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August 10, 2006

1357 '06 AUG 17 P1:45

Document Mail Center (HFZ-215)
Center for Devices and Radiological Health
Food and Drug Administration
1350 Piccard Drive
Rockville, Maryland 20857

RE: Reclassification Petition
Bone Heterograft (21 C.F.R. 888.3015)

Dear Sir/Madam:

This submission is a reclassification petition for the "Bone Heterograft" regulation as defined in 21 C.F.R. 888.3015. The information was prepared in accordance with 21 C.F.R. 860.123 and contains the following information:

Reclassification Overview Document

FDA Form 3429, General Device Classification Questionnaire

FDA Form 3427, Supplemental Data Sheet

List of Relevant FDA Controls and Guidances

Special Control Summary for a Bone Heterograft Vertebral Body Replacement Device

Literature Overview

If you have any questions or require further information regarding this submission, please contact me by telephone at 386-418-8888 (ext. 4326), via facsimile at 386-418-3607 or by email at lsimpson@rtix.com.

Sincerely,

Lisa Simpson

Lisa Simpson
Director, Regulatory Affairs

2006P-0334

CCP 1

RECLASSIFICATION PETITION FOR BONE HETEROGRAFTS

REGENERATION TECHNOLOGIES, INC.

AUGUST 10, 2006

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I. Introduction

In accordance with Section 513(f)(3) of the Federal Food, Drug, and Cosmetic Act ("FFDCA"),[1] Regeneration Technologies, Inc. ("RTI") is requesting that bone heterografts for use in the spine (21 C.F.R. § 888.3015) be reclassified from Class III to Class II by the U.S. Food and Drug Administration ("FDA").

The bone heterograft is intended to replace bone following surgery in the spinal column. The device may or may not be load bearing and may or may not require use of supplemental fixation. The device may or may not be used with bone grafting materials.

Because FDA reserves Class III for new technology and high risk devices, the down-classification of bone heterografts is justified based on important information that has become available in the past almost 30 years since the classification regulation was promulgated.

Such information would include advances in science and development of standards capable of demonstrating safety of the bone heterograft material for this specific application. In addition, in recognition of advances in science and technology, FDA has issued guidance documents that are applicable to both the material (heterograft, xenograft) and to the relevant indications and intended use. Further, the petitioner contends that precedent exists in market clearance under Class II regulations for both these materials and their intended use.[2] This petition will detail all such standards, guidance, and precedents, and their relevance.

II. Request for Reclassification

The content and form of this petition for reclassification of bone heterografts is submitted in accordance with 21 C.F.R. § 860.123. Also included is a discussion of how general and special controls will provide reasonable assurance of safety and effectiveness in accordance with 21 C.F.R. § 860.7.

A. Specification of the device[3]

The classification name for the device requested to be down-classified to Class II is "Bone Heterograft." The product code is "NVC," and includes bone heterografts intended to be implanted that are made from mature (adult) bovine bones and used to replace human bone following surgery in the cervical region of the spinal column.

Prior to the Medical Device Amendments of 1976[4] ("the amendments") to the Federal Food, Drug and Cosmetic Act,[5] bone heterografts were classified as drugs. The

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1 21 U.S.C. § 360c(f)(3).

2 The implant devices already cleared are: K051615 - Sterling Chips & Cubes; K060253 - Sterling Interference HT & ST; K052405 - Sterling Interference HT; and K050767 - Sterling Interference ST.

3 21 C.F.R. § 860.123(a)(1).

4 Pub. L. 94-295.

amendments included transitional provisions to assure that devices formerly regarded as drugs continued to be subject to appropriate regulatory controls as the amendments were implemented. These devices were automatically classified into Class III unless the Agency, in response to a petition, reclassified them into Class I or Class II. FDA codified the statutory Class III designation of bone heterografts per 21 C.F.R. § 888.3015 in 1987 (Docket No. 78N-3028).

B. Action requested[6]

It is requested that bone heterografts intended for use as a replacement for human bone in the spine be reclassified from a Class III device to a Class II device. It is further requested that the specific reference to cervical spine be removed.

C. Supplemental data sheet[7]

A completed supplemental data sheet (FDA Form 3427) is submitted as Attachment 1.

D. Classification questionnaire[8]

A completed product classification questionnaire (FDA Form 3429) is submitted as Attachment 2.

E. Statement of the basis for disagreement with the present classification status

The basis of this reclassification request is that the current classification of bone heterograft to replace human bone in the spine as Class III is no longer appropriate, given the standards and guidance documents that are currently available for the regulation of spinal systems and animal-derived devices. Specifically, the bases for disagreement are:

1. **Precedents.** Devices used to replace bone in the spine are classified under Class II, and implants made from bovine heterograft with indications for use both in the spine and other anatomical sites, have been cleared as Class II devices.

2. **Appropriateness of Class II classification.** Class II and the 510(k) pathway is an appropriate route to market for the bovine bone heterograft used to replace bone in the spine. Intended use, rather than material composition, properly should dictate the appropriate classification.

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5 21 U.S.C. Sections 301 through 392.

6 21 C.F.R. § 860.123(a)(2).

7 21 C.F.R. § 860.123(a)(3) (FDA Form 3427).

8 21 C.F.R. § 860.123(a)(4) (FDA Form 3429).

3. **Special controls.** Although the device differs from other Class II spinal devices with respect to material composition, the data presented in this petition demonstrate that the characteristics associated with the material do not affect the safety and effectiveness relative to other spinal vertebral body replacement devices. The petitioner believes that the reclassification petition establishes the basis for such determination using the special controls defined by the FDA along with other acceptable scientific methods employed consistently under consensus standards and established FDA review practices. These established standards allow for the full understanding of biomechanical properties and the biological safety and performance of bone heterograft.

4. **Safety and effectiveness.** In the past 30 years, there have been both advances in science and development of standards that are capable of supporting and demonstrating safety and effectiveness under the 510k standards applied to Class II devices.

5. **The current bone heterograft classification regulation (21 C.F.R. § 888.3015) does not apply.** This classification regulation was related to a specific product that was progressing through an IND during the transition to medical device regulation (Docket No. 78N-3028, September 4, 1987), and this device did not complete the PMA process (PMA P800044), there has been no device approved under the classification regulation to date. Additionally, current proposed uses of bone heterograft are not restricted to the cervical spine, as specified in this regulation.

6. **Least Burdensome principles.** The reclassification of bone heterograft to Class II is consistent with the "least burdensome" principles of the Food and Drug Administration Modernization Act of 1997 ("FDAMA").

F. Full statement of reasons and supporting data for reclassification, and how the proposed classification will provide reasonable assurance of the safety and effectiveness of the device[9]

1. Precedents

The design and proposed intended use of bone heterograft in the spine aligns completely with other Class II 510(k) devices intended to replace bone in the spine (i.e., vertebral body replacement ("VBR") devices, 21 C.F.R. § 888.3060).[10] Specifically, the proposed intended use of bone heterograft includes use in the spine to replace a diseased vertebral body resulting in anterior decompression of the spinal cord and neural tissues and restoration of the height of the vertebral body.

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9 21 C.F.R. § 860.123(a)(6).

10 See, e.g., K990148 (Stackable Cage™ System); K032812 (EndoSkeleton TA VBR).

Bovine bone-derived devices previously have been cleared for use in the spine and other anatomical regions as Class II devices. For example, the petitioner's "Sterling Cancellous Chips, Sterling Cancellous Cubes" (K051615), which are comprised of bovine bone, are "indicated for bony void or gaps that are not intrinsic to the stability of the bony structure. They are indicated to be placed into bony voids or gaps of the skeletal system (e.g., extremities, *spine*, ilium, and/or pelvis [emphasis added]. These defects may be surgically created osseous defects or osseous defects created from traumatic injury to the bone. The product provides a void filler that remodels into the recipient's skeletal system."

2. Appropriateness of Class II Classification

As the Agency is aware, spinal device classification regulations have very little accompanying preambular explanation, except where down-classifications have been made. However, based on a review of the composite of all spinal device classifications defined by regulation or proposed regulation,[11] the following conclusions may be drawn with respect to prior Agency interpretations and applications through precedents.

- **Material composition** -- None of the spinal regulations and proposed regulations, by application, are defined or limited in scope by material composition. The regulation at 21 C.F.R. § 888.3015 cannot be interpreted as defining all bone heterograft materials (K051615), since (as noted above), by precedent, the petitioner's bovine bone material has been cleared under another regulation that includes the spinal region (at 21 C.F.R. § 888.3045). Material composition, therefore, should not drive interpretations and decisions concerning the proper scope of spinal classification regulations.

  As a matter of equity, the petitioner requests that FDA consider the principle that similar products should be treated similarly. Since the petitioner's bovine material already has been cleared for use in the spine (K051615), the bovine material alone should not be a basis to differentiate its classification.[12]

- **Titles/Intended Use** -- The title of regulations contains useful guidance on the overall intent and orientation of these regulations. Of the six spinal device classifications, all but the regulation in question -- 21 C.F.R. § 888.3015 -- evidence an intent to classify products by functionality rather than composition.[13]

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11 Regulations reviewed included: 21 C.F.R. §§ 888.3015, 888.3045, 888.3050, 888.3060, 888.3070, and intervertebral body fusion devices (proposed reclassification pending).

12 Airmark Corp. v. FAA, 758 F.2d 685 (D.C. Cir. 1985), quoting United States v. Diapulse Corp., 748 F.2d 56, 62 (2d Cir. 1984) (although courts generally grant "[d]eference to agency authority ... [and] expertise, such deference is not a license to ... treat like cases differently"); United States v. Diapulse Corp., 748 F.2d at 62 (FDA may not "[deny] to one person the right to do that which it [grants] another similarly situated").

13 Although 21 C.F.R. § 888.3045 discusses both functionality and material in the regulation title, experience demonstrates that FDA has not considered material determinative, and has regulated a variety of materials under this regulation, if the intended use is bone void filler applications.

The composite of these titles, thus, suggests that functionality (i.e., intended use) should drive interpretations and decisions concerning the proper scope of spinal classification regulations.

- **References to cervical region** – References to (or exclusions of) the cervical region in this set of regulations, suggest that the cervical region historically has been treated differently only in a few instances. Specifically, 21 C.F.R. §§ 888.3015 is limited to the cervical region, and 888.3070 excludes cervical applications. Both regulations suggest that, for these particular uses, the cervical region warrants separate focus. (Importantly, the petitioner has been able to identify no precedent that has been approved under 21 C.F.R. § 888.3015, so that regulation, by both interpretation and application, remains limited to cervical use.)

  Cervical applications will eventually be permitted for intervertebral body fusion devices, but only pursuant to reclassification.

  The petitioner contends that a VBR used in the cervical region of the spine does not pose any additional risks relative to VBR used in the other regions of the spine.

- **Load-bearing devices** -- All devices that have Class II spinal claims (i.e., intended uses) do not fall out of Class II status if they are load-bearing, provided that they are intended to be used with supplemental fixation, or are themselves supplemental fixation products.

- **Fusion vs. replacement and repair** -- All spinal device classification references to "replacement" and "repair" (e.g., replacing bone, filling bone, immobilizing bone, applying force), are Class II, with the exception of 21 C.F.R. § 888.3070, which excludes cervical applications, and 21 C.F.R. § 888.3015, which is a Class III regulation that speaks specifically to the cervical region.

Thus, the composite of these regulations support that bone heterograft properly should be regulated as a Class II device, rather than as a Class III device under 21 C.F.R. § 888.3015. The material composition, intended use, use with or without fixation, and use in load bearing or non-load bearing applications, all demonstrate consistency with Class II spinal regulation.

3. Special Controls

In the years since 1976, standards for testing and demonstration of both safety and performance have been developed and been recognized and accepted within the FDA product evaluation process under the 510k paradigm. In addition, FDA guidance documents addressing spinal implants[14] and materials derived from animal sources[15] have

[14] FDA. 2004. Guidance for Industry and FDA Staff, Spinal System 510(k)s (May 3, 2004).

been developed and have been widely used. The Quality System Regulation (21 C.F.R. Part 820) provides for validation and controls of the design of the Class II devices, as well as ongoing validation and process control requirements.

Additional testing methods and quality control criteria have been developed to support the market clearance of implants of bovine heterograft origin as Class II devices. These include both *in vitro* and *in vivo* testing for specific biological and potential antigenic characteristics and criteria to assure the standard of the source of animal material. Attachment 3, which lists relevant guidance and standards that could serve as special controls for bone heterografts, identifies these additional tests/criteria in italic script. The application of these special controls to bone heterograft is described in detail in Attachment 4.

4. Safety and Effectiveness

The safety of bone heterografts has been established through standard biocompatibility testing (ISO 10993) and *in vivo* biocompatibility in rats and sheep. See Attachment 4, Section 3 for a summary of biocompatibility testing results on bone heterograft) The effectiveness (performance) of bone heterograft for use in the spine likewise has been established through biomechanical testing (see Attachment 4, Section 4).

The safety and effectiveness of bovine bone for use in spinal applications is also supported by published literature. A review of available literature (see Attachment 5) demonstrates that the bovine cortical bone is as safe and effective as human allograft for use as a cortical ring spacer in vertebral surgeries.

5. The current bone heterograft classification regulation (21 C.F.R. § 888.3015) does not apply.

Because FDA reserves Class III for new technology and high risk devices, the down-classification of bone heterografts is justified based on important information that has become available concerning the safety of these devices in the past almost 30 years since this classification regulation was promulgated (see discussion above). Moreover, the language of 21 C.F.R. § 888.3015 (i.e., restriction to use in the cervical region of the spine) is not relevant to the proposed intended uses for bone heterograft in the spine.

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[15] FDA. 1998. Guidance for FDA Reviewers and Industry, Medical Devices Containing Materials Derived from Animal Sources (Except for In Vitro Diagnostic Devices) (Nov. 6, 1998).

6. Least Burdensome Principles

Reclassification of bone heterograft to Class II is consistent with the "least burdensome" principles of FDAMA. FDAMA requires consideration of the least burdensome appropriate means of evaluating device effectiveness that would have a reasonable likelihood of resulting in marketing approval. Given the special controls in place, the existence of several Class II precedents with either similar intended uses in the spine or similar material composition, and the established safety and effectiveness of bone heterograft for use in the spine, a determination of substantial equivalence to marketed products via a 510(k) premarket notification should be sufficient to clear bone heterograft for use in the spine.

Consistent with least burdensome principles, the goal of FDA's classification process is to seek the least restrictive level of regulatory control necessary to ensure the safety and effectiveness of the device. FDA's "least burdensome" guidance acknowledges that reclassification should be used to ensure that the proper level of regulatory control is applied to a device type, and reinforces "the Medical Device Amendments of 1976 directive to continue to consider the lowest appropriate level of regulatory control sufficient to provide reasonable assurance of the safety and effectiveness of the device."[16]

G. Representative data and information unfavorable to reclassification as Class II[17]

The petitioner is unaware of any data and information that is unfavorable to reclassification of bone heterografts as Class II devices.

III. Financial Certification[18]

Financial certification and disclosure by clinical investigators, consistent with 21 C.F.R. Part 54, are required for clinical studies submitted in support of reclassification petitions for medical devices.[19] Because no clinical studies are included in this request for reclassification, financial certification and disclosure forms are not being submitted.

IV. Conclusions

In conclusion, the petitioner is requesting that bone heterograft for use in the spine be reclassified from Class III to Class II by FDA. In the 30 years since the Class III regulation for bone heterograft (21 C.F.R. § 888.3015) was published, there have been significant advances in science and development of standards capable of demonstrating safety of the bone heterograft

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16 FDA. 2002. The Least Burdensome Provisions of the FDA Modernization Act of 1997: Concept and Principles; Final Guidance for FDA and Industry, 17 (Oct. 4, 2002).

17 21 C.F.R. § 860.123(a)(7).

18 21 C.F.R. § 860.123(a)(10).

19 21 C.F.R. § 54.1(a).

material for this specific application. In addition, in recognition of advances in science and technology, FDA has issued guidance documents that are applicable to both the material (heterograft, xenograft) and to the relevant indications and intended use.

Further, the existence of 510(k)-cleared precedents with similar indications for use and 510(k)-cleared precedents comprised of the same material that can be used in the spine supports the down-classification of bone heterograft. There is valid scientific evidence, including biocompatibility and biomechanical testing, published literature, international standards, voluntary guidances from national and international organizations, and lower classification by regulatory authorities in the EU, that demonstrates that general and specific controls would provide reasonable assurance of the safety and effectiveness of bone heterografts.

FDA reserves Class III for new technology and high risk devices, and, consistent with least burdensome principles, the goal of FDA's classification process is to seek the least restrictive level of regulatory control necessary to ensure the safety and effectiveness of the device. Bone heterograft properly should not be considered high risk or new technology devices warranting Class III status, and down-classification is justified.

Attachments:

#1: FDA Form 3429, General Device Classification Questionnaire

#2: FDA Form 3427, Supplemental Data Sheet

#3: List of Relevant FDA Controls and Guidances

#4: Special Control Summary for a Bone Heterograft Vertebral Body Replacement Device

#5 Literature Overview

Hanna, Myrna

From: Lisa Simpson [lsimpson@rtix.com]
Sent: Wednesday, August 16, 2006 5:53 PM
To: Hanna, Myrna
Cc: Butler, Jennie C
Subject: RTI Bone Heterograft Reclassification Petition

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Dear Myrna,

I wanted to let you know that none of the information submitted in the "Reclassification Petition, Bone Heterograft", dated August 10th 2006 is considered to be confidential by RTI. As such, I am giving FDA permission to distribute the information as necessary in support of the reclassification efforts.

Thank you,
Lisa

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