

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 888

[Docket No. FDA-2011-N-0661]

Effective Date of Requirement for Premarket Approval for Two Class III Preamendments
Devices

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed order.

SUMMARY: The Food and Drug Administration (FDA) is proposing to require the filing of a premarket approval application (PMA) or a notice of completion of a product development protocol (PDP) for the following two class III preamendments devices: Hip joint metal/metal semi-constrained, with a cemented acetabular component, prosthesis; and hip joint metal/metal semi-constrained, with an uncemented acetabular component, prosthesis. The Agency is also summarizing its proposed findings regarding the degree of risk of illness or injury designed to be eliminated or reduced by requiring the devices to meet the statute's approval requirements and the benefits to the public from the use of the devices. In addition, FDA is announcing the opportunity for interested persons to request that the Agency change the classification of any of the aforementioned devices based on new information. This action implements certain statutory requirements.

DATES: Submit either electronic or written comments on the proposed order by [INSERT DATE 90 DAYS AFTER DATE OF PUBLICATION IN THE FEDERAL REGISTER]. FDA intends that, if a final order based on this proposed order is issued, anyone who wishes to

continue to market the device will need to file a PMA or a notice of completion of a PDP within 90 days of the publication of the final order. See section X of this document for the proposed effective date of a final order based on this proposed order.

ADDRESSES: You may submit comments, identified by Docket No. FDA-2011-N-0661, by any of the following methods:

Electronic Submissions

Submit electronic comments in the following way:

- Federal eRulemaking Portal: <http://www.regulations.gov>. Follow the instructions for submitting comments.

Written Submissions

Submit written submissions in the following ways:

- FAX: 301-827-6870
- Mail/Hand delivery/Courier (for paper or CD-ROM submissions):

Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

Instructions: All submissions received must include the Agency name and Docket No. FDA-2011-N-0661 for this rulemaking. All comments received may be posted without change to <http://www.regulations.gov>, including any personal information provided. For additional information on submitting comments, see the "Comments" heading of the SUPPLEMENTARY INFORMATION section of this document.

Docket: For access to the docket to read background documents or comments received, go to <http://www.regulations.gov> and insert the docket number, found in brackets in the heading

of this document, into the "Search" box and follow the prompts and/or go to the Division of Dockets Management, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT:

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I. Background--Regulatory Authorities

The Federal Food, Drug, and Cosmetic Act (the FD&C Act), as amended by the Medical Device Amendments of 1976 (the 1976 amendments) (Public Law 94-295), the Safe Medical Devices Act of 1990 (the SMDA) (Public Law 101-629), the Food and Drug Administration Modernization Act of 1997 (FDAMA) (Public Law 105-115), the Medical Device User Fee and Modernization Act of 2002 (Public Law 107-250), the Medical Devices Technical Corrections Act (Public Law 108-214), the Food and Drug Administration Amendments Act of 2007 (Public Law 110-85), and the Food and Drug Administration Safety and Innovation Act (FDASIA) (Public Law 112-144), among other amendments, establish a comprehensive system for the

regulation of medical devices intended for human use. Section 513 of the FD&C Act (21 U.S.C. 360c) established three categories (classes) of devices, reflecting the regulatory controls needed to provide reasonable assurance of their safety and effectiveness. The three categories of devices are class I (general controls), class II (special controls), and class III (premarket approval).

Under section 513 of the FD&C Act, devices that were in commercial distribution before the enactment of the 1976 amendments, May 28, 1976 (generally referred to as preamendments devices), are classified after FDA has: (1) Received a recommendation from a device classification panel (an FDA advisory committee); (2) published the panel's recommendation for comment, along with a proposed regulation classifying the device; and (3) published a final regulation classifying the device. FDA has classified most preamendments devices under these procedures.

Devices that were not in commercial distribution prior to May 28, 1976 (generally referred to as postamendments devices), are automatically classified by section 513(f) of the FD&C Act into class III without any FDA rulemaking process. Those devices remain in class III and require premarket approval unless, and until, the device is reclassified into class I or II or FDA issues an order finding the device to be substantially equivalent, in accordance with section 513(i) of the FD&C Act, to a predicate device that does not require premarket approval. The Agency determines whether new devices are substantially equivalent to predicate devices by means of premarket notification procedures in section 510(k) of the FD&C Act (21 U.S.C. 360(k)) and 21 CFR part 807.

A preamendments device that has been classified into class III and devices found substantially equivalent by means of premarket notification (510(k)) procedures to such a preamendments device or to a device within that type (both the preamendments and substantially

equivalent devices are referred to as preamendments class III devices) may be marketed without submission of a PMA until FDA issues a final order under section 515(b) of the FD&C Act (21 U.S.C. 360e(b)) requiring premarket approval. Section 515(b)(1) of the FD&C Act directs FDA to issue an order requiring premarket approval for a preamendments class III device.

On July 9, 2012, FDASIA was enacted. Section 608(b) of FDASIA (126 Stat. 1056) amended section 515(b) of the FD&C Act changing the process for requiring premarket approval for a preamendments class III device from rulemaking to an administrative order.

Section 515(b)(1) of the FD&C Act sets forth the process for issuing a final order. Specifically, prior to the issuance of a final order requiring premarket approval for a preamendments class III device, the following must occur: Publication of a proposed order in the Federal Register; a meeting of a device classification panel described in section 513(b) of the FD&C Act; and consideration of comments from all affected stakeholders, including patients, payors, and providers. FDA has held a meeting of a device classification panel described in section 513(b) of the FD&C Act with respect to metal/metal hip systems, and therefore, has met this requirement under section 515(b)(1) of the FD&C Act. As explained further in section IV of this document, a meeting of a device classification panel described in section 513(b) of the FD&C Act took place in 2001 to discuss whether metal/metal hip systems should be reclassified or remain in class III and the panel recommended that the devices remain in class III because there was insufficient information to establish special controls. FDA is not aware of new information that would provide a basis for a different recommendation or findings. Indeed, the additional information received since the 2001 panel meeting and discussed further in section IV of this document highlights the need to review these devices under a PMA and reinforces the recommendation and findings of the panel.

Section 515(b)(2) of the FD&C Act provides that a proposed order to require premarket approval shall contain: (1) The proposed order, (2) proposed findings with respect to the degree of risk of illness or injury designed to be eliminated or reduced by requiring the device to have an approved PMA or a declared completed PDP and the benefit to the public from the use of the device, (3) an opportunity for the submission of comments on the proposed order and the proposed findings, and (4) an opportunity to request a change in the classification of the device based on new information relevant to the classification of the device.

Section 515(b)(3) of the FD&C Act provides that FDA shall, after the close of the comment period on the proposed order, consideration of any comments received, and a meeting of a device classification panel described in section 513(b) of the FD&C Act, issue a final order to require premarket approval or publish a document terminating the proceeding together with the reasons for such termination. If FDA terminates the proceeding, FDA is required to initiate reclassification of the device under section 513(e) of the FD&C Act, unless the reason for termination is that the device is a banned device under section 516 of the FD&C Act (21 U.S.C. 360f).

A preamendments class III device may be commercially distributed without a PMA or a notice of completion of a PDP until 90 days after FDA issues a final order (a final rule issued under section 515(b) of the FD&C Act prior to the enactment of FDASIA is considered to be a final order for purposes of section 501(f) of the FD&C Act (21 U.S.C. 351(f))) requiring premarket approval for the device, or 30 months after final classification of the device under section 513 of the FD&C Act, whichever is later. For metal/metal hip systems, the preamendments class III devices that are the subject of this proposal, the later of these two time periods is the 90-day period. Since these devices were classified in 1987, the 30-month period

has expired (52 FR 33686 at 33706, September 4, 1987). Therefore, if the proposal to require premarket approval for metal/metal hip systems is finalized, section 501(f)(2)(B) of the FD&C Act requires that a PMA or a notice of completion of a PDP for such device be filed within 90 days of the date of issuance of the final order. If a PMA or notice of completion of a PDP is not filed for such device within 90 days after the issuance of a final order, the device would be deemed adulterated under section 501(f) of the FD&C Act.

Also, a preamendments device subject to the order process under section 515(b) of the FD&C Act is not required to have an approved investigational device exemption (IDE) (see part 812 (21 CFR part 812)) contemporaneous with its interstate distribution until the date identified by FDA in the final order requiring the filing of a PMA for the device. At that time, an IDE is required only if a PMA or notice of completion of a PDP has not been filed. If the manufacturer, importer, or other sponsor of the device submits an IDE application and FDA approves it, the device may be distributed for investigational use. If a PMA or notice of completion of a PDP is not filed by the later of the two dates, and the device is not distributed for investigational use under an IDE, the device is deemed to be adulterated within the meaning of section 501(f)(1)(A) of the FD&C Act, and subject to seizure and condemnation under section 304 of the FD&C Act (21 U.S.C. 334) if its distribution continues. Other enforcement actions include, but are not limited to, the following: Shipment of devices in interstate commerce will be subject to injunction under section 302 of the FD&C Act (21 U.S.C. 332), and the individuals responsible for such shipment will be subject to prosecution under section 303 of the FD&C Act (21 U.S.C. 333). In the past, FDA has requested that manufacturers take action to prevent the further use of devices for which no PMA or notice of completion of a PDP has been filed and may determine

that such a request is appropriate for the class III devices that are the subject of this proposed order, if finalized.

In accordance with section 515(b) of the FD&C Act, interested persons are being offered the opportunity to request reclassification of two types of metal/metal hip systems, the preamendments class III devices that are the subject of this proposal.

II. Dates New Requirements Apply

In accordance with section 515(b) of the FD&C Act, FDA is proposing to require that a PMA or a notice of completion of a PDP be filed with the Agency for two preamendments class III devices, hip joint metal/metal semi-constrained, with a cemented acetabular component, prosthesis, and hip joint metal/metal semi-constrained, with an uncemented acetabular component, prosthesis, within 90 days after issuance of any final order based on this proposal. An applicant whose device was legally in commercial distribution before May 28, 1976, or whose device has been found to be substantially equivalent to such a device, will be permitted to continue marketing such class III device during FDA's review of the PMA or notice of completion of the PDP provided that the PMA or notice of completion of the PDP is timely filed. FDA intends to review any PMA for the device within 180 days, and any notice of completion of a PDP for the device within 90 days of the date of filing. FDA cautions that under section 515(d)(1)(B)(i) of the FD&C Act, the Agency may not enter into an agreement to extend the review period for a PMA beyond 180 days unless the Agency finds that "the continued availability of the device is necessary for the public health."

FDA intends that under § 812.2(d), the publication in the Federal Register of any final order based on this proposal will include a statement that, as of the date on which a PMA or a notice of completion of a PDP is required to be filed, the exemptions from the requirements of

the IDE regulations for preamendments class III devices in § 812.2(c)(1) and (c)(2) will cease to apply to any device that is: (1) Not legally on the market on or before that date, or (2) legally on the market on or before that date but for which a PMA or notice of completion of a PDP is not filed by that date, or for which PMA approval has been denied or withdrawn.

If a PMA or notice of completion of a PDP for a class III device is not filed with FDA within 90 days after the date of issuance of any final order requiring premarket approval for the device, the device would be deemed adulterated under section 501(f) of the FD&C Act. The device may be distributed for investigational use only if the requirements of the IDE regulations are met. The requirements for significant risk devices include submitting an IDE application to FDA for review and approval. An approved IDE is required to be in effect before an investigation of the device may be initiated or continued under § 812.30. FDA, therefore, recommends that IDE applications be submitted to FDA at least 30 days before the end of the 90-day period after the issuance of the final order to avoid interrupting any ongoing investigations.

III. Proposed Findings With Respect to Risks and Benefits

As required by section 515(b) of the FD&C Act, FDA is publishing its proposed findings regarding: (1) The degree of risk of illness or injury designed to be eliminated or reduced by requiring that these devices have an approved PMA or a declared completed PDP, and (2) the benefits to the public from the use of the devices.

These findings are based on the reports and recommendations of the advisory committee (panel) for the classification of these devices along with information submitted in response to the 515(i) Order (74 FR 16214, April 9, 2009), and any additional information that FDA has obtained. Additional information regarding the risks as well as classification associated with

these device types can be found in the following proposed and final rules and notices published in the Federal Register: 47 FR 29052 (July 2, 1982), 52 FR 33686 (September 4, 1987), 54 FR 550 (January 6, 1989), 59 FR 23731 (May 6, 1994), and 67 FR 57024 (September 6, 2002).

IV. Devices Subject to This Proposal

A. Hip Joint Metal/Metal Semi-constrained, With a Cemented Acetabular Component, Prosthesis

(21 CFR 888.3320)

1. 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 (21 CFR 888.3027).

2. Summary of Data

The 1982 Orthopedic Device Classification Panel (the 1982 Panel) recommended that while general controls alone were not sufficient, sufficient information existed to establish a performance standard to provide a reasonable assurance of safety and effectiveness for metal/metal hip systems. FDA disagreed with the 1982 Panel's recommendation and classified the devices as class III stating insufficient information existed to support the conclusion that performance standards or general controls will provide reasonable assurance of the safety and effectiveness of these devices.

On August 8, 2001, the Orthopaedic and Rehabilitation Devices Panel (the Panel)

recommended five to two that the hip joint metal/metal semi-constrained prostheses (cemented and uncemented) not be reclassified from class III to class II. The Panel concluded the following:

- There was insufficient clinical and preclinical testing information to establish special controls.
- The length and rate of long-term patient followup data were inadequate to demonstrate that special controls would provide reasonable assurance of the safety and effectiveness of these devices.
- In terms of preclinical testing, the Panel also concluded that validation of wear simulation, non-ideal preclinical wear testing, and biological evaluation of metallic wear debris generated by the device were not established. The particle size of the metallic wear debris generated by these devices is substantially smaller than the particle size of the metallic wear debris generated by other hip joint prostheses and the short-and long-term biological effects from human retrievals or preclinical evaluation of these smaller size metallic wear particles are unknown.

FDA agreed with the Panel and believes the Panel's concerns are still relevant today. Current wear testing methods for metal/metal bearings are limited, and importantly can underestimate bearing wear by an order of magnitude compared to clinical outcomes. There are also no standardized wear methods or consensus among researchers for investigating joint micro-separation, dislocation, cup deformation, demanding gait activities and third-body abrasion. In addition, there is a lack of wear measurements from retrieved metal/metal bearings, so it is a challenge to correlate wear rates from modern devices to adverse events demonstrated clinically like pseudotumors. To complicate matters further, metal/metal bearings have shown unpredictable wear trends in simulator testing, which have not been explained. Therefore, it is a

challenge to introduce sufficient special controls to mitigate the risks of modern metal/metal hip devices. The summary of information provided in response to FDA's order issued under sections 515(i) and 519 of the FD&C Act (21 U.S.C. 360e(i) and 360i) (refer to docket FDA-2009-M-0101) is not adequate to identify special controls sufficient to ensure safety and effectiveness and therefore not adequate to support reclassification of metal/metal hip systems.

Recent reports and evaluations further support that reclassification of metal/metal hip systems is not appropriate. The United Kingdom's (UK) Medicines and Healthcare Products Regulatory Agency (MHRA) published several alerts in 2010 outlining concerns associated with metal/metal hip systems, including soft tissue reactions (Ref. 1). The final report, published in October 2010, outlines that acetabular cup angle, femoral head size, and metal ion levels are all risk factors that will affect the outcome of metal/metal hip systems. Moreover, a recent publication in the Journal of Bone and Joint Surgery outlines case reports of arthroprosthetic cobaltism in metal/metal hip patients (Ref. 2).

The Australian Orthopaedic Association National Joint Replacement Registry's Hip and Knee Arthroplasty Annual Report of 2010 states that the "metal/metal bearing surface has the highest risk of revision compared to all other bearing surfaces." The report found the cumulative percent revision rate at 7 years is 6.3 percent for metal/metal, compared to 4.0 percent for ceramic/ceramic, 3.7 percent for ceramic/polyethylene and 4.2 percent for metal/polyethylene (Ref. 3).

In December 2011, the American Academy of Orthopedic Surgeons (AAOS) published "Modern Metal-on-Metal Hip Implants: A Technology Overview" (Ref. 4). The AAOS overview provides a summary of clinical outcomes in patients with metal/metal hip systems in comparison to other bearing surface combinations, addresses patient, implant, and surgical factors that may

predict successful and unsuccessful outcomes of metal/metal hip systems and discusses the prevalence of adverse clinical problems from metal/metal hip systems in comparison to other bearing surface combinations. The report concludes that “analyses conducted on objective patient-oriented outcomes by two joint registries indicate that, overall, patients who receive metal-on-metal total hip arthroplasty and hip resurfacing are at greater risk for revision than patients who receive total hip arthroplasty using a different bearing surface combination.” The report references the aforementioned Australian registry.

A recent article published in a scientific journal raised serious concerns about the failure rates of metal/metal hip systems for the UK population (Ref. 5). This peer-reviewed journal article presented the following findings regarding primary metal/metal total hip replacements: (1) Increased failure rate at 5 years for metal/metal total hip replacements related to larger head sizes; (2) significantly higher risk for revision in female patients (Note: In the United States, labeling includes warnings to discourage the use of metal/metal total hip replacements in females of child bearing age); and (3) revisions for dislocation in men with metal/metal hip replacements were slightly lower, showing some benefit to larger head sizes.

These reports, as well as recent recalls of devices from the U.S. market, have indicated that preclinical testing currently used to support marketing clearance of these devices has not been sufficient to mitigate the risks associated with these devices and identify potential clinically-relevant failure modes. These reports suggest that additional study is necessary before special controls can be identified and these devices can be reclassified.

3. Risks to Health

a. Loss or reduction of joint function. Improper design or inadequate mechanical properties of the device, such as its lack of strength and resistance to wear, may result in the loss

or reduction of joint function due to excessive wear, fracture, deformation of the device components, or loosening of the device in the surgical cavity.

b. Adverse tissue reaction. Inadequate biological or mechanical properties of the device or its breakdown products, such as its lack of biocompatibility, may result in an adverse tissue reaction due to dissolution or wearing away of the articulating surfaces of the device and the release of materials from the device to the surrounding tissues and the systemic circulation.

c. Increased risk of premature device failure. Elevated adverse event rates for these devices may lead to an increased risk of premature revision.

d. Infection. The presence of the prosthesis within the body may lead to an increased risk of infection.

The distinctive risks associated with metal/metal total hip replacements in comparison to other types of bearing surfaces are the wear particles generated and release of metal ions. These wear particles and metal ions may cause adverse tissue reactions in addition to the standard osteolysis seen with different bearings for total hip replacements and may lead to an increased risk of premature device revision. These adverse tissue reactions include metallosis, hypersensitivity/allergy, tumor (pseudo) or aseptic lymphocyte dominated vasculitis associated lesion (ALVAL).

4. Benefits of the Device

The hip joint metal/metal semi-constrained, with a cemented acetabular component, prosthesis is intended to be implanted to replace a hip joint. Like other artificial hip devices on the market, the potential benefits intended from implantation of the device are relief of disabling pain and restoration of joint function, which may result in a return to daily activities and an

improved quality of life. Metal/metal hip prostheses offer the potential to be especially beneficial in young, active patients.

B. Hip Joint Metal/Metal Semi-constrained, With an Uncemented Acetabular Component,
Prosthesis (21 CFR 888.3330)

1. 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 (21 CFR 888.3027).

2. Summary of Data

The 1982 Panel recommended that while general controls alone were not sufficient, sufficient information existed to establish a performance standard to provide a reasonable assurance of safety and effectiveness for metal/metal hip systems. FDA disagreed with the 1982 Panel's recommendation and classified the devices as class III stating that insufficient information existed to support the conclusion that performance standards or general controls will provide reasonable assurance of the safety and effectiveness of these devices.

On August 8, 2001, the Panel recommended five to two that the hip joint metal/metal semi-constrained prostheses (cemented and uncemented) not be reclassified from class III to class II. The Panel concluded the following:

- There was insufficient clinical and preclinical testing information to establish special

controls.

- The length and rate of long-term patient followup data were inadequate to demonstrate that special controls would provide reasonable assurance of the safety and effectiveness of these devices.

- In terms of preclinical testing, the Panel also concluded that validation of wear simulation, non-ideal preclinical wear testing, and biological evaluation of metallic wear debris generated by the device were not established. The particle size of the metallic wear debris generated by these devices is substantially smaller than the particle size of the metallic wear debris generated by other hip joint prostheses and the short-and long-term biological effects from human retrievals or preclinical evaluation of these smaller size metallic wear particles are unknown.

FDA agreed with the Panel and believes the Panel's concerns are still relevant today. Current wear testing methods for metal/metal bearings are limited, and importantly can underestimate bearing wear by an order of magnitude compared to clinical outcomes. There are also no standardized wear methods or consensus among researchers for investigating joint micro-separation, dislocation, cup deformation, demanding gait activities, and third-body abrasion. In addition, there is a lack of wear measurements from retrieved metal/metal bearings, so it is a challenge to correlate wear rates from modern devices to adverse events demonstrated clinically like pseudotumors. To complicate matters further, metal/metal bearings have shown unpredictable wear trends in simulator testing, which have not been explained. Therefore, it is a challenge to introduce sufficient special controls to mitigate the risks of modern metal/metal hip devices. The summary of information provided in response to FDA's order issued under sections 515(i) and 519 of the FD&C Act (refer to docket FDA-2009-M-0101) is not adequate to identify

special controls sufficient to ensure safety and effectiveness and therefore not adequate to support reclassification of metal/metal hip systems.

Recent reports and evaluations further support that reclassification of metal/metal hip systems is not appropriate. The MHRA published several alerts in 2010 outlining concerns associated with metal/metal hip systems, including soft tissue reactions. The final report, published in October 2010, outlines that acetabular cup angle, femoral head size, and metal ion levels are all risk factors that will affect the outcome of metal/metal hip systems (Ref. 1). Moreover, a recent publication in the Journal of Bone and Joint Surgery outlines case reports of arthroprosthetic cobaltism in metal/metal hip patients (Ref. 2).

The Australian Orthopaedic Association National Joint Replacement Registry's Hip and Knee Arthroplasty Annual Report of 2010 states that the "metal/metal bearing surface has the highest risk of revision compared to all other bearing surfaces." The report found the cumulative percent revision rate at 7 years is 6.3 percent for metal/metal, compared to 4.0 percent for ceramic/ceramic, 3.7 percent for ceramic/polyethylene and 4.2 percent for metal/polyethylene (Ref. 3).

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resurfacing are at greater risk for revision than patients who receive total hip arthroplasty using a different bearing surface combination.” The report references the aforementioned Australian registry.

A recent article published in a scientific journal raised serious concerns about the failure rates of metal/metal hip systems for the UK population (Ref. 5). This peer-reviewed journal article presented the following findings regarding primary metal/metal total hip replacements: (1) Increased failure rate at 5 years for metal/metal total hip replacements related to larger head sizes; (2) significantly higher risk for revision in female patients (Note: In the United States, labeling includes warnings to discourage the use of metal/metal total hip replacements in females of child bearing age); and (3) revisions for dislocation in men with metal/metal hip replacements were slightly lower, showing some benefit to larger head sizes.

These reports, as well as recent recalls of devices from the U.S. market, have indicated that preclinical testing currently used to support marketing clearance of these devices has not been sufficient to mitigate the risks associated with these devices and identify potential clinically-relevant failure modes. These reports suggest that additional study is necessary before special controls can be identified and these devices can be reclassified.

3. Risks to Health

a. Loss or reduction of joint function. Improper design or inadequate mechanical properties of the device, such as its lack of strength and resistance to wear, may result in the loss or reduction of joint function due to excessive wear, fracture, deformation of the device components, or loosening of the device in the surgical cavity.

b. Adverse tissue reaction. Inadequate biological or mechanical properties of the device or its breakdown products, such as its lack of biocompatibility or resistance to wear, may result

in an adverse tissue reaction due to dissolution or wearing away of the articulating surfaces of the device and the release of materials from the device to the surrounding tissues and the systemic circulation.

c. Increased risk of premature device failure. Elevated adverse event rates for these devices may lead to an increased risk of premature revision.

d. Infection. The presence of the prosthesis within the body may lead to an increased risk of infection.

The distinctive risks associated with metal/metal total hip replacements in comparison to other types of bearing surfaces are the wear particles generated and release of metal ions. These wear particles and metal ions may cause adverse tissue reactions in addition to the standard osteolysis seen with different bearings for total hip replacements and may lead to an increased risk of premature device revision. These adverse tissue reactions include metallosis, hypersensitivity/allergy, tumor (pseudo) or ALVAL.

4. Benefits of the Device

The hip joint metal/metal semi-constrained, with an uncemented acetabular component, prosthesis is intended to be implanted to replace a hip joint. Like other artificial hip devices on the market, the potential benefits intended from implantation of the device are relief of disabling pain and restoration of joint function, which may result in a return to daily activities and an improved quality of life. Metal/metal hip prostheses offer the potential to be especially beneficial in young, active patients.

V. PMA Requirements

A PMA for these devices must include the information required by section 515(c)(1) of the FD&C Act. Such a PMA should also include a detailed discussion of the risks identified

previously, as well as a discussion of the effectiveness of the device for which premarket approval is sought. In addition, a PMA must include all data and information on: (1) Any risks known, or that should be reasonably known, to the applicant that have not been identified in this document; (2) the effectiveness of the device that is the subject of the application; and (3) full reports of all preclinical and clinical information from investigations on the safety and effectiveness of the device for which premarket approval is sought.

A PMA must include valid scientific evidence to demonstrate reasonable assurance of the safety and effectiveness of the device for its intended use (see § 860.7(c)(1) (21 CFR 860.7(c)(1))). Valid scientific evidence is "evidence from well-controlled investigations, partially controlled studies, studies and objective trials without matched controls, well-documented case histories conducted by qualified experts, and reports of significant human experience with a marketed device, from which it can fairly and responsibly be concluded by qualified experts that there is reasonable assurance of the safety and effectiveness of a device under its conditions of use. . . . Isolated case reports, random experience, reports lacking sufficient details to permit scientific evaluation, and unsubstantiated opinions are not regarded as valid scientific evidence to show safety or effectiveness." (see § 860.7(c)(2)).

VI. PDP Requirements

A PDP for any of these devices may be submitted in lieu of a PMA, and must follow the procedures outlined in section 515(f) of the FD&C Act. A PDP must provide, among other things: (1) A description of the device, (2) preclinical trial information (if any), (3) clinical trial information (if any), (4) a description of the manufacturing and processing of the device, (5) the labeling of the device, and (6) all other relevant information about the device. In addition, the

PDP must include progress reports and records of the trials conducted under the protocol on the safety and effectiveness of the device for which the completed PDP is sought.

VII. Opportunity to Request a Change in Classification

Before requiring the filing of a PMA or notice of completion of a PDP for a device, FDA is required by section 515(b)(2)(D) of the FD&C Act to provide an opportunity for interested persons to request a change in the classification of the device based on new information relevant to the classification. Any proceeding to reclassify the device will be under the authority of section 513(e) of the FD&C Act.

A request for a change in the classification of these devices is to be in the form of a reclassification petition containing the information required by 21 CFR 860.123, including new information relevant to the classification of the device.

VIII. Environmental Impact

The Agency has determined under 21 CFR 25.34(b) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

IX. Paperwork Reduction Act of 1995

This proposed order refers to collections of information that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501-3520).

The collections of information in 21 CFR part 814 have been approved under OMB control number 0910-0231. The collections of information in 21 CFR part 807, subpart E, have been approved under OMB control number 0910-0120. The effect of this order, if finalized, is to shift certain devices from the 510(k) premarket notification process to the PMA process. To

account for this change, FDA intends to transfer some of the burden from OMB control number 0910-0120, which is the control number for the 510(k) premarket notification process, to OMB control number 0910-0231, which is the control number for the PMA process. FDA estimates that it will receive seven new PMAs as a result of this order, if finalized. Based on FDA's most recent estimates, this will result in a 2,421 hour burden increase. FDA also estimates that there will be seven fewer 510(k) submissions as a result of this order, if finalized. Based on FDA's most recent estimates, this will result in a 318 hour burden decrease. Therefore, on net, FDA expects a burden hour increase of 2,103 due to this proposed regulatory change.

The collections of information in 21 CFR part 812 have been approved under OMB control number 0910-0078.

X. Proposed Effective Date

FDA is proposing that any final order based on this proposed order become effective 90 days after date of publication of the final order in the Federal Register.

XI. Comments

Interested persons may submit either written comments regarding this document to the Division of Dockets Management (see ADDRESSES) or electronic comments to <http://www.regulations.gov>. It is only necessary to send one set of comments. Identify comments with the docket number found in brackets in the heading of this document. Received comments may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday, and will be posted to the docket at <http://www.regulations.gov>.

XII. References

The following references have been placed on display in the Division of Dockets Management (see ADDRESSES), and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. Medicines and Healthcare Products Regulatory Agency (MHRA), "Report of the Expert Advisory Group Looking at Soft Tissue Reactions Associated With Metal-on-Metal Hip Replacements," October, 2010.

2. Tower, S. S., "Arthroprosthetic Cobaltism: Neurological and Cardiac Manifestations in Two Patients with Metal-on-Metal Arthroplasty: A Case Report," Journal of Bone and Joint Surgery, 92, 2847-2851, 2010.

3. Australian Orthopaedic Association National Joint Replacement Registry, Hip and Knee Arthroplasty Annual Report 2010. Adelaide: Australian Orthopaedic Association, 2010.

4. American Academy of Orthopedic Surgeons (AAOS), "Modern Metal-on-Metal Hip Implants: A Technology Overview," December 2011.

5. A.J. Smith, et al., "Failure Rates of Stemmed Metal-on-Metal Hip Replacements: Analysis of Data From the National Joint Registry of England and Wales," Lancet, 2012:S0140-6736(12)60353-5, March 13, 2012.

List of Subjects in 21 CFR Part 888

Medical devices.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, it is proposed that 21 CFR part 888 be amended as follows:

PART 888--ORTHOPEDIC DEVICES

1. The authority citation for 21 CFR part 888 continues to read as follows:

Authority: 21 U.S.C. 351, 360, 360c, 360e, 360j, 371.

2. Section 888.3320 is amended by revising paragraph (c) to read as follows:

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

* * * * *

(c) Date PMA or notice of completion of PDP is required. A PMA or notice of completion of a PDP is required to be filed with the Food and Drug Administration on or before [A DATE WILL BE ADDED 90 DAYS AFTER DATE OF PUBLICATION OF A FUTURE FINAL ORDER IN THE FEDERAL REGISTER], for any hip joint metal/metal semi-constrained prosthesis with a cemented acetabular component that was in commercial distribution before May 28, 1976, or that has, on or before [A DATE WILL BE ADDED 90 DAYS AFTER DATE OF PUBLICATION OF A FUTURE FINAL ORDER IN THE FEDERAL REGISTER], been found to be substantially equivalent to any hip joint metal/metal semi-constrained prosthesis with a cemented acetabular component that was in commercial distribution before May 28, 1976. Any other hip joint metal/metal semi-constrained prosthesis with a cemented acetabular component shall have an approved PMA or declared completed PDP in effect before being placed in commercial distribution.

3. Section 888.3330 is amended by revising paragraph (c) to read as follows:

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

* * * * *

(c) Date PMA or notice of completion of PDP is required. A PMA or notice of completion of a PDP is required to be filed with the Food and Drug Administration on or before [A DATE WILL BE ADDED 90 DAYS AFTER DATE OF PUBLICATION OF A FUTURE FINAL ORDER IN THE FEDERAL REGISTER], for any hip joint metal/metal semi-constrained prosthesis with an uncemented acetabular component that was in commercial distribution before May 28, 1976, or that has, on or before [A DATE WILL BE ADDED 90 DAYS AFTER DATE OF PUBLICATION OF A FUTURE FINAL ORDER IN THE FEDERAL REGISTER], been found to be substantially equivalent to any hip joint metal/metal semi-constrained prosthesis with an uncemented acetabular component that was in commercial distribution before May 28, 1976. Any other hip joint metal/metal semi-constrained prosthesis with an uncemented acetabular component shall have an approved PMA or declared completed PDP in effect before being placed in commercial distribution.

Dated: January 14, 2013.

Leslie Kux,

Assistant Commissioner for Policy.

[FR Doc. 2013-01006 Filed 01/17/2013 at 8:45 am; Publication Date: 01/18/2013]