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May 6, 2002

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

RE: Docket Nos: 91D-0407 and 01N-0411 ; Class II Special Controls Guidance Document: Resorbable Calcium Salt Bone Void filler Device; Draft Guidance for Industry and FDA AND Orthopedic Devices; Proposed Classification for the Resorbable Calcium Salt Bone Void Filler Device

Dear Sir or Madam:

The Orthopedic Surgical Manufacturers Association (OSMA), whose members represent companies which produce over 85% of all orthopedic implants intended for clinical use in the United States, welcomes this opportunity to provide comments on the subject document.

We wish to highlight our main concerns for FDA's consideration, since we believe that they are relevant to the successful and complete implementation of the regulation.

I. Intent to apply this guidance document to DBM products deemed to be medical devices.

We are aware of the FDA communication sent to manufacturers of such products or products in development, which indicated FDA's intent to review and regulate such products under the medical device premarket notification provisions of the Act. (L. D. Spears, CDRH Office of Compliance letter, March 12, 2002).

Additionally, we understand that FDA intends that the subject guidance document apply not only to Resorbable Calcium Salt Bone Void Filler Devices, but also to DBM products deemed to be medical devices.

We have two concerns:

- a. There are fundamental differences between DBM products and resorbable calcium salt bone void filler devices; these differences are not feasibly addressed in one guidance document. Additionally DBM products deemed to be medical devices do, and likely will continue to, reflect additives other than resorbable calcium salts. OSMA strongly recommends that FDA reconsider the intent to apply this guidance to DBM products deemed to be medical devices. OSMA would prefer, for the reasons given above, that a separate guidance document be applied for such products. Our members would be willing, when appropriate, to assist in drafting such a guidance document.

01N-0411

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- b. The procedure used by the agency to determine that DBM products should be treated as medical devices remains of great concern to OSMA and its members. As we have indicated in previous communications, we urge the agency to obtain comment from stakeholders in rulemaking. We believe that FDA should apply regulatory standards for notice and opportunity for comment, to ensure transparency and minimized regulatory burden.

In the event that FDA disagrees and does chose to apply this guidance document to DBM products deemed to be medical devices, OSMA requests an extension of the comment period, to allow us to provide more extensive comments regarding this guidance document.

- II. Vague and imprecise criteria that may lead to a lack of uniformity and transparency in regulatory practice. It is important to OSMA member companies that requirements are clear and unambiguous. Even if there may be a consensus on how these terms are interpreted and applied at one point in time, there is a potential that, without clear terminology, inconsistent, unreliable, and unpredictable regulatory opinions will occur in the future. OSMA is concerned about the implementation of regulatory policies which may be misinterpreted and wrongly applied.

Our detailed comments further describe these concerns, and provide other technical clarifications. (See attachment). We trust you find these comments of value, and request the opportunity to discuss these concerns with the FDA directly if necessary.

In closing, OSMA appreciates the opportunity to comment on this draft guidance document, and we look forward to continuing to work cooperatively with the FDA in the important work of engaging stakeholders in a dialog specific to emerging regulations.

Sincerely,



Tom Craig, President
Orthopedic Surgical Manufacturers Association (OSMA)

Federal Express
Attachment

**Comments by
Orthopedic Surgical Manufacturers Association (OSMA) on**

**Class II Special Controls Guidance Document: Resorbable Calcium Salt Bone Void filler
Device; Draft Guidance for Industry and FDA AND Orthopedic Devices; Proposed
Classification for the Resorbable
Calcium Salt Bone Void Filler Device**

**Docket Nos: 91D-0407 AND 01N-0411,
[Federal Register: February 7, 2002 (Volume 67, Number 26)]**

OSMA is pleased to provide these comments on the subject document. These comments are identified by the section of the proposed regulation in which the text appears.

Scope

If the FDA's intent is to apply this guidance document to DBM products deemed to be medical devices, this should be clearly stated in the Scope section. As indicated, OSMA believes that this guidance document should not be applied to such products and that a separate guidance document be drafted.

Should this guidance document be applied to DBM products deemed to be medical devices, an inconsistency will exist with the FDA's summary of data upon which the recommendation is based (Section V, Docket 01N-0411). Specifically, FDA's summary indicates that "the device (resorbable calcium salt bone void filler) provides an alternative treatment to use of either autogenous bone grafts, ... or use of allogeneic bone grafts, without the potential risk of disease transmission, including virus transmission" (emphasis added).

Risks to Health

To our knowledge, transient hypercalcemia is a risk associated with calcium sulfate products only, and as such is not applicable to the broadened classification name resorbable calcium salt bone void filler device. If it is to be included, it is recommended that the wording be revised to "transient hypercalcemia, for calcium sulfate salts."

Disease transmission and undesirable immune response associated with use of a device material derived from a biological source is not applicable to the broadened classification resorbable calcium salt bone void filler products. As indicated previously, this stated risk to health creates a conflict with FDA's statement that "the device (resorbable calcium salt bone void filler) provides an alternative treatment to use of either autogenous bone grafts, ... or use of allogeneic bone grafts, without the potential risk of disease transmission, including virus transmission" (emphasis added). If the concern is processing aids which may be biologically sourced, it is our opinion that the ISO 10993 and QSR requirements are adequate. We request removal of this specific risk to health from the list.

Controls

3. a. 3. The term “the phase(s) of the material” should be clarified. If it is intended to refer to the crystalline phases of the material, it should be specified. Additionally, the second sentence of this section is redundant and should be removed.

3. b. 1. The porosity proposal (surface, internal and interconnectivity characterization) is unnecessarily excessive. The need to characterize a product’s porosity can be addressed through common methods of mercury intrusion porosimetry. Surface, internal and interconnectivity porosity characterization will require SEM or other such methodologies, adding cost to the test, without justified benefit.

In addition, the method of testing porosity impacts the results. If the intent is to simulate conditions of use, it should be so stated. Since such tests are not standardized, must the test data reflect comparison to predicate?

3. b. 2. It is assumed that this statement refers to the properties of the crystal, and it is requested that it be stated as such.

3. b. 3. Mass to volume ratio is more appropriately defined as density. In addition, it should be clarified if this requirement applies to the product *with hydration media*, where hydration media are used. Alternatively, the overall requirement should be supplemented with the verbiage “as intended for implantation”.

4. a. The term “calcium salt additive derived from a biological source” should be clarified or removed in order to ensure that this document is appropriately interpreted and consistently applied. For example, are coralline based HA or collagen additives included, and if so, how are the proposed controls appropriate?

There is no definition of “adequate processing” that would assist an entity in determining whether its procedures were considered adequate. Examples of what does or does not constitute adequate processing are needed. For instance, is sterilization an implied requirement? And what is reasonable assurance of adequate processing? Would the requirement be an SAL of 10^{-6} ? (This concern is discussed further below). The term “adequately processed” should be clarified. Alternatively, reference to existing consensus standards should be included.

There is substantial concern among our members that this Guidance makes reference to the FDA Guidance Document, “510(k) Sterility Review Guidance K90-1” dated 2/12/90. If it is FDA’s intent to apply the Calcium Salts Guidance document to DBM products deemed to be medical devices, is it also a requirement (as stated in the K90-1 document) that 510(k)s are required to include “the sterility assurance level specification (SAL) (e.g., 10^{-6} for all devices...)”?

Two statements at the end of this section, related to hip joint metal/polymer constrained prosthesis, appear to have been added in error, and do not relate to the subject matter.

4. b. The term “information” requires clarification to ensure that this document is appropriately interpreted and consistently applied with respect to sourcing and processing of any component from a biological source. If it is intended that the requirement reflect other developing industry standards or guidance documents such as that for BSE, it should be so stated.

5. a. 2. The statement “*In vitro* solubility and dissolution testing” implies that the other tests in this section are performed *in vivo* and we request that the term *in vitro* be removed, since all of the tests proposed are typically performed under simulated use and *in vitro*.

5. b. The statement “may be necessary” requires clarification. Under what circumstances are biomechanical property test data necessary? If these products are purported for use in bony voids not intrinsic to the stability of the bone, and, as such, they are used in conjunction with fixation, why is biomechanical strength of the new bone of importance? There may be more of a need to reflect integration of surrounding bone with the material remaining, and therefore it is recommended that the requirement be adequately defined.

Additionally, the term “appropriate biomechanical tests” requires further clarification to ensure fair and consistent implementation. There are at least eight different protocols for biomechanical strength found in literature. The examples given (torsion or three point bending) may not be appropriate tests for some indications, such as a cavitation defect, and other tests such as tension, flexion or compression may be more appropriate methods of assessing strength in certain defects. It is recommended that examples be all inclusive or eliminated entirely.

“Bone formation” is notoriously subjective. We are aware of discrepancies in interpretations by agency reviewers regarding these assessments. Specific areas of concern include what bone should be tested, whether the defect should be critically sized, what constitutes a critical size (literature reports vary) and definition of the appropriate model. As indicated before, OSMA is concerned about the implementation of regulatory policies which may be misinterpreted and wrongly applied, and strongly recommends clarification or omission of this requirement.