



Office of Combination Products
15800 Crabbs Branch Way
Suite 200 (HFG-3)
Rockville, MD 20855

Food and Drug Administration
Rockville MD 20857

October 11, 2007

[REDACTED]

Re: Request for Reconsideration
Cerament™/Bone Void Filler
Our file: RFD 2007.036
Dated: September 26, 2007
Received and filed: September 26, 2007

Dear [REDACTED]:

The Food and Drug Administration (FDA) has completed its review of the request for reconsideration, dated September 26, 2007, that you submitted on behalf of BoneSupport AB. The Office of Combination Products received and filed your request for reconsideration on September 26, 2007. You request that we reconsider the conclusion contained in our September 12, 2007 letter for the Cerament™/Bone Void Filler product. That letter responded to your July 18, 2007 Request for Designation (RFD), recommending that the Cerament™/Bone Void Filler be classified as a device and assigned to the Center for Devices and Radiological Health (CDRH) for review under the device provisions of the Food, Drug, and Cosmetic Act (the Act).

Our September 12, 2007 letter concluded that the Iohexol solution contained in the Cerament™/Bone Void Filler is a drug, and that the Cerament™/Bone Void Filler is a drug-device combination product with the primary mode of action (PMOA) attributable to the device component of the product, a ceramic filler. Accordingly, our September 12, 2007 letter assigned the co-packaged Cerament™/Bone Void Filler to CDRH as the lead agency center for premarket review and regulation.

We have reconsidered the information provided in the initial RFD and in your request for reconsideration. After careful consideration, we affirm our determination that the Cerament™/Bone Void Filler is a drug-device combination product with the primary mode of action (PMOA) attributable to the device component of the product. Therefore, for reasons stated in this letter and in our designation letter of September 12, 2007, we affirm the classification and assignment of your product to CDRH.

Original RFD Submission

Your RFD, submitted on July 18, 2007, describes Cerament™/Bond Void Filler as an injectable bone void filler with a powder component (a ceramic filler) and a liquid component (an Iohexol solution). These two components, along with an injection device, will be co-packaged. The ceramic filler consists of hydroxyapatite, calcium sulfate hemihydrate, and calcium sulfate dihydrate. The Iohexol solution consists of Iohexol in solution containing . These components, upon mixing, create a viscous material for percutaneous injection into a bone void.

The RFD states that the Iohexol solution provides enhanced radio-opacity to aid in visualization during implantation of the bone void filler. More specifically, the RFD states that during a surgical procedure, a health care provider would inject or implant the product with placement guided by the radio-images provided by the Iohexol solution. The ceramic filler provides a scaffold for bone growth.

According to the RFD, the ceramic filler received 510(k) clearance as a device and is currently sold by itself as Cerament™. It contains labeling for use with separately distributed Omnipaque® (Iohexol).¹ The RFD notes that Omnipaque® has New Drug Application approval and does not contain cross-labeling for use with the separately distributed Cerament™ ceramic filler. Your RFD therefore concludes that the separately provided Cerament™ and Omnipaque® do not meet the regulatory definition of a combination product and instead the two separately provided components are regulated as a “single entity device product.”

The RFD recommends that “even if FDA views the Iohexol as contributing a drug mode of action -- making the overall product a drug-device combination product -- CDRH should have primary jurisdiction based upon the primary mode of action of the powder component in providing a scaffold for bone growth.”

Request for Reconsideration

The request for reconsideration recommends, as you recommended in the initial RFD dated July 18, 2007, that the Cerament™/Bone Void Filler, when co-packaged with the Iohexol solution, should be classified as single entity device, consisting of a ceramic filler, syringes, and Iohexol solution. Your letter states that “the Iohexol makes the device more radio-opaque, which aids in visualizing the device location *vis a vis*, the surrounding tissues. Thus, the Iohexol achieves its primary intended purpose without chemical or metabolic action within or on the body, *i.e.*, it has a device mode of action.” You further state that “the function of the increased Iohexol volume, however, would still be to enhance radio-opacity aid in visualization of the device during implantation.”

¹ The RFD alternately refers to the currently marketed Iohexol solution as 180 mg of Omnipaque® (Iohexol), Omnipaque® Iohexol, Omnipaque®, 180 mg of Omnipaque® brand Iohexol, or Iohexol.

In your request for reconsideration, you reference three products containing barium sulfate that are regulated under the premarket notification provisions (k033230, k041584, and k062424). Your letter states that the barium sulfate in these three products is used to aid in the visualization of bone cement during implantation or as a device accessory. Your letter concludes that "Iohexol is not intended to have a chemical action in or on the body and no drug-like claims will be made for it."

Reconsideration Assessment: Combination Product

In our letter of September 12, 2007 we concluded that the action of the Iohexol solution in providing radiocontrast enhancement is a drug mode of action. This recognition of the drug mode of action of the Iohexol solution described in the RFD is consistent with the Agency's regulation of radioopaque contrast agents, which provide or enhance images through a chemical action within the human body, as drugs and not as devices.^{2 and 3}

The use of imaging contrast agents such as iodine-based radioopaque agents to enhance images to localize a device in therapeutic procedures is a longstanding imaging technique for real-time monitoring. For example, radiocontrast agents to enhance fluoroscopy are used before or during a procedure to guide the placement of a catheter, or a therapeutic or diagnostic device.

In this instance, in order to ensure the location of the ceramic filler, the Iohexol component of CeramentTM/ Bone Void Filler, an iodine-based radioopaque agent, acts to delineate and differentiate tissue structure within and adjacent to the bone void itself, to thereby localize the entire injected product and adjacent tissues. Iohexol permits the radiologic visualization of the ceramic filler within the bone defect and tracks any dispersal/diffusion of the cement into adjacent soft tissues, differentiating the tissue structure to make this assessment. This differentiation occurs through the physicochemical interaction between the contrast media particles and the surrounding tissues. The physicochemical interaction of Iohexol with cellular and tissue structures alters the distribution and concentration of the agent in the tissues and structures and conveys diagnostic information by increasing the relative difference of imaging signal intensities in adjacent regions. Therefore, the Iohexol component serves a drug role in providing radiocontrast in delineating and differentiating the structural tissue within and adjacent to the skeletal bone void or gap along with location of the bone void filler.

² See, for example, 47 Fed. Reg. 4406, 4412 (Jan. 29, 1982)

³ See also Citizens Petition Response 96P-0511\CP1, Sup.1, and Sup.2 (Bracco), CP2 (Sonus), CP3 and PSA3 (DuPont Merck), and PSA4 (ImaRx), July 28, 1997; and Guidance for Industry: Developing Medical Imaging Drug and Biological Products, Part 1: Conducting Safety Assessment, and Part 2: Clinical Indications (June 2004). Both Part 1 and Part 2 describe medical imaging agents as drugs and define a contrast agent as "a medical imaging agent used to improve the visualization of tissues, organs, and physiological processes by increasing the relative difference of imaging signal intensities in adjacent regions of the body." Contrast agents are further defined in the Guidance documents to include, but not be limited to, "iodinated compounds used in radiography or CT" Part 1 at 2, Part 2 at 3.

Moreover, recognition of this chemical action in providing visualization is consistent with the Agency's regulation of radioopaque contrast agents as drugs.⁴

Further we affirm that we do not agree with your statement that the currently cleared version of Cerament™ ceramic filler with labeling for use with Omnipaque® (a separately distributed Iohexol solution) renders the drug a "single entity device." As stated in our letter of September 12, 2007, the clearance for the separately distributed Cerament™ ceramic filler was for the device (calcium compound).⁵ You state that Omnipaque is not cross-labeled for use with Cerament™ ceramic filler. However, as you note in your initial RFD, Omnipaque is a drug under NDA approval. The fact that Omnipaque was not relabeled for use with Cerament™ ceramic filler when marketed separately does not affect the classification of Omnipaque [or Iohexol] as a drug.

You also identify three products under premarket notification (k033230, k041584, and k062424) that use barium sulfate to provide radiocontrast when mixed with a specific bone cement for cranioplasty or repair of fractures of the vertebral body. The request for reconsideration states that the products are marketed as single entity devices. Significantly, you have not cited any documentation to support the conclusion that the barium sulfate, which provides radiocontrast visualization in these products, does not perform a drug role in delineating and differentiating the structural tissue within and adjacent to the skeletal tissue along with localization of the cement. Further, the fact that these products are regulated under the device provisions does not demonstrate that the products are not combination products. In fact, under appropriate circumstances, a combination product will be regulated under a single application.

In summary, we affirm our September 12, 2007 conclusion that Cerament™/Bone Void Filler is a drug-device combination product with a PMOA attributable to the device constituent part. Accordingly, we reaffirm our assignment to CDRH's Division of General, Restorative, and Neurological Devices will have lead responsibility for the combination product's premarket review and regulation. For further information about review requirements, contact Ted Stevens, Chief, Orthopedic Spine Devices Branch, at 240-276-3676 or theodore.stevens@fda.hhs.gov. The current RFD and Request of Reconsideration concern a co-package of the Cerament™/Bone Void Filler that includes your Iohexol solution. These documents, and our decisions, do not apply to separate marketing of your Iohexol solution.

In addition, the Office of Combination Products is a resource that is available to you throughout the development and review of your product. For example, if you have questions about the application of current good manufacturing practice for combination products as you develop your Iohexol solution, we encourage you to contact our office for additional information.

⁴ *FDA Guidance for Industry: Developing Medical Imaging Drugs and Biological Products: Clinical Indications*; <http://www.fda.gov/cder/guidance/5742prt2.pdf>

⁵ Each of the predicate devices for Cerament™ are calcium compounds.

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You may request further internal agency review of this decision under 21 CFR §10.75. The Office of Combination Products reports to Dr. Murray M. Lumpkin, Deputy Commissioner for International and Special Programs. Dr. Lumpkin would be the appropriate reviewing official if you choose to request further review. Dr. Lumpkin's address is 5600 Fishers Lane (HF-3), Rockville, MD 20857. There is no time limit to submitting a request for internal agency review.

Sincerely,

A handwritten signature in black ink, appearing to read 'Patricia Y. Love', with a long horizontal flourish extending to the right.

Patricia Y. Love, MD, MBA,
Acting Director
Office of Combination Products

cc: Ted Stevens



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Re: Request for Designation
Cerament™/Bone Void Filler
Our file: RFD 2007.036
Dated: July 18, 2007
Received and filed: July 18, 2007

Dear [REDACTED]:

The Food and Drug Administration (FDA) has completed its review of the request for designation (RFD) for the Cerament™/Bone Void Filler product that you submitted on behalf of BoneSupport AB. The Office of Combination Products (OCP) received and filed the RFD on July 18, 2007. We have determined that the product is a combination product, and we have assigned it to the Center for Devices and Radiological Health (CDRH) as the lead agency center for premarket review and regulation based upon our determination of the product's primary mode of action (PMOA).

Description of the Product

According to the RFD, Cerament™ is an injectable bone void filler with a powder component (a ceramic filler) and a liquid component (an lohexol solution). The ceramic filler consists of hydroxyapatite, calcium sulfate hemihydrate, and calcium sulfate dihydrate. The lohexol solution consists of lohexol [REDACTED] in solution containing [REDACTED]. The RFD explains that mixing the ceramic filler and the lohexol solution creates a viscous material suitable for percutaneous injection into a bone void. The RFD states that the ceramic filler provides a scaffold for bone growth and the lohexol solution provides enhanced radio-opacity to aid in visualization during implantation.

The RFD states that the Cerament™/Bone Void Filler product is intended to be injected into bony voids or gaps in the skeletal system, i.e., extremities, spine, and pelvis. The RFD explains that these defects may be surgically created osseous defects or osseous defects from traumatic injury to the bone. According to the RFD, during a surgical procedure, a health care provider would inject or implant the product into a bone void, with placement guided by the radio-images provided by the lohexol solution. The calcium sulfate hemihydrate would be gradually resorbed, leaving hydroxyapatite particles with an interconnecting pore system formed between the particles. This pore

system is intended to allow bone ingrowth. According to the Bone Support AB website, the Iohexol solution would be resorbed and eliminated in parallel with the implant resorption.

According to the RFD, the ceramic filler has received 510(k) clearance as a device, is currently sold by itself as Cerament™, and is labeled for use with the separately distributed Omnipaque® (Iohexol).¹ The RFD states that Omnipaque® has New Drug Application approval and is not cross-labeled for use with the separately distributed Cerament™ ceramic filler. Therefore, the RFD asserts that, when used in this way, Cerament™/Bone Void Filler and Omnipaque® do not meet the regulatory definition of a combination product. The RFD concludes that CDRH regulates the Cerament™/ Bone Void Filler and the separately marketed Omnipaque® as a "single entity device product."

The RFD explains that Bone Support AB proposes to [REDACTED] Iohexol to be co-packaged with the ceramic filler. The RFD notes that Bone Support AB may also in the future seek clearance for additional bone void filler indications, which may involve an increase in the volume of Iohexol solution from that described in the current proposed use.² The RFD states that the "revised product configuration" (even with additional indications for use) should be considered a "single-entity device." In the alternative, the RFD recommends that even if FDA views the Iohexol as contributing a drug mode of action -- making the overall product a drug-device combination product -- CDRH should have primary jurisdiction based upon the primary mode of action of the powder component in providing a scaffold for bone growth.

Product Classification: Combination Product

We conclude that the Cerament™/Bone Void Filler product described in your RFD is a co-packaged combination product consisting of device components and a drug component. As discussed below, the ceramic filler and the syringes constitute the device components and the Iohexol solution constitutes the drug component. Because your proposed product would be comprised of co-packaged device and drug components, it is a combination product within the meaning of section 503(g) of the Act and Title 21 of the Code of Federal Regulations (CFR) section 3.2(e)(3). In accordance with 21 CFR section 3.4, assignment of a lead Center to conduct the review of a combination product is based on the Agency's determination of the product's PMA.

Assignment of a Lead Center: CDRH

We have considered the information in the RFD and discussed the issues with staff in CDRH, the Center for Drug Evaluation and Research (CDER), and the Office of the General Counsel.

¹ The RFD alternately refers to the currently marketed Iohexol solution as 180 mg of Omnipaque® (Iohexol), Omnipaque® Iohexol, Omnipaque®, 180 mg of Omnipaque® brand Iohexol, or Iohexol.

² We note that this jurisdictional determination is based upon the product described in this RFD and any change(s) to the drug or device components or the intended use of the product would require a new jurisdictional determination.

This product has two modes of action. One action is that of the ceramic bone substitute to fill skeletal bone voids or gaps and provide a scaffold for bone growth. The other action is that of the iodine-based radioopaque contrast agent, Iohexol, to delineate and differentiate tissue structure within and adjacent to the bone void or gap by acting chemically within the body and creating differences in distribution and concentration of contrast medium. This occurs through the physicochemical interaction between the contrast media particles and the cellular components of the tissues. We have determined that the product's PMOA is attributable to the role of the ceramic bone substitute in filling the skeletal bone voids or gaps and providing a scaffold for bone growth. The drug component serves a secondary role in delineating and differentiating the structural tissue within and adjacent to the skeletal bone void or gap to assist in the implantation of the ceramic bone filler.

Bone Support AB's proposal to [REDACTED] and to co-package the drug with the Cerament™ ceramic filler does not change the status of the Iohexol solution as a drug. Our recognition of the drug mode of action of the Iohexol solution described in the RFD is consistent with the Agency's regulation of radioopaque contrast agents as drugs and not as devices. See, for example, 47 Fed. Reg. 4406, 4412 (1982).³

We do not agree with your assertion that the currently cleared version of Cerament™ ceramic filler, which you state is labeled for use with Omnipaque® (a separately distributed Iohexol solution), renders the drug (the Iohexol solution) and device (the Cerament™ ceramic filler) a "single entity device." The Cerament™ ceramic filler was cleared, by itself, as a device (calcium compound).⁴ Iohexol solutions for radio-imaging uses remain drugs as defined in the Federal Food, Drug, and Cosmetic Act (Act).

In accordance with 21 CFR 3.4(a) (2), in recognition of the primary mode of action provided by the ceramic bone substitute, we are assigning the product to CDRH as lead center. We note that you propose [REDACTED]

[REDACTED] We recommend that you consult FDA regarding this aspect of development of your product.

CDRH's Division of General, Restorative, and Neurological Devices will have lead responsibility for the combination product's premarket review and regulation. CDRH will consult with CDER as appropriate with respect to your combination product.

³ See also Citizens Petition Response 96P-0511\CP1, Sup.1, and Sup.2 (Bracco), CP2 (Sonus), CP3 and PSA3 (DuPont Merck), and PSA4 (ImaRx), July 28, 1997; and Guidance for Industry: Developing Medical Imaging Drug and Biological Products, Part1: Conducting Safety Assessment (June 2004), and Part 2: Clinical Indications (June 2004), each defining medical imaging agents as drugs and defining a contrast agent as "a medical imaging agent used to improve the visualization of tissues, organs, and physiological processes by increasing the relative difference of imaging intensities in adjacent regions of the body." Contrast agents are further defined in the Guidance documents to include, but not be limited to, "iodinated compounds used in radiography or CT, ..."

⁴ Each of the predicate devices for Cerament™ are calcium compounds.

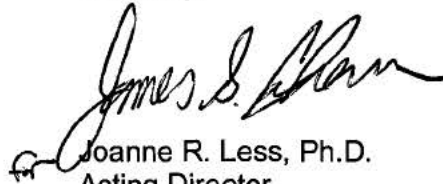
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For further information about review requirements, contact Ted Stevens, Chief, Orthopedic Spine Devices Branch, at 240-276-3676. Please include a copy of this letter with your initial submission to CDRH. For your information, FDA has published a draft guidance document, Current Good Manufacturing Practice for Combination Products⁵, which provides information about current good manufacturing practice for combination products.

You may request reconsideration of the classification or assignment of your product within 15 days of receipt of this letter. If you wish to request reconsideration, or for any other questions about this letter, please contact James S. Cohen at 301-427-1934. Finally, the Office of Combination Products is available to you as a resource for questions or issues that may arise throughout the development of your product. You may reach us at the above address or by email at combination@fda.gov.

Sincerely,



Joanne R. Less, Ph.D.
Acting Director
Office of Combination Products

cc: Ted Stevens

⁵ Available at <http://www.fda.gov/oc/combination/OCLove1dft.html>.