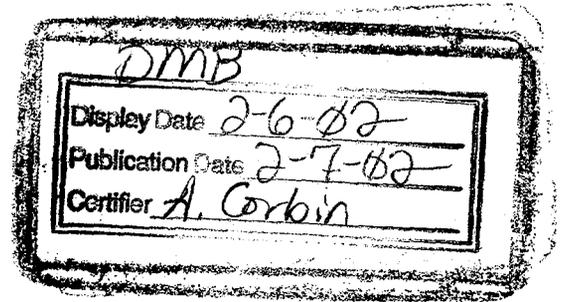


DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 888

[Docket No. 01 N-041 1]



**Orthopedic Devices; Proposed Classification for the Resorbable Calcium Salt Bone Void Filler Device**

**AGENCY:** Food and Drug Administration, HHS.

**ACTION:** Proposed rule.

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**SUMMARY:** The Food and Drug Administration (FDA) is proposing to classify the resorbable calcium salt bone void filler device intended to fill bony voids or gaps, caused by trauma or surgery, that are not intrinsic to the stability of the bony structure into class II (special controls). The agency is also publishing the recommendation of the Orthopedic and Rehabilitation Devices Panel (the Panel) regarding the classification of this device. After considering public comments on the proposed classification, FDA will publish a final regulation classifying this device. This action is being taken to establish sufficient regulatory controls that will provide reasonable assurance of the safety and effectiveness of this device. Elsewhere in **this** issue of **the Federal Register**, FDA is publishing a notice-of availability of a draft guidance document that the agency proposes to use as a special control for the device.

**DATES:** Submit written or electronic comments by *[insert date 90 days after date of publication in the Federal Register]*. See section XIII of this document for the proposed effective date of a final rule based on this document.

**ADDRESSES:** Submit written comments to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic comments to <http://www.fda.gov/dockets/ecomments>.

**FOR FURTHER INFORMATION CONTACT:** Nadine Y. Sloan, Center for Devices and Radiological Health (HFZ-410), Food and Drug Administration, 9200 Corporate Blvd., Rockville, MD 20850, 301-594-1296.

**SUPPLEMENTARY INFORMATION:**

**I. Regulatory Authorities**

The Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 301 et seq.), 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) and the Food and Drug Administration Modernization Act of 1997 (FDAMA) (Public Law 105-115) established a comprehensive system for the regulation of medical devices intended for human use. Section 513 of the act (21 U.S.C. 360c) established three categories (classes) of devices, depending on 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 the 1976 amendments, class II devices were defined as those devices for which there is insufficient information to show that general controls themselves will ensure safety and effectiveness, but for which there is sufficient information to establish performance standards to provide such assurance.

The SMDA broadened the definition of class II devices to mean those devices for which there is insufficient information to show that general controls themselves will assure safety and effectiveness, but for which there is sufficient information to establish special controls to provide such assurance. Special controls may include performance standards, postmarket surveillance, patient registries, development and dissemination of guidelines, recommendations, and any other appropriate actions the agency deems necessary (section 513(a)(1)(B) of the act).

Under section 513 of the act, devices that were in commercial distribution before May 28, 1976 (the date of enactment of the 1976 amendments), generally referred to as preamendments devices, are classified after FDA has met the following three requirements: (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 classified automatically by statute (section 513(f) of the act (21 U.S.C. 360c(f)) into class III without any FDA rulemaking process. Those devices remain in class III and require premarket approval, unless and until: (1) The device is reclassified into class I or II; (2) FDA issues an order classifying the device into class I or II in accordance with section 513(f)(2) of the act as amended by FDAMA; or (3) FDA issues an order finding the device to be substantially equivalent, in accordance with section 513(i) of the act, to a predicate device that does not require premarket approval.

The agency determines whether new devices are substantially equivalent to previously offered devices by means of **premarket notification** procedures in section 510(k) of the act (21 U.S.C. 360(k)) and 21 CFR part 807 of the regulations. A preamendments device that has been classified into class III may be marketed, by premarket notification, without submission of a premarket approval application (PMA) until FDA issues a final regulation under section 515(b) of the act (21 U.S.C. 360e(b)) requiring premarket approval.

In 1987, when other orthopedic devices were classified (52 FR 33686 at 33702, September 4, 1987), FDA was not aware that the calcium sulfate bone void filler device, a resorbable bone void filler, intended for orthopedic use in filling bony voids or gaps not intrinsic to the stability of the bony structure, was a preamendment device and inadvertently omitted classifying it. On December 12, 1997, FDA received a Classification Proposal and Summary of Safety and Effectiveness Information for the **OsteoSet™ Calcium Sulfate Bone Void Filler** from Wright Medical Technology, Inc., requesting that the device be classified into class II (Ref. 1). Consistent

with the act and the regulations, FDA consulted with the Panel regarding the classification of this device.

## **II. Device Identification**

FDA is proposing the following device name and identification name based on the Panel's recommendation (Ref. 2) and the agency's review:

A resorbable calcium salt bone void **filler device** is a resorbable implant intended to fill bony voids or gaps caused by trauma or surgery that are not intrinsic to the stability of the bony structure.

FDA has broadened the classification name and identification of the resorbable calcium salt bone void filler device because of the similarity of the calcium sulfate bone void filler device to other resorbable calcium salt bone void filler devices.

## **III. Recommendation of the Panel**

During a public meeting on January 12 and 13, 1998, the Panel unanimously recommended that the calcium sulfate **bone void filler device** be classified into class II (Ref. 2). The Panel believed that classification in class II with the recommended special controls of FDA guidance documents and FDA recognized voluntary consensus standards would provide reasonable assurance of the safety and effectiveness of the device.

## **IV. Summary of the Reasons for the Recommendation**

The Panel believed that the calcium sulfate bone void filler device, a resorbable calcium salt bone void filler device, should be classified into class II because special controls, in addition to general controls would provide reasonable assurance of the safety and effectiveness of the device, and there is sufficient information to establish special controls to provide such assurance. Because FDA believes that the safety and effectiveness of bone void filler devices composed of other resorbable calcium salts may also be assured **through** special controls, in addition to general controls, the agency has broadened the device name to resorbable calcium salt bone void filler device to include bone void filler devices made of other resorbable calcium salts.

## **V. Summary of the Data Upon Which the Recommendation is Based**

The Panel based its recommendation on the information contained in the petition, the information provided by FDA, and their personal knowledge of the device. In addition to information concerning the potential risks to health associated with the use of the resorbable calcium salt bone void filler device described in section VI of this document, there is reasonable knowledge of the benefits of the device. Specifically, the device provides an alternative treatment to use of either autogenous bone grafts, without the potential adverse effects of pain and morbidity associated with a bone harvest procedure, or use of allogeneic bone grafts, without the potential risk of disease transmission, including virus transmission. The device is also more readily and plentifully available than both alternative treatments.

## **VI. Risks to Health**

After considering the information in the petition, the Panel's deliberations, as well as the published literature and medical device reports (MDRs), FDA has evaluated the risks to health associated with the use of the resorbable calcium salt bone void filler device. There were no MDRs for the OsteoSet™ calcium sulfate bone void filler, nor were there any MDRs for any other preamendments resorbable calcium sulfate bone void filler or postamendments resorbable calcium salt bone void filler. FDA now believes that the following are risks to health associated with use of the device: Infection of the soft tissue and/or bone (osteomyelitis) and fever; adverse tissue reaction; transient hypercalcemia; incomplete bone ingrowth, delayed union, and nonunion; fracture of the newly formed bone; and disease transmission and undesirable immune response associated with use of a biological source device material.

### *A. Infection of the Soft Tissue and/or Bone (Osteomyelitis) and Fever*

Infection of the soft tissue and/or bone (osteomyelitis) and fever are potential risks to health associated with all surgical procedures and implanted orthopedic devices (Ref. 1). Improper or impure material composition may irritate the wound and exacerbate a preexisting infection and

improper sterilization or packaging may increase the risk of infection. Use of a device that is not pyrogen-free may elicit a fever response.

#### *B. Adverse Tissue Reaction*

Adverse tissue reaction is a potential risk to health associated with all implanted devices (Ref. 1). The use of this device in a wound will elicit a mild acute inflammatory reaction typical of a normal foreign body response. Inappropriate or impure device material composition may increase the severity of a local tissue reaction or may cause a systemic tissue reaction. Also, for a device intended to set in vivo, inappropriate device material composition may result in a significantly more exothermic setting reaction that may cause tissue necrosis.

#### *C. Transient Hypercalcemia*

Inappropriate material composition may lead to substantially more rapid resorption of the implant, which may contribute to, or may cause, transient hypercalcemia. For patients receiving resorbable calcium sulfate bone void filler, transient hypercalcemia usually resolves without any adverse clinical sequelae (Ref. 1). Implanting the resorbable calcium salt bone void filler device in a patient with a preexisting calcium metabolism disorder (e.g., hypercalcemia) may lead to elevated, unsafe, transient hypercalcemia.

#### *D. Incomplete Bone Ingrowth, Delayed Union, and Nonunion*

Incomplete bone growth into the treated void or gap, delayed union, and nonunion are potential risks to health that may require further surgical treatment. Device-related factors that may contribute to these risks are an improper material composition that resorbs too quickly or too slowly, or causes an infection or a severe local tissue reaction. Other factors, not related to the device, which may also contribute to incomplete **ingrowth** of new bone include inadequate preparation of the osseous defect and improper placement of the device.

### *E. Fracture of the Newly Formed Bone*

Formation of new bone that is not as strong as the host bone may occur, and may result in fracture of the bone that may require further surgical treatment.

### *F. Disease Transmission and Undesirable Immune Response Associated With Use of a Device Material Derived From a Biological Source*

Disease transmission, including virus transmission, and an undesirable immune response may occur if a calcium salt or calcium salt additive derived from a biological source, e.g., either animal or human tissue, is used that has not been adequately deproteinated or immunologically inactivated.

## **VII. Special Controls**

FDA believes that the class II special control draft guidance document entitled “Class II Special Controls Guidance Document: Resorbable Calcium Salt Bone Void Filler Device,” in addition to general controls, is adequate to control the identified risks to health associated with use of the resorbable calcium salt bone void filler device. FDA agrees with the Panel that FDA guidance documents and voluntary consensus standards are appropriate special controls to reasonably assure the safety and effectiveness of the device. FDA believes that the class II special controls draft guidance document, which incorporates FDA guidance documents, voluntary consensus standards, material characterization, performance testing, and instructions for use, addresses the Panel’s recommendation for a guidance document and voluntary consensus standard special controls.

The class II special controls draft guidance document addresses the risks to health associated with the resorbable calcium salt bone void filler device in the following five ways: (1) Adherence to the FDA guidance documents will assure that the device is safe for long-term implantation, control the risk of infection by assuring that only a sterile device is implanted, minimize the additional risk of eliciting a fever response, and assure that only a biocompatible material is used; (2) adherence to the voluntary consensus standards in the guidance document will assure that the

device material has an appropriate composition and purity; (3) adherence to the material characterization recommendation will assure that the device has appropriate material properties for bone ingrowth and device resorption; (4) adherence to the performance testing recommendation will assure that implantation of the material provides an adequate environment for bony ingrowth and has the intended dissolution properties. For a calcium salt intended to set in vivo, it will also assure that the device material has an appropriate composition so that the setting reaction is not significantly exothermic to cause tissue necrosis. It will also assure that the device material has an appropriate composition to achieve the intended bone formation and material resorption, and that the newly formed bone is sufficiently strong. Finally, adherence to this section will help control the risks of disease transmission, including virus transmission, and undesirable immune response associated with implantation of a calcium salt or calcium salt additive derived from a biological source, e.g., either animal or human bone that has been inadequately deproteinated or immunologically inactivated; and (5) adherence to the instructions for use will help control the risk of an elevated, unsafe, transient hypercalcemia in patients with a preexisting calcium metabolism disorder.

### **VIII. Proposed Classification**

Based on the available information, FDA believes that the resorbable calcium salt bone void filler device should be classified into class II because special controls, in addition to general controls, would provide reasonable assurance of the safety and effectiveness of the device with the identified risks to health associated with the use of the device, and there is sufficient information to establish special controls to provide such assurance.

### **IX. 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.

## **X. Analysis of Impacts**

FDA has examined the impacts of the proposed rule under Executive Order 12866 and the Regulatory Flexibility Act (5 U.S.C. 601-612) (as amended by subtitle D of the Small Business Regulatory Fairness Act of 1996 (Public Law 104-121)), and the Unfunded Mandates Reform Act of 1995 (Public Law 104-4). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). The agency believes that this proposed rule is consistent with the regulatory philosophy and principles identified in the Executive order. In addition, the proposed rule is not a significant regulatory action as defined by the Executive order and so is not subject to review under the Executive order.

The Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. As unclassified devices, these devices are already subject to general controls such as premarket notification. The premarket notification guidance document will not substantially change the way in which these devices are regulated. The agency therefore certifies that this proposed rule, if issued, will not have a significant economic impact on a substantial number of small entities. In addition, this proposed rule will not impose costs of \$100 million or more on either the private sector or State, local, and tribal governments in the aggregate, and therefore a summary statement or analysis under section 202(a) of the Unfunded Mandates Reform Act of 1995 is not required.

## **XI. Paperwork Reduction Act of 1995**

This proposed rule does not contain information collection provisions that are subject to review by the Office of Management and Budget under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501-3520).

## **XII. Submission of Comments**

Interested persons may submit to the Dockets Management Branch (address above) written or electronic comments regarding this proposal by *[insert date 90 days after date of publication in the **Federal Register**]*. Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the Dockets Management Branch between 9 a.m. and 4 p.m., Monday through Friday.

## **XIII. Proposed Dates**

FDA proposes that any final regulation based on this proposal become effective 30 days after its publication in the **Federal Register**.

## **XIV. References**

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

1. Wright Medical Technology, Inc., Arlington, TN, Classification Proposal and Summary of Safety and Effectiveness Information for the OsteoSet™ Calcium Sulfate Bone Void Filler, received December 12, 1997.
2. Transcript of the Orthopedic and Rehabilitation Devices Panel meeting, January 12 and 13, 1998, pp. 1-10 and 299-372.

## **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 888.3045 is added to subpart D to read as follows:

**§ 888.3045 Resorbable calcium salt bone void filler device.**

(a) *Identification.* A resorbable calcium salt bone void filler device is a resorbable implant intended **to** fill bony voids or gaps, caused by trauma or surgery, that are not intrinsic to the stability of the bony structure.

(b) *Classification.* Class II (special controls). The special control for this device is the FDA guidance document entitled “Class II, Special Controls Guidance: Resorbable Calcium Salt Bone Void Filler Device.”

Dated: 10/5/01  
October 5, 2001.

Linda S. Kahan

Linda S. Kahan,  
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Center for Devices and Radiological Health.

[FR Doc. <sup>02</sup>01-~~?????~~ Filed <sup>02</sup>??-??-01; 8:45 am]

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1/30/02

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