The patient should be advised that the expected life of the joint replacement components is difficult to estimate, and that many factors may contribute to the longevity of the prosthesis. The patient can expect a restoration of mobility and reduction of pain, however device components cannot be expected to indefinitely withstand the activity level and loads of normal healthy bone.
4. Adverse effects may necessitate reoperation, revision, or fusion of the involved joint. Products are Supplied Sterile
<insert sterilization method>

Do not resterilize. Do not use any component from an opened or damaged package. Caution: Federal Law (USA) restricts this device to sale by or on the order of a physician.

FOLLOWING ARE TESTS AND TEST METHODS RECOMMENDED FOR USE TO ESTABLISH SUBSTANTIAL EQUIVALANCE

Following are specific tests that may be requested by the FDA to establish substantial equivalence in premarket notifications under Section 510(k). These are the specific tests recommended from the list of special controls that are important to establish substantial equivalence to the metal-on-metal hip devices to be reclassified by this petition. Of course, the FDA has the authority to specify other tests as deemed necessary by the Agency on a case by case basis. Copies of the applicable standards and publications describing these tests are provided at the end of this section.

1. KINEMATICS

The range of motion of the ball-acetabular cup combination should be evaluated and reported.

2. PUSH-OUT AND LEVER-OUT TESTING

The purpose of this testing is to evaluate the locking integrity of the metal/metal shell system. Push-out and lever-out integrity of the lock detail is considered to be important for in vivo longevity of an acetabular system.

Applicable documents include:

Tradonsky, S., Postak, P.D., Froimson, A.I. and Greenwald, A.S., A comparison of the disassociation strength of modular acetabular components. *Clinical Orthopaedics and Related Research*, 296: 14-160 (1993)

3. CYCLIC WEAR, DEGRADATION, AND CORROSION

Specimens should be cyclically loaded on a joint simulator or other appropriate instrumentation. This testing may be performed in accordance with ASTM F-1714-96 Standard Guide for Gravimetric Wear Assessment of Prosthetic Hip Designs in Simulator Devices, and in accordance to the FDA Guidance Document for Testing Acetabular Cup Prostheses.

4. HIP SIMULATOR TESTS

Metal-on-metal hip bearings should be subjected to hip simulator wear tests in order to evaluate their wear performance in a more physiologically realistic scenario. Of additional value would be comparative wear assessments of candidate materials against similarly-classified and 510(k)-cleared implants for which similar hip simulator data have been generated.

Applicable documents include:

Chan, Frank, W., J. Dennis Bobyn, John B. Medley, Jan Krygier and Michael Tanzier, Wear and Lubrication of Metal-on-Metal Hip Implants. *Clinical Orthopaedics and Related Research*, 369: 10-24, Dec. 1999.

5. OTHER TESTS

The FDA may require other tests to establish substantial equivalence deemed necessary by the Agency on a case by case basis.

FDA Comments: In the reclassification petition, the petitioner provided the above list of proposed test methods that are intended to control specific risks. In order to control the risks associated with metal/metal wear, they proposed the use of hip simulator testing. Because there are many different types of hip simulators and test protocols that produce varying results, please provide a guidance that would identify the issues to consider when conducting hip simulator testing and when considering hip simulator test results as a surrogate endpoint for clinical data (i.e. when providing a clinical validation or bridging data between hip simulator testing and the clinical data).

Response and FDA comments: After several conversations with the Orthopedics Devices Branch and the petitioner, it was concluded that some type of guidance was needed for this special control. The petitioner said they would draft a proposed guidance and ask the agency for our comments.

The petitioner sent in a draft of the proposal on March 11, 2001. This proposal states the following.

The American Society for Testing and Materials (ASTM) standard F1714-96 entitled Gravimetric Wear Assessment of Prosthetic Hip Designs in Simulator Devices would provide information related to the in vitro simulator wear assessment of bearing surfaces for total hip arthroplasty. A version is attached herein for review.

Rather than the use of absolute wear quantities (e.g. run-in wear, total wear, or wear rate), it is proposed that the performance benchmark would be 28 mm metal-metal devices (control group) tested concurrently with the candidate devices (experimental group). The articulating surfaces of the control devices would necessarily satisfy the ranges set forth for Item 4 (see below). It is believed that the use of these control devices to establish a benchmark would be appropriate because the implants for which clinical data are available and presented in the petition had design parameters within these said ranges. Furthermore, comparison to such a control group would effectively identify and eliminate the candidature of the first generation implants with sub-optimum design and quality of manufacture.

The design parameters (clearance, roughness, sphericity, material, grain size) for the articulating surfaces of 28 mm metal-metal hip implants would be required to fall within the ranges set forth as follows.

Parameter	Range
Diametrical Clearance	30 to 200 μm
Sphericity	$\leq 7 \mu\text{m}$
Surface Roughness (R_a)	$\leq 30 \text{ nm}$
Material and material properties/characterization	ASTM F75-98, F799-96, F1537-94

For implants with a diameter other than 28 mm, the diametrical clearance should be specified such that the effective radius of the implant will fall within that for 28 mm implants with the above-specified clearance range. Given the specific radii of the articulating surfaces of the head and liner, the effective radius can be calculated as shown in Chan et al⁹⁶. All other specifications should remain as shown above for all implant sizes.

It is believed that these specifications are appropriate because they encompass the range of design parameters for those implants for which clinical data are presented in the petition. Moreover, a number of in vitro simulator studies have identified these as the generally appropriate ranges of design parameters for reproducible, low wear of metal-metal bearings for total hip arthroplasty.^{88-90,100,107,129}

The design parameters for which ranges should be established to form a basis for design controls for down-classified devices have only been recently identified to be relevant in governing the wear of metal-metal bearings for the hip. In response to the recognition of polyethylene particle-induced osteolysis as the most important problem associated with total hip arthroplasty in the 1990s, there was a resurgence of interest in metal-metal technology as an alternative bearing combination to metal-on-conventional polyethylene. Concomitant to the revival in metal-metal interest was a concerted research and development effort in the orthopaedic community to identify the salient engineering issues affecting the wear of these bearings. Prior to the early work carried out to this end^{80,83-100,103,107,108,115-122,126-130,133,134,140-142}, none of which were published before 1990 except for three studies^{135,138,139}, there was no documented knowledge identifying these as relevant design parameters or any indication of their quantities in the early first generation devices from the 1960s and 1970s.

After reviewing the proposal for wear testing of the metal/metal hips we have "accepted" the proposal for the most part, but have several concerns about what OSMA proposes. These concerns are mainly over the validation of the wear test proposed, and exactly how they are to determine a "good" metal/metal device. These questions will be sent to the sponsor and similar concerns will be brought to the Orthopedic and Rehabilitation Advisory Committee (Panel). The following questions were concerns about the proposed test method to examine wear of metal/metal hips:

1. According to the proposal, wear testing results of an investigational device are to be compared to wear testing results of already marketed 28mm metal/metal hip system. However, you have not provided

data to demonstrate that hip simulator testing is able to discriminate between "good" and "bad" wear couples and thereby act as a surrogate endpoint for clinical data. In addition, we are aware that ASTM F1714-96 does not identify a specific type of wear simulator or a set of specific test methods to be used but lists several. Therefore, in order to demonstrate that a specific type of wear simulator using a set of specific test methods (per ASTM F1714-96 or some other test method) is able to discriminate between clinically "bad" or "first generation" and clinically "good" metal/metal wear couples, please complete the following:

- a. Please provide a complete test report that includes wear testing comparing a clinically "bad" metal/metal wear couple (e.g. "first generation characteristics") and a clinically "good" metal/metal wear couple.
 - b. Please include a summary of clinical data and/or literature references that prove that the clinical results of the wear couple chosen to represent the clinically "bad" metal/metal wear couple are indeed poor due to excessive wear formation and design parameters.
 - c. Please include a summary of clinical data and/or literature references that prove that the "good" wear couple test results represents in vivo wear from explanted devices.
2. You stated that the articulating surfaces of the control devices should necessarily satisfy the ranges set forth for the series of parameter ranges outlined in the proposal. However, you have not provided data to demonstrate that all combinations of materials and diametrical clearances that fall within the parameter ranges outlined in the proposal are clinically successful. In order to address the potential that a "bad" wear couple may fall within the design parameter ranges or the potential that by identifying a set of parameters, you may limit new technology; we are rejecting the idea that the design parameters set forth in the proposal are design requirements for metal-metal devices. We are planning to use the design parameters stated in the proposal as descriptive information of the devices used in the nonpublished clinical studies in the petition and comparison data for "new" devices. We will not, however, use these design parameters as a special control limiting new designs to these ranges.

The FDA views the special controls as the most important part of the reclassification petition. It has been shown by the petitioner that the first generation devices had some long term problems in patients which required the device to be revised or removed. Most of these problems were due to inadequate means of fixation, but also some of these were due to dislocation, infection, and wear. Science has made steps towards minimizing these risks such as better metallurgy, and smaller size heads. One thing that cannot be looked at is the wear of these devices, because no long term data has been done. These are relatively new devices (second generation hips), with limited follow-up. One concern that the agency has is the risk of wear and how these special controls are to predict the wear outcome at long term dates. The proposed wear control only has 5 million cycles which approximately represents 5 years of data, but many of the first generation hips failed after the 5 year time point.

8. Regulatory History

The use of metal/metal hip joint replacement devices predates the Medical Devices Amendments of 1976. Prior to the enactment of these regulations, the FDA chartered the Orthopaedic Device Classification Panel to study orthopedic devices and to make recommendations on their classification.

Although the Orthopedic Device Classification Panel was terminated by the FDA in 1978 in favor of reestablishment as the Orthopedic Device Section of the Surgical and Rehabilitation Devices Panel (The Panel), review of device classification continued. On July 2, 1982, after reviewing the recommendations of the Panel, the FDA issued a Proposed Rule (47 FR 29052) classifying 77 orthopedic devices. Metal/metal hip joint replacement prostheses with cemented acetabular components (CFR 888.3320) and metal/metal hip joint replacement prostheses with uncemented acetabular components (CFR 888.3330) were proposed for class III.

The Final Rule classifying orthopedic devices was published September 4, 1987 (52 FR 33686). Although this formally established metal/metal hip joint replacement prostheses as preamendments class III devices, no date was established for a call for PMAs for these devices. Since that time manufacturers were allowed to market metal/metal semi-constrained total hip joint replacement prostheses via the premarket notification, i.e., the 510(k) provision of the Act, provided the FDA determined them to be substantially equivalent to preamendments predicate devices. FDA disclosed to applicants filing premarket notifications that data from a clinical trial of the device, or from a similar device, would be required in support of substantial equivalence to a preamendments device.

On April 19, 1994, a memorandum from the Acting Director of the Office of Device Evaluation was released outlining the strategy for implementation of the provision of the Safe Medical Devices Act of 1990 that mandated further activity on these class III devices. This strategy was also published May 6, 1994 (59 FR 23731). Three groups were created regarding these devices:

- Group 1 Devices that have fallen into disuse and are unlikely to result in viable PMAs or reclassification petitions;
- Group 2 Devices that FDA believed to have a high potential for reclassification; and
- Group 3 Devices not at the time considered for reclassification and for which PMAs would be called.

The memorandum also set forth dates on which the FDA would take various actions on these groups of devices. Metal/metal semi-constrained total hip prostheses (21 CFR 888.3320 and 888.3330) were placed in Group 3 with a call for PMAs scheduled for 1994.

On September 7, 1995 FDA published a Proposed Rule (60 FR 46717) that outlined the date on which PMAs or PDPs for 43 class III devices would be required. The period for written comments closed on January 5, 1995. On September 27, 1996, the Final Rule was published (61 FR 50704) for 41 of the 43 class III devices requiring PMAs or PDPs by December 26, 1996.

The Orthopedic Surgical Manufacturers Association (OSMA) formed seven committees to work on several reclassification petitions for orthopedic devices that were subject to calls for PMAs or PDPs. One of those committees was assigned the responsibility of submitting a reclassification petition for metal/metal semi-constrained total hip joint prostheses. This petition is the result of those efforts.

9. Financial Disclosure

Based upon review of the Agency Final Rule, the petitioner believes that financial disclosure by clinical investigators is applicable to this submission.

FDA Comments: Financial disclosure is applicable for this petition, but the petitioner has failed to provide the necessary information concerning financial interests of the clinical investigators.

Response: After consulting with Joanne Less, it was decided that the petitioner could fill out form 3454 and the Financial Disclosure deficiency would be resolved.

10. Medical Device Reports (MDRs)

METAL/METAL SEMI-CONSTRAINED TOTAL HIP PROSTHESES

Inclusive dates: January 1, 1992 to June 29, 2000.

A reasonable effort was made to find all adverse reports made for these devices under the Medical Device Reporting (MDR) regulations and under the vigilance reporting requirements for medical devices under Article 10 of the European Medical Devices Directive (MDD). A search of the publicly available information yielded

one report filed for metal/metal semi-constrained total hip prostheses. However, it is possible that a small number of additional reports could have been made using improper product codes, erroneous device descriptions, etc. In addition, the FDA may have access to additional reports made after June 29, 2000.

A review of the published literature was performed to provide a summary of the device related adverse events reported for metal/metal hip prostheses.

A. MDR/Vigilance Reports

A summary of the one MDR report obtained for a metal/metal hip prosthesis is provided below. There were no vigilance reports obtained from searches conducted of the databases available for the member states comprising the European Economic Community (EEC).

Manufacturer: Sulzer Orthopaedics, Inc.
9900 Spectrum
Austin, TX 78717

Device Description: Acetabular Insert 28x55 Metasul APR
MDR Report Key: 29355620-2000-00012
Product Code: KWA
Report Date: 4/24/2000
Catalog No.: 4340-28-055
Device Lot No.: 1251199
Event Description: Allegedly the anti-rotation pin became dislodged from the polyethylene acetabular insert.
Patient Outcome: Hospitalization.

B. Summary of Published Adverse Events

A survey of the published literature resulted in the following adverse events reported for these devices.

1. Wagner, Michael and Heinz Wagner. "Preliminary Results of Uncemented Metal on Metal Stemmed and Resurfacing Hip Replacement Arthroplasty."; Clin. Orthop., No. 329S (1996): S78-S88.

This article reports on a series of 70 patients in Europe with metal/metal semi-constrained total hips implanted during 1990-1992. There was one early dislocation with the patient refusing further treatment; one late infection requiring removal of the prosthetic implant components. Periarticular calcification in two patients requiring reoperations was also reported.

2. Dorr, L. D., K. R. Hilton, Z. Wan, G.D. Markovich, and R. Bloebaum, Ph.D." Modern Metal on Metal Articulation for Total Hip Replacements."; Clin. Orthop., No. 333 (1996): 108-117.

This article reports on a series of 54 patients treated in the U.S. with metal on metal semi-constrained total hips from 1991-1994. There was one infection and two dislocations; one of these dislocations required revision of the prosthesis three years postoperatively.

3. Weber, B.G. "Experience With the Metasul Total Hip Bearing System."; Clin. Orthop., No. 329S (1996): S69-S77.

This article reports on a series of 110 patients treated in Europe with metal on metal semi-constrained total hips from 1988-1992. There were five early failures attributed to loosening reported. There were two additional complications of trochanteric bursitis (one case) and painful ectopic ossification (one case), neither case required reoperation.

- Hilton, K.R., L.D. Dorr, Z. Wan and E.J. McPherson. "Contemporary Total Hip Replacement With Metal on Metal Articulation."; Clin. Orthop. No. 329S (1996): S99-S105.

This article updates a previous report by Dorr, et al. (See ref. 2) There was one additional dislocation reported for this series.

- Doom, P.F., J.M. Mirra, P.A. Campell, and H.C. Amstutz. "Tissue Reaction to Metal on Metal Total Hip Prostheses."; Clin. Orthop. No. 329S (1996): S187-S205.

Nine metal/metal hip implants retrieved from nine patients underwent histological evaluation to study the tissue reaction around the prostheses. Four McKee-Farrar, one APR and one Apollo metal/metal total hip prostheses and three McMinn metal/metal total surface replacement hip prostheses were evaluated. The duration of implantation ranged between seven months and 25 years. Implants were retrieved due to aseptic loosening (4), pain (2), dislocation (1), femoral fracture (1), and death (1). While many of the common tissue responses to metal/polyethylene articulations were also noted for the metal/metal devices, however, overall these reactions appeared less intense.

- Iida, H., E. Kaneda, H. Takada, K. Uchida, K. Kawanabe, and T. Nakamura. "Metallosis Due to Impingement Between the Socket and the Femoral Neck in a Metal-on-Metal Bearing Total Hip Prosthesis: A Case Report."; J Bone Joint Surg. Vol. 81(A) (1999): 400-3.

This article reports on a single patient who suffered a failure of her metal-on-metal hip prosthesis 12 months following her surgery. The patient had no prior history of dislocation or other major complication. The prosthesis was shown to be loose on x-rays at 12 months and osteolysis was suspected in the calcar and trochanter regions of the femur. Examination of the retrieved titanium alloy femoral prosthesis and the cobalt-chrome alloy acetabular prostheses revealed markings consistent with impingement between the socket and the femoral neck during maximum hip flexion. Histological examination of the pseudocapsular tissue revealed particles of titanium, but cobalt and chromium were not detected. The authors concluded that the source of the metal debris was from the femoral prosthesis. The authors further concluded that this type of complication can occur anytime, without symptoms or associated complications and questioned the use of titanium in the manufacture of this implant.

- Campell, P., H. McKellop, R. Alim, J. Mirra, S. Nutt, L. Dorr, and H.C. Amstutz. "Metal-On-Metal Hip Replacements: Wear Performance and Cellular Response to Wear Particles." In Cobalt-Based Alloys for Biomedical Applications. ASTM STP 1365., editors J.A. Disegi, R.L. Kennedy and R. Pilliar, 193-209. West Conshohocken, PA: ASTM publishers.

This article reports on 20 second generation metal-on-metal hip prostheses retrieved from patients after use ranging from nine months to 6.5 years. The specific aims of this study of retrieved devices were to examine the amount of wear, study the histological appearance of the periprosthetic tissues and characterize the wear particles generated *in vivo*. There were 10 total hip and 10 surface replacement hip prostheses configurations available for evaluation. Implants were made available due to a variety of reasons including loosening, debonding, component breakage, infection and death.

Eighteen of the 20 retrieved prostheses had at least one component measured for wear. For those components in which wear could be measured, the amount of wear ranged from 3-32 microns. Two of the total hip prostheses exhibited clusters of micropits in the main bearing area, but these did not appear to be associated with high wear.

Histological evaluation revealed metallosis occurred in five cases. Impingement of the titanium alloy

femoral components with the acetabular shell, debonding of the porous coating and breakage of the femoral component were cited as the likely causes in four of these cases. For the fifth case, discoloration was likely due to cobalt-chrome particles released during the wear-in phase of the components. The histology for another case revised due to distal femoral osteolysis, was inconsistent with wear-induced osteolysis. Extensive necrosis was noted for two other cases, but no clear association between necrosis and metal wear particles could be made. Except for the five metallosis cases, there were fewer macrophages and wear particles than is typically seen in tissues around metal-polyethylene hip prostheses. Two consistent forms of cobalt-chrome particles were noted. One was a dense elongated form that commonly had a defined edge. The second, and the most common, form had less defined edges with a non-homogeneous, amorphous texture. Particle size was comparable between the total hip and surface replacement hip prostheses.

Conclusions are summarized as follows: 1) wear of the metal-on-metal articulations was substantially lower than for metal-polyethylene articulations, 2) third body damage was noted in varying degrees on all components, 3) histology and particle morphology were consistent with the low wear of these bearings, 4) cellular reaction to the metal particles could be described as mild, and 5) further histopathological studies and measurements of *in vivo* wear of metal-on-metal total hip replacements are recommended.

8. Albrecht-Olsen, P, Owen-Falkenberg, T, Burgaard, P, Andersen, PB. Nine-Year Follow-up of the Cementless Ring Hip. *Acta Orthop Scand*, 60:1:77-80, 1989.

Albrecht-Olsen et al. reviewed 238 Ring prostheses implanted during the period 1968-1979. Of those cases, 127 with a median follow-up of 9 years were available for evaluation with 90% of those patients demonstrating excellent/good results upon self assessment. Using the Charnley scale, 87% had a pain score of 4 or greater (score of 6 = no pain), 76% had a motion score of 4 or greater, and 57% had a walking score of 4 or greater. The author cites an infection rate of 2.5% (6 deep infections, 16 superficial infections). Four dislocations were also encountered. At the time of this evaluation, 17% (n=40) of the patients had been revised, mainly due to pain. Overall results predicted an 81% survival rate at 12 years, comparable to outcomes seen with metal-on-polyethylene articulation

9. Almy, B, Hierton, T. Total Hip Replacement: A Ten-Year Follow-up of an Early Series. *Acta Orthop Scand*, 53:397-406, 1982.

Almy reported on 93 patients receiving the Muller device, 57% of which had been followed for more than 10 years. Using the Charnley scale (6 possible points in each category), 90% had pain rating of 4 or better or a range of motion greater than 1000. Nine deep infections were reported. Thirty patients died (26 unrelated to device, 1 embolus, 1 ileus, 1 renal failure, 1 septic). Twenty-nine patients were revised (19 aseptically loose, 7 septically loose, 4 stem fractures, 1 fracture). Twenty-three acetabular and 16 femoral components showed signs of loosening. Femoral loosening was secondary to calcar resorption and cement settling in most cases. Survivorship in this series was calculated to be approximately 80% at 5 years and 57% at 10 years.

10. Andrew, T.A., Berridge, D, Thomas, A, Duke, RNF. Long-term Review of Ring Total Hip Arthroplasty. *Clinical Orthopedics and Related Research*, 201:111-122, 1980.

Andrew presented his results of 116 Ring patients followed for 8 years. Using the Harris scoring system (100 points possible), 33% of the patients had 80 points or greater with another 13% exhibiting total scores of 70-80. Using the Ring evaluation, 49% of the patients rated excellent or good. Two deep infections and 4 dislocations were encountered. Other complications included grade IV heterotopic ossification (5), fracture (4), embolic event (7), and sciatic palsy (1).

11. Djerf, K, Wahlstrom, O. Total Hip Replacement Comparison Between the McKee-Farrar and Charnley Prostheses in a 5-Year Follow-up Study. *Acta Orthop. Scand.*, 105:158-162, 1986.

Djerf presents results on 107 McKee-Farrar and 70 Charnley devices with 5 years follow-up. Analysis revealed 94% of patients to have no pain and 78% to have improved flexion. Unrelated death occurred in 12% of the patients. Six infections (3.4%) and 4 dislocations (2.3%) were reported. Other complications included trochanteric problems (2.8%), nerve injury (1.7%), deep venous thrombosis (1.7%), pulmonary embolus (0.6%), fracture (0.6%), and ossification (0.6%). Loosening was evident in 32% of the cases. Analyses showed no significant difference in the outcomes of either implant.

12. August, AC, Aldam, CH, Pynsent, PB. The McKee-Farrar Hip Arthroplasty: A Long Term Study. *Journal of Bone and Joint Surgery*, 68B:4:520-527, Aug. 1986.

Results of 175 patients with the McKee-Farrar device at an average 13.9 years of follow-up are presented by August. Using the Harris evaluation, the average total score was 76.4, with 48.9% having excellent/good outcomes. On self assessment, 90% of the patients rated themselves as having a satisfactory outcome. Sixty-four patients were revised, mainly for loosening, stem fracture and bone fracture. Over 50% of the stems and cups showed signs of loosening radiographically. Additionally, the cup showed signs of protrusion in 62.5% of rheumatoid patients. Heterotopic ossification (grade-IV) was reported in 2.7% of the cases. August calculated survival at 84.3% at 14 years and 27.5% at 20 years.

13. Jantsch, S, Schwagerl, W, Zenz, P, Semlitsch, M, Fertschak, W. Long-term Results After Implantation of McKee-Farrar Total Hip Prostheses. *Acta Orthop. Scand*, 110:230-237, 1991.

Jantsch analyzed follow-up at 14 years in a series of 248 patients with 330 McKee-Farrar devices. Only 56% of the patients were followed clinically to this period (24% died, 17% untraceable, 3% refused participation). Using the Mayo rating system, 48% of the patients were found to have excellent/good ratings (62% if revisions are excluded). Based on radiographs available, 34% of the cups and 26% of the stems were unstable. There were 36 retrievals (22 cup and stem, 7 cup, 7 stem).

14. McKee, GK, Chen, SC. The Statistics of the McKee-Farrar Method of Total Hip Replacement. *Clinical Orthopedics and Related Research*, 95:26-33, Sept. 1973.

McKee reports on four series of patients treated with the various iterations of the McKee-Farrar device from 1956-1971. As shown in the attached tables, postoperative outcome improved through each design iteration, with approximately 89% achieving excellent or good outcomes in the 1965-69 series (4-7 year follow-up) and 97% achieving excellent or good outcomes in the 1971 series (2 year or less follow-up). Retrievals have occurred in 4% of the 1965-69 series and 0% of the 1971 series. Fifteen (15) deaths were reported in the 1965-69 series; two were reported in the 1971 series. The reported rate of infection was 4% in the 1965 series and 0% in the 1971 series. Two dislocations (2%) were also reported in each of these series. Other complications include pulmonary embolus, deep venous thrombosis, shaft perforation, hematoma and heterotopic ossification.

15. Ring, P. Press-Fit Prostheses: Clinical Experience. *Osteoarthritis in the Young Adult Hip: Options for Surgical Management*. Pp. 220-232, edited by D Reynolds and M Freeman, Churchill Livingstone Publishing, 1989.

Ring presents results on 106 metal-metal Ring prostheses with 7-17 years follow-up. Postoperatively, 83% were assessed as excellent/good clinically. Outcomes of the various design iterations are again presented in this article. Thirteen retrievals have occurred (7 femoral failures, 2 pelvic failures, 3 combination failures, 1 ankylosis). Survivorship of patients implanted from 1968-73 was 81% at 18 years; survivorship was 95% at 16 years for those implanted from 1972-79.

16. Schmalzried, TP, Szuszczewicz, ES, Akizulci, KH, Petersen, TD, Amstutz, HC. Factors Correlating with

Long Term Survival of McKee-Farrar Total Hip Prostheses. *Clinical Orthopedics and Related Research*, 329S:48-59, Aug. 1996.

Thirteen McKee-Farrar patients (15 devices) with an average follow-up of 23.7 years are presented by Schmalzried. The average Harris hip score of these patients was 86 with 11 patients having an excellent/good rating. These patients outscored a matched metal-on-poly control population on the SF-36 Health Status questionnaire. Activity levels were also reported to exceed the averages for this age population. The only complication reported is that of lysis in three femurs and one acetabulum.

17. Zaoussis, AL, Patikas, AF. Experience with Total Hip Arthroplasty in Greece, the First 20 Years: A Particular Reference to long-term Results with the McKee-Farrar Technique. *Clinical Orthopedics and Related Research*, 246:39-47, Sept. 1989.

Zaoussis presents results on 38 McKee-Farrar patients followed for 12-20 years, with 26 having greater than 15 years follow-up. At the time of this evaluation, 45% were found to have very good outcomes. Fifty-three percent (53%) of the patients were pain free and 79% had 60-90° range of motion. Three infected components and four loose components were retrieved. There have been five dislocations (all in one patient). Nine components show looseness. Other complications include five peroneal nerve palsies, one cortical perforation and one ossification.

FDA Comments: The petitioner only looked at MDR reports from 1992 to the present. We felt, since these devices are pre-amendment devices, that more MDRs could exist. We asked the petitioner to conduct a MDR search for the 1984 to the present.

Response and FDA comments: The petitioner responded to this deficiency by stating that they were having trouble accessing the MDR reports before 1992. It was concluded that we would conduct the MDR search using our databases. We had Dan MacGunagle conduct a MDR search on every possible product code, every possible device name, along with the terms "metal on metal", "metal/metal", and "metal metal". He only came up with one MDR report.

Manufacturer: ?

Device Description: Thompson Hip Prosthesis

MDR Report Key: 1400460000-1992-0029

Product Code: KWA

Report Date: 1/18/93

Catalog No.: ?

Device Lot No.: ?

Event Description: Patient fell and sustained a fractured left femur. Received a Thompson Hip Prosthesis. Developed lengthening of left lower extremity and c/o pain in the lower back and left hip.

Patient Outcome: Hospitalization.

I conducted a search on my own using MAUDE through the FDA website. I found several more MDR reports under the pro codes KWA and JDL. The following MDRs were found:

1. Manufacturer: Sulzer Orthopaedics, Inc.
9900 Spectrum
Austin, TX 78717

Device Description: Acetabular Insert 28x53 Metasul APR

MDR Report Key: 290650

Product Code: KWA
Report Date: 7/21/2000
Catalog No.: 4340-28-053
Device Lot No.: 1187760
Event Description: It was reported that: Revision hip surgery was performed due to impingement between the femoral stem and the acetabular insert.
Patient Outcome: Hospitalization required Intervention.

2. Manufacturer: Sulzer Orthopaedics, Inc.
9900 Spectrum
Austin, TX 78717

Device Description: Acetabular Insert 28x49 Metasul APR
MDR Report Key: 2935620-2000-00062
Product Code: KWA
Report Date: 11/6/2000
Catalog No.: 4340-28-049
Device Lot No.: 1303668
Event Description: It was reported: The pin in the Metasul insert came out after 1.5 years.
Patient Outcome: Hospitalization required Intervention.

3. Manufacturer: Sulzer Orthopaedics, Inc.
9900 Spectrum
Austin, TX 78717

Device Description: Acetabular Insert 28x49 Metasul APR
MDR Report Key: 310957
Product Code: KWA
Report Date: 12/8/2000
Catalog No.: 4340-28-049
Device Lot No.: 1187760
Event Description: It was reported: Patient underwent total hip arthroplasty (THA) in 1998. Subsequently the patient was revised 3 times due to dislocations. Patient underwent the last THA in 2000 where the insert and ball head were replaced.
Patient Outcome: Hospitalization required Intervention.

4. Manufacturer: Sulzer Orthopaedics, Inc.
9900 Spectrum
Austin, TX 78717

Device Description: Acetabular Insert 28x49 Metasul APR
MDR Report Key: 316925
Product Code: KWA
Report Date: 1/23/2001
Catalog No.: 4340-28-049
Device Lot No.: 1230114
Event Description: It was reported: 11/13/2000: Sudden "Clunk" in hip could not walk, x-ray in emergency dept: Disassociation of Metasul Insert from APR II shell. Patient experienced two heavy falls, one onto their back in March 2000 and another fall forward in July 2000.
Patient Outcome: Hospitalization required Intervention.

5. Manufacturer: Sulzer Orthopaedics, Inc.
 9900 Spectrum
 Austin, TX 78717
- Device Description: Acetabular Insert 28x55 Metasul APR
MDR Report Key: 278978
Product Code: KWA
Report Date: 4/24/2000
Catalog No.: 4340-28-055
Device Lot No.: 1251199
Event Description: It was reported: Allegedly the anti-rotational pin became dislodged from the polyethylene acetabular cup.
Patient Outcome: Hospitalization required Intervention.

10. Filing Deficiencies

The following deficiencies were sent to the petitioner:

1. The disclosure of compensation and financial information is applicable to this reclassification petition. Applicants must certify to the absence of certain financial interests of clinical investigators on Financial Interest Form: Certification: Financial Interests and Arrangements of Clinical Investigators FDA Form 3454 (<http://forms.psc.gov/forms/FDA/fda3454.pdf>) or to disclose those financial interests on Financial Interest Forms: Disclosure: Financial Interests and Arrangements of Clinical Investigators FDA Form 3455 (<http://forms.psc.gov/forms/FDA/fda3455.pdf>).

The information that must be disclosed include the following:

- Compensation made to the investigator in which the value of the compensation could be affected by the study outcome.
- Significant payments to the investigator or institution with a monetary value of \$25,000 or more (e.g. grants, equipment, retainers for ongoing consolation, or honoraria) over the cost of conducting the trial. Any such payments to the investigator or institution during the time the investigator is conducting the study and for one year following study completion, must be reported.
- Proprietary interest in the device, such as a patent, trademark, copyright, or licensing agreement.
- Significant equity interest in the sponsor such as ownership, interest, or stock options. All such interests whose value cannot be readily determined through reference to public prices must be reported. If the sponsor is a publicly traded company, any equity interest whose value is greater than \$50,000 must be reported. Any such interests held by the investigator while the investigator was conducting the study and for one year following study completion must be reported.

Please provide the financial disclosure information for the four clinical studies conducted in the United States and included in the reclassification petition. **After further review of the deficiency, and consultation from Joanne Less, it was concluded that the sponsor could complete Form 3454. This form applies to the petitioners situation. Deficiency adequately resolved.**

2. In your reclassification petition you have described four unpublished clinical studies (Study A, B, C, and D). The following deficiencies relate to those four studies:
- a. You have presented clinical data from four non-published studies, but you have not provided a complete summary of the timecourse distributions of the clinical data or patient accounting information (e.g. Harris Hip Score levels: Excellent, Good, Fair, and Poor) over the course of

each study (e.g. pre-op, post-op, 6 months, 12 months, 24 months). This information would allow us to adequately analyze primary clinical endpoints and patient accountability information for each unpublished clinical study. Please provide timecourse distribution of the clinical data and patient accountability information for Study A, Study B, Study C, and Study D. The enclosed guidance "General ORDB Outline for Clinical Data Presentation in Premarket Notifications (510(k)) Submissions, Investigational Device Exemptions (IDE) Annual Reports, or Premarket Approval (PMA) Applications" dated June 1991, should be used as a guide for formatting these data. **The petitioner responded to this deficiency saying that they would supply the patient accounting information for all the studies except for Study D. This study will be used for adjunctive data only.**

- b. You have not provided complete radiographic data for the patients in the four unpublished clinical studies. For example, in Studies A, B, C you did not provide any radiographic data on acetabular cup migration, radiolucencies, or other signs of acetabular loosening. In addition, there was no radiographic information on the presence of heterotopic ossification. In Study D, you did not provide any radiographic data. Although Study D contained clinical data, radiographs provide essential information, including early signs of loosening. Please provide complete radiographic data from all four unpublished clinical studies including acetabular cup migration, radiolucencies, or other signs of acetabular loosening. If radiographic data are not available for Study D, please explain why this information is unavailable. **It was determined that this information was in the submission, and would not be needed. Study D will only be used as adjunctive data. Deficiency adequately resolved.**
- c. When describing each device used in each unpublished clinical study, you provided a picture of the device and device materials, but did not provide the name and specifications of the device (e.g. femoral head size, acetabular cup size, type of cup). Please provide the specific name of the device and specific sizes and measurements of each device used in Study A, Study B, Study C, and Study D. **The petitioner responded to this deficiency by saying that releasing the types of devices might give an unfair advantage to the company. We in return asked for specific values of each device, and/or a range of values.**
- d. Please provide the investigational protocols for Study A, Study B, Study C, and Study D. **The petitioner provided the study protocols for Study A, B and C. The study protocol for study B is incomplete.**
- e. In each study, you compared the data from metal/metal hip joint prostheses to data from metal/polyethylene hip joint prostheses by providing only the means of various clinical endpoints. Please provide an analysis of the results for each study based on the analysis in the study protocol. Additionally, please describe the criteria for individual patient success, based on clinical and radiographic parameters, and provide a comparison of the results of the studies individually, if this type of analysis was not described in the protocol. Please provide an analysis of the pooled study results looking at individual patient success as well. In your analysis, the time after surgery at which an assessment for effectiveness was made needs to be taken into account. **The petitioner stated that by doing a statistical comparison would underpower the results of the study. The FDA believes that some sort of comparison needs to be done with the data. Other submissions have compared means scores, and the protocols for those devices will be used to draft a proposal to the petitioner on how they should compare the data. I consulted with Ted Stevens and Mel Siedman on a PDP for a Ceramic/Ceramic hip I which the sponsor compared the C/C mean Harris Hip Scores with Metal/Poly mean HHS. The sponsor responded to this deficiency, by providing a poolability analysis for the unpublished multicenter studies data that includes patient demographics and total scores, perform a similar analysis for the literature reference**

articles for early metal/metal hip designs. Data from these articles that were determined to be poolable are used for a meta-analysis of the unpublished studies. The meta-analysis is to include comparative statistics for revision rates, success rates, etc, and perform the same poolability analysis for the literature reference articles for contemporary metal/metal hip designs.

- f. For some of the clinical studies you provided the number of revisions and removals of the device in Study A, B, D but did not provide this data for Study C. Please provide the number of revisions, reoperations, and removals for all of the unpublished clinical studies. **There were no revisions reported for the study.**
3. In your reclassification petition, you have provided a list of proposed test methods that are intended to control specific risks. In order to control the risks associated with metal/metal wear, you proposed the use of hip simulator testing. Because there are many different types of hip simulators and test protocols that produce varying results, please identify important issues to consider when conducting and evaluating hip simulator testing. Please describe the test methods that would predict clinical wear and the evidence supporting the use of those methods in order to show the risk can be addressed with this special control. **The petitioner will provide a draft proposal on how wear testing should be reviewed. We will provide the petitioner with comments. See comments and deficiencies at the end. These will be presented to OSMA and to the Panel.**
4. In the reclassification petition, you have identified geometry and surface finish of the femoral head and acetabular component as two important design considerations for a metal/metal semi-constrained hip joint prosthesis but did not provide any specific values. Some of these features such as sphericity, clearance, and surface roughness play an important role in the success of a metal/metal hip prosthesis. Please provide a table of values for the sphericity, clearance, and surface roughness for each metal/metal semi-constrained hip joint prosthesis identified in the published literature and unpublished clinical data contained in this petition. **The petitioner will provide a range of values for the pertinent design characteristics of the metal/metal devices. See range of values above in the memo.**
5. In the reclassification petition, you have provided a summary of different published literature articles on clinical studies performed using metal/metal hip joint prosthesis. The following deficiencies relate to the published clinical data:
- a. In Tables 8 and 9 of the petition, titled "Clinical Outcomes of Published Literature" and "Adverse Effects of Published Literature", you have provided follow-up, pre-op score, post-op score, and several other categories for analyzing the published literature. However, you have not provided copies of the literature articles upon your summaries were based. Therefore, please provide copies of all literature articles cited in Tables 8 and 9.
- b. In the reclassification petition, you have summarized several published articles but you have not identified how your literature search was performed including:
- Name(s) of the databases;
 - Search terms (i.e. keywords);
 - Range of years; or
 - Acceptance and rejection criteria for each journal article.
- Therefore, in order to insure that you have performed a complete search to fully characterize the risks associated with metal/metal prosthesis, please provide this information in your next submission. **See above memo for deficiency response. Deficiency adequately resolved.**

6. In your reclassification petition, you have identified only one medical device report (MDR) between January 1, 1992 and June 29, 2000. Because the reclassification petition contains both pre-amendments and recently cleared devices, please review all MDRs for metal/metal hip joint prostheses from January 1, 1984 to the present, and identify all risks included in these reports. **The petitioner was having trouble accessing the databases before 1992. It was concluded that the FDA will conduct an MDR search and report their findings. Deficiency adequately resolved.**

Deficiencies concerning the Wear Proposal

1. According to the proposal, wear testing results of an investigational device are to be compared to wear testing results of already marketed 28mm metal/metal hip system. However, you have not provided data to demonstrate that hip simulator testing is able to discriminate between "good" and "bad" wear couples and thereby act as a surrogate endpoint for clinical data. In addition, we are aware that ASTM F1714-96 does not identify a specific type of wear simulator or a set of specific test methods to be used but lists several. Therefore, in order to demonstrate that a specific type of wear simulator using a set of specific test methods (per ASTM F1714-96 or some other test method) is able to discriminate between clinically "bad" or "first generation" and clinically "good" metal/metal wear couples, please complete the following:
 - a. Please provide a complete test report that includes wear testing comparing a clinically "bad" metal/metal wear couple (e.g. "first generation characteristics") and a clinically "good" metal/metal wear couple.
 - b. Please include a summary of clinical data and/or literature references that prove that the clinical results of the wear couple chosen to represent the clinically "bad" metal/metal wear couple are indeed poor due to excessive wear formation and design parameters.
 - c. Please include a summary of clinical data and/or literature references that prove that the "good" wear couple test results represents in vivo wear from explanted devices.
2. You stated that the articulating surfaces of the control devices should necessarily satisfy the ranges set forth for the series of parameter ranges outlined in the proposal. However, you have not provided data to demonstrate that all combinations of materials and diametrical clearances that fall within the parameter ranges outlined in the proposal are clinically successful. In order to address the potential that a "bad" wear couple may fall within the design parameter ranges or the potential that by identifying a set of parameters, you may limit new technology; we are rejecting the idea that the design parameters set forth in the proposal are design requirements for metal-metal devices. We are planning to use the design parameters stated in the proposal as descriptive information of the devices used in the nonpublished clinical studies in the petition and comparison data for "new" devices. We will not, however, use these design parameters as a special control limiting new designs to these ranges.

Deficiencies For Amendment 2

1. In Amendment 2, Exhibit 2, Table 1, page 16, you identified the Study A femoral stem component as the S-ROM. However, in the investigational protocols (Protocol 19603, page 56, and Protocol 19602, page 84) provided in Exhibit 3, the femoral stems included both the P.F.C. Hip system and the S-ROM Hip system femoral components. You also identified the Study B femoral stem components as including the S-ROM, as well as the ULTIMA, ULTIMA LX, ULTIMA TPS, and P.F.C., whereas the investigational protocol provided in Exhibit 3, page 113, does not include the S-ROM femoral stems. The investigational protocol for Study C did not identify the specific femoral stem components. Please rectify these discrepancies.

2. Please provide statistical comparisons between the pooled articles for the early metal-metal hips and the contemporary metal-metal hips with the pooled results of Study A, Study B, and Study C for patient age, diagnosis, gender, and length of follow-up to justify comparability of the groups.
3. In Amendment 1, Appendix 1, Table 5, the number of revisions, reoperations, and removals are not documented. For Study A and Study B, the number of revisions, reoperations, and removals were documented in Table 5 of those sections. Although you state that there were no revisions, reoperations, and removals in Study C, it should be positively documented in the data tables. Please provide this table.
4. You have calculated the percent missing as follows:

$(\text{Past Due} + \text{Number Due in Interval}) / \text{Expected Due}$

However, the "percent missing" number should represent the percentage of the expected number of patient that have no evaluations. Therefore, we believe the definition of percent missing should be calculated as follows:

$(\text{Expected} - \text{On File}) / \text{Expected}$.

Please revise your accountability tables accordingly.

Overall Concerns and Deficiencies and Final Thoughts

After lengthy discussions about the poor follow-up in the unpublished clinical trials, it was agreed upon that the clinical trials only gave us limited information about the long term success and performance of the second generation hips. We still had concerns over the long term risks that these hips have shown in the first generation designs. Much of the first generation designs were revised due to loosening. The method of fixation has changed dramatically since the first implantation of the metal/metal hips. BUT, it still is a concern that the fact that in metal/metal hips, you have two very hard materials loading against one another. This load is very different than the load seen in the metal/poly hips. Also a similar type hard on hard load is seen in ceramic/ceramic hips, but these types of hips also do not have long term data. This loosening concern was brought about through the failure mechanisms of the first generation devices, and the high radiolucency rate of the unpublished clinical trials. Radiolucencies are a sign that loosening might be occurring. This concern will be addressed to the panel.

Another concern to be brought to the panel is the discussion of the wear that these devices experience. Most of background information provided by the sponsor cited that metal/metal hips produce 50-100 times less wear than the metal/poly hips. The petitioner proposes to test the second generation hip devices be wear tested by the ASTM 1714. The device should be compared to a legally marketed 28mm size hip, with the design parameters that are outlined in the memo above. This is a fairly good proposal for the short term performance of wear, but it cannot predict long term wear. This risk may be crucial in the determining the life of a metal/metal hip. This concern will also be proposed to the panel.

Along the same lines, how is the wear testing supposed to prove that the result it obtains is not the same as a first generation device. We feel there is a need to establish a positive control to determine if actually the results in the wear test are good predictors of the second and first generation devices. Meaning, that the first generation devices would produce a lot of wear when tested and the second generation devices would produce less wear. This concern will be brought to the panel also.

The sponsor proposes the new classification of these devices to include the old devices. With the above concerns, it is unclear whether or not the petitioner has actually addressed all the risks associated with the first generation devices, and proposed the necessary special controls to minimize the risks of the first generation devices. This might be a concern also for the panel to look at, but this is a more regulatory question, which panel does not comment on.

Lastly, as mentioned before, the follow-up rates for the unpublished clinical data was very low. The petitioner stated that they had better follow-up than what they provided in the petition, but were unable to provide before we could review, therefore this review is on the low follow-up. With this low follow-up, it is impossible to determine the true extent of the data, meaning that we don't know what happened to over half the patients. Therefore, whether this data can be used to stake a claim that these devices are safe cannot be determined. The extent to how this data can be used will be asked to the panel.

In conclusion, the petition was written really not expressing the true risks of metal/metal hips. They provided a lot of information, but did not address what that data was supposed to tell us as far as risks and controls. There are risks involved with metal/metal hips such as wear, loosening, and dislocation. Some of these risks have been minimized through materials and design over the years. But with any new design comes new risks that are not foreseen. The petition did not address any of these. They also did not elaborate on how to minimize the risks of the metal/metal hips in the long run of 4-10 years after implantation. These are the basis for what controls should be put forth by the petitioner, panel, and FDA to ensure the safety of these.