DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

Regeneration Technologies, Inc.
% Ms. Lisa Simpson
Director, Regulatory Affairs
P.O. Box 2650
11621 Research Circle
Alachua, Florida 32616-2650

OCT 25 2007

Re: Reclassification of Bone Heterograft (21 CFR 888.3015)
Docket No. 2006P-0334
Dated: August 10, 2006
Amended: March 21, 2007 and June 4, 2007

Dear Ms. Simpson:

The Food and Drug Administration has reviewed the above referenced petition for reclassification pursuant to section 520(l) of the Federal Food, Drug, and Cosmetic Act (Act). (We note you had requested review under 513(f)(3) of the Act.) Bone heterograft devices for use in the cervical region of the spine are currently class III, requiring premarket approval (PMA), as per 21 CFR 888.3015. This petition seeks reclassification of Bone Heterograft, defined as implants made from mature (adult) bovine bones and used to replace human bone following surgery in the cervical region of the spinal column, from class III to class II. The purpose of a reclassification petition is to demonstrate that the risks previously identified for a class III device, in light of new information, can be adequately addressed by either general, or general along with special, controls, and, therefore, should be reclassified. In the case of bone heterograft for use in the cervical spine, there are no known legally marketed devices which fall within the device category proposed for reclassification that have been approved through the PMA process and there is no known clinical experience on the subject device. In fact, the only PMA for bone heterograft (Kiel Surgibone) was denied by FDA due to a lack of evidence to support the device is safe and effective for its intended use based on the probable risk of adverse immunological reaction and potential failure of long-term osseous union associated with resorption of the device. As discussed in detail with you and your associates during our July 25, 2007 teleconference call, because this classification regulation (21 CFR 888.3015) is based on a transitional device, one formerly regulated by the Center for Drug Evaluation and Review, and subsequently denied as a PMA, reclassification of this type of device will require that you identify special controls, including all the risks and how to mitigate those known risks, to provide reasonable assurance of the safety and effectiveness for this device type. Alternatively, as discussed with you, you may attempt to distinguish your device from the Kiel Surgibone and propose reclassification of your specific device. Please consider the information conveyed during our teleconference call when deciding whether to pursue reclassification of the entire class of devices or reclassification of your device distinguished from the overall class. In addition, you should address the following issues as they relate to your reclassification.

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LET 1

Clinical Evidence of Safety and Effectiveness

1. You state that the safety of a bone heterograft has been established through standard biocompatibility testing (ISO 10993) and *in vivo* biocompatibility testing in rats and sheep and that the effectiveness of a bone heterograft for use in the spine has been established through biomechanical testing. You further state the safety and effectiveness of bovine bone for use in spinal applications is supported by available literature that demonstrates that the bovine cortical bone is as safe and effective as human allograft for use as a cortical ring spacer in vertebral surgeries; however, the literature information provided is limited to a comparison of mechanical properties of bovine bone and human allograft and does not include any clinical data on the use of the bone heterograft device. The basis for reclassification is that there is reasonable evidence to provide assurance that the risks of the device type for the stated use are well understood and we know how to mitigate those risks. At the class II level, that would mean that we could identify special controls for the type of device. As discussed above, there never has been a legally marketed device which falls within the bone heterograft (21 CFR 888. 3015) device classification that has been approved through the PMA process. The only PMA for bone heterograft was denied by FDA due to a lack of evidence to support the device was safe and effective for its intended use. Therefore, clinical data should be provided for your device so that we can determine whether the device type requested for reclassification is reasonably safe and effective under the identified conditions of use and can be regulated at the class II level with special controls. The clinical study should provide valid scientific evidence (as defined in 21 CFR 860.7) and should also address the following:

    a. The clinical study should be designed with sufficient follow-up in order to determine the safety and effectiveness of the device. We believe 2 year follow-up will be necessary to assess the safety and effectiveness of the device as an implant to replace bone, restore vertebral body height and decompress the spinal cord and neural tissues in the cervical region of the spine.

    b. Please refer to FDA's "Guidance Document for the Preparation of IDEs for Spinal Systems" for general principles regarding clinical studies for devices for use in the spine. Although this guidance does not specifically address biological materials, it does include information that should be useful in developing a clinical study for generating valid scientific evidence to provide reasonable assurance of the safety and effectiveness of your device type.

Identification of Risks

2. Adequate safety and effectiveness information has not been submitted to provide a thorough understanding of the risks and benefits of the device. For a device type to be reclassified, you must clearly identify the risks associated with the category of devices requested for reclassification and for a class II type device, identify adequate special controls to mitigate the risks and thus provide reasonable assurance of the safety and

effectiveness of the device type. Therefore, please address the following with respect to identification of risks:

a. You provide animal data that clearly point to the presence of antigenic components in minimally processed (traditional) bone grafts. You discuss that these components are present at levels that are capable of evoking a recall or memory response when peripheral blood mononuclear cells from the recipients were tested. The study also indicated that your specific BioCleanse Tissue Sterilization Process was able to significantly reduce these bone associated antigenic elements to levels incapable of eliciting a significant recall response. However, the risk that bovine heterograft in the cervical spine is associated with a significant immune response and inflammation that hinders, or may hinder, the attainment of bone ingrowth and remodeling or fusion, should be addressed as a special control for the device. The special control ultimately written will depend on whether you plan to pursue reclassification of the general class of devices identified in the regulation or your specific device, distinguished from the general class. As discussed during our July 25, 2007 teleconference call, if you intend to pursue reclassification of the entire class of devices, including the Kiel Surgibone, you will need to identify special controls that, if they had been in place, would have captured the issues seen with the Kiel Surgibone for which denial of the PMA was based.

b. You provide in vivo biocompatibility testing (rat model and sheep study) to address the risk of the processing and materials adversely affecting bone formation (associated with an immune or other biocompatibility response). Because it is anticipated that your device will remain in the body for greater than 30 days, please additionally provide the results of chronic toxicity biocompatibility testing for your device.

c. Please provide animal data on the use of the device under the condition of use proposed in the petition. Please attempt to mimic worst case conditions (e.g., whether endplates are intact, etc.) and provide your rationale for the model(s) selected.

d. Please provide clinical data to evaluate the safety and effectiveness of the device and to help in writing adequate special controls that will mitigate the risks, including risks not previously identified. Once clinical data are available on the device, please amend your petition to provide the following for each identified risk:

   i. The incidence rate
   ii. Cause
   iii. Sequelae of the risk

iv. Information demonstrating that the stated risk is not a potential hazard of the device, if available.

e. Based on our current understanding of the bone heterograft device, we have identified the following additional risks not specifically identified in your petition:

- virus transmission;
- nidus for infection and risk of sequestration that may lead to lack of bone growth and inability to place hardware;
- device resorption (prior to bone formation/fusion);
- lack of bone growth/remodeling and/or incomplete fusion;
- collapse of the device;
- device subsidence and/or migration;
- device failure with need for subsequent surgical intervention;
- risks associated with the close proximity to neural tissues – neurological complications, paralysis, death; and
- risks associated with residual chemicals from the cleansing process (e.g., lack of bone growth, adverse tissue reaction/inflammation, byproducts from the cleansing process altering the biocompatibility of the device material as new bone grows into the biological material and contacts the cleansing byproducts that may be contained in the interior of the implant).

f. The risks mentioned above, along with the risks identified in your petition (Supplemental Data Sheet and Attachment 4, Special Control Summary), should be presented in a separate section of the petition entitled "Identification of Risks."

Special controls

4. You provide a Supplemental Data Sheet that identifies (item 5) the risks to health presented by the device. You also provide a summary that describes how FDA "special controls" were applied to your Sterling Impacted Cortical Ring intervertebral body replacement device. However, you do not specifically identify the special and/or general controls that may be used to mitigate the individual risks associated with the device. Please revise your petition to identify the specific controls for each risk. Additionally, please consider the following:

a. Please identify special controls that will assure predictable and reliable results to address each of the following risks: infection, immune response or other adverse tissue response, inadequate bone ingrowth/remodeling and/or failed fusion) associated with the device for its intended use.

b. With respect to the ASTM standard (ASTM F2077-03) cited as a special control for mitigating the risk of pain and loss of function (page 16 of 20 of your petition), it is unclear whether this is appropriate/adequate considering the biologic material composition of the bone heterograft. The standard, originally written for metallic devices, not biological materials, does not address the anisotropic nature of the bone heterograft or inherent biological variability. Please provide further information that supports the applicability and adequacy of the proposed ASTM standard as a special control and whether this can reasonably be applied to the bovine bone heterograft material.

5. Please revise your petition to identify special controls intended to mitigate each of the risks identified. This information should be provided for either the entire class of devices or your specific device, depending on whether you plan to pursue reclassification of the general class of devices or your specific device distinguished from the entire class.

6. With respect to the additional risk of virus transmission (item 3 above), please note it will be necessary to conduct a viral inactivation validation of the manufacturing process or to provide information that demonstrates the ability of the manufacturing process to remove and inactivate viruses. We suggest you refer to the following guidances for information to support adequate inactivation and removal of viruses from the animal derived material.

a. "Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin" (ICH Guideline)
http://www.fda.gov/cder/guidance/Q5A-fnl.PDF

b. "<1050> Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin" U.S.P. 24

c. "Guidance for the Preparation of a Premarket Notification Application for a Surgical Mesh"

Identification of the Device for Reclassification

7. As discussed above, if you intend to reclassify your specific device only, you will need to distinguish your device from the general class. Please define the device type and intended use for this reclassification. Please note that the intended use will ultimately be driven by the clinical data provided.

8. You originally requested in this petition that bone heterografts intended for use as a replacement for human bone in the spine be reclassified from class III to II and, additionally, that the specific reference to cervical spine be removed. In order that your reclassification request not overlap with our previous decision that bovine heterograft for replacing bone in the thoracic and lumbar spine is not a transitional device, we requested that you amend your petition to limit the scope back to cervical spine only. You amended your petition on March 21, 2007 with a letter to the docket requesting that you would like to retain reference to the cervical region of the spine in the subject regulation. We agree with this change; however, we have noted that the modification warrants additional changes throughout the petition in that this change impacted some of the rationale provided. Please review the reclassification petition in its entirety and revise all sections that have been affected by your request to reinstate reference to cervical spine, accordingly. For example, please amend the following sections of your petition based on this change:

   a. On page 4, Appropriateness of Class II Classification, you assert that material composition should not drive interpretations and decisions concerning the proper scope of spinal classification regulations. Since the regulation is being driven by the device used in the *cervical* region of the spine, this section should be revised.

   b. On page 2, Statement for basis for disagreement with the present classification, Section II, E, 1, you refer to the spine in general and not specifically or exclusively to the cervical spine. This section should be revised.

   c. On Page 3, Section II, E, 2 and 3, you refer to material composition only, not also the cervical region as the basis for the class III designation. This discussion should be amended to reflect the cervical region of use upon which the regulation is based.

   d. You conclude (Attachment 5, Rationale for Bovine Cortical Ring Xenograft – A Literature Overview) that "...it is not necessary to perform in vivo studies, and that bovine cortical bone is at least as safe and effective as human allografts for use as a cortical ring spacer in non cervical vertebral surgeries." Reference to "non cervical" should be changed to reflect the current status of the petition.

The deficiencies identified above represent the issues that we believe need to be resolved before our review of your reclassification petition can be completed. In developing the deficiencies, we carefully considered the burden that may be incurred in your attempt to respond to the deficiencies. We believe that we have considered the least burdensome approach to resolving these issues. If, however, you believe that information is being requesting that is not relevant to the regulatory decision or that there is a less burdensome way to resolve the issues, you should follow the procedures outlined in the "A Suggested Approach to Resolving Least Burdensome Issues" document. It is available on our Center webpage at:
http://www.fda.gov/cdrh/modact/leastburdensome.html

If you submit information addressing these deficiencies, we will reevaluate your reclassification petition. Please provide five (5) copies of your response to this letter. The information should reference the above docket number (2006P-0334) and be submitted to:

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

If you have any questions related to reclassification, please contact Ms. Marjorie Shulman at (240) 276-4040. For scientific and technical assistance, please contact Ms. Nadine Y. Sloan at (240) 276-3604.

Sincerely yours,

Donna-Bea Tillman, Ph.D.
Director
Office of Device Evaluation
Center for Devices and
Radiological Health