DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

Medtronic Sofamor Danek USA, Inc.
% Ms. Michelle Obenauer
Regulatory Affairs Supervisor
1800 Pyramid Place
Memphis, Tennessee 38132

OCT 10 2008

Re: H040004
HUD #03-0130
INFUSE/MASTERGRAFT™ Posterolateral Revision Device
Filed: September 8, 2005
Amended: December 14, 2005, January 12, March17, May 8, and June 6, 23 and 28, August 15 and 21, and November 17 and 21, 2006, January 26, February 22, April 24, June 1, July 6, October 9 and December 31, 2007 and January 14, April 25, and May 19, 2008
Product Code: OJZ

Dear Ms. Obenauer:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your humanitarian device exemption (HDE) application for the INFUSE/MASTERGRAFT™ Posterolateral Revision Device. This device is indicated for the repair of symptomatic, posterolateral lumbar spine pseudarthrosis. This device is intended to address a small subset of patients for whom autologous bone and/or bone marrow harvest are not feasible or are not expected to promote fusion. These patients are diabetics and smokers. This device is indicated to treat two or more levels of the lumbar spine. CDRH is pleased to inform you that your HDE is approved subject to the enclosed "Conditions of Approval." You may begin commercial distribution of the device after you have submitted an amendment to this HDE with copies of the approved labeling in final printed form.

In addition to the general conditions of approval outlined in the attachment, you have agreed to the following conditions:

1. Maintain a plan for surgeon training in the use of INFUSE/MASTERGRAFT™ Posterolateral Revision Device that includes information related to potential benefits and risks present in the exposure to osteogenic factors, *e.g.*, immune response issues for the general population, immune response issues specific to women of child-bearing potential and issues related to tumor formation or promotion. Any changes to the type(s) of instructional information to be provided, including descriptions of "hands-on" sessions, should be outlined in an annual report prior to implementation.

2. Continue to submit reports describing diagnoses of cancer in patients receiving any product containing rhBMP-2. These reports should be submitted within a reasonable time after you learn of these diagnoses and should include the following information:

    - age at onset, gender and ethnicity of the patient;
    - how many antibody titres were drawn and what were the results;
    - time of symptom onset in relation to the index surgical procedure and patient age;
    - time to diagnosis from index surgical procedure;
    - location of the tumor;
    - concomitant medications at the time of surgery;
    - any lab work results;
    - co-morbid medical conditions at the time of surgery (any fractures or HO noted during or after the spinal surgery);
    - patient complaints of any adverse events or secondary surgeries or adverse radiographic findings during the study period;
    - the final clinical outcome for the patient; and
    - a pathology report which describes the histopathology of the tumor.

The sale, distribution, and use of this device are limited to prescription use in accordance with 21 CFR 801.109 within the meaning of section 520(e) of the Federal Food, Drug, and Cosmetic Act (the act) under the authority of section 515(d)(1)(B)(ii) of the act. In addition, in order to ensure the safe use of the device, FDA has further restricted the device within the meaning of section 520(e) of the act under the authority of section 515(d)(1)(B)(ii) of the act insofar as the sale, distribution, and use must not violate sections 502(q) and (r) of the act.

FDA wishes to remind you that failure to comply with any postapproval requirement constitutes a ground for withdrawal of the HDE. Commercial distribution of a device that is not in compliance with these conditions is a violation of the act.

CDRH will notify the public of its decision to approve your HDE by making available a summary of the safety and probable benefit of the device upon which the approval was based. The information can be found on the FDA CDRH Internet HomePage located at http://www.fda.gov/cdrh/ode/hdeinfo.html. Written requests for this information can also be made to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers

Lane, Rm. 1061, Rockville, MD 20852. The written request should include the HDE number or docket number. Within 30 days from the date that this information is placed on the Internet, any interested person may seek review of this decision by requesting an opportunity for administrative review, either through a hearing or review by an independent advisory committee, under section 515(g) of the act.

You are reminded that, as soon as possible and before commercial distribution of your device, you must submit an amendment to this HDE submission with copies of all approved labeling in final printed form. The labeling will not routinely be reviewed by FDA staff when HDE applicants include with their submission of the final printed labeling a cover letter stating that the final printed labeling is identical to the labeling approved in draft form. If the final printed labeling is not identical, any changes from the final draft labeling should be highlighted and explained in the amendment.

Any information to be submitted to FDA regarding this HDE should be submitted in triplicate, unless otherwise specified, to the address below and should reference the above HDE number to facilitate processing:

Document Mail Center (HFZ-401)
Office of Device Evaluation
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Blvd.
Rockville, Maryland 20850

If you have any questions concerning this approval order, please contact Mr. Aric D. Kaiser at (240) 276-3676.

Sincerely yours,

Jeanette Y. Michaels, MD. FOR DR. TILLMAN

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

Enclosure

CONDITIONS OF APPROVAL FOR AN HDE

I. APPROVED LABELING

As soon as possible and before commercial distribution of the device, the holder of an HDE should submit three copies of the approved labeling in final printed form as an amendment (if submitted prior to HDE approval) or supplement (if submitted after HDE approval) to the HDE. The amendment/supplement should be submitted to the Document Mail Center (HFZ-401), Office of Device Evaluation, Center for Devices and Radiological Health, Food and Drug Administration (FDA), 9200 Corporate Blvd., Rockville, Maryland 20850.

II. ADVERTISEMENTS

Advertisements and other descriptive printed materials issued by the HDE holder or private label distributor with respect to this device should not recommend or imply that the device may be used for any use that is not included in the FDA approved labeling for the device. If the FDA approval order has restricted the sale, distribution and use of the device to prescription use in accordance with 21 CFR 801.109 and specified that this restriction is being imposed in accordance with the provisions of section 520(e) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 360j(e)) under the authority of section 515(d)(1)(B)(ii) of the act (21 U.S.C. 360e(d)(1)(B)(ii)), all advertisements and other descriptive printed material issued by the holder or distributor with respect to the device shall include a brief statement of the intended uses of the device and relevant warnings, precautions, side effects, and contraindications.

III. HDE SUPPLEMENTS

Before making any change affecting the safety or probable benefit of the device, the HDE holder should submit a supplement for review and approval by FDA unless a "Special HDE Supplement" is permitted as described under 21 CFR 814.39(d)(2) or an alternate submission is permitted as described under 21 CFR 814.39(e). All HDE supplements or alternate submissions must comply with the applicable requirements under 21 CFR 814.39 of the Premarket Approval (PMA) regulation and under 21 CFR 814.108 of the Humanitarian Device Exemption regulation. The review timeframe for HDE supplements is 75 days except for those submitted under 21 CFR 814.39(e).

Since all situations which require an HDE supplement cannot be briefly summarized, please consult the HDE regulation for further guidance. The guidance provided below is only for several key instances. In general, an HDE supplement must be submitted:

1) When unanticipated adverse effects, increases in the incidence of anticipated adverse effects, or device failures necessitate a labeling, manufacturing, or device modification; or

2) If the device is to be modified, and animal/laboratory or clinical testing is needed to determine if the modified device remains safe and continues to provide probable benefit.

HDE supplements submitted under 21 CFR 814.39(d)(2) "Special HDE Supplement - Changes Being Effected" are limited to the labeling, quality control, and manufacturing process changes as specified under this section of the regulation. This provision allows for the addition of, but not the replacement of previously approved, quality control specifications and test methods. These changes may be implemented upon acknowledgment by FDA that the submission is being processed as a "Special HDE Supplement - Changes Being Effected." Please note that this acknowledgment is in addition to that issued by the Document Mail Center for all HDE supplements submitted. This procedure is not applicable to changes in device design, composition, specifications, circuitry, software, or energy source.

Alternate submissions permitted under 21 CFR 814.39(e) apply to changes that otherwise require approval of an HDE supplement before implementation and include the use of a *30-day HDE supplement* or *periodic postapproval report*. FDA must have previously indicated in an advisory opinion to the affected industry or in correspondence to the HDE holder that the alternate submission is permitted for the change. Before this can occur, FDA and the HDE holder must agree upon any needed testing, the testing protocol, the test results, the reporting format, the information to be reported, and the alternate submission to be used.

Please note that unlike the PMA process, a supplement may not be submitted for a new indication for use for a humanitarian use device (HUD). An HDE holder seeking a new indication for use for an HUD approved under the provisions of Subpart H of 21 CFR 814, must obtain a new designation of HUD status for the new indication for use and submit an original HDE application in accordance with §814.104. The application for the new indication for use may incorporate by reference any information or data previously submitted to the agency.

IV. POSTAPPROVAL RECORD KEEPING REQUIREMENTS

An HDE holder is required to maintain records of the names and addresses of the facilities to which the HUD has been shipped, correspondence with reviewing institutional review boards (IRBs), as well as any other information requested by a reviewing IRB or FDA.

V. POSTAPPROVAL REPORTING REQUIREMENTS

Continued approval of the HDE is contingent upon the submission of postapproval reports required under 21 CFR 814.84 and 21 CFR 814.126.

A. ANNUAL REPORT

Annual reports should be submitted at intervals of 1 year from the date of approval of the original HDE. Reports for supplements approved under the original HDE should be included in the next and subsequent periodic reports for the original HDE unless otherwise specified in the approval order for the HDE supplement. Three copies identified as "Annual Report" and bearing the applicable HDE reference number are to be submitted to the HDE Document Mail Center (HFZ-401), Center for Devices and Radiological Health, Food and Drug Administration, 9200 Corporate Blvd., Rockville,

Maryland 20850. Reports should indicate the beginning and ending date of the period covered by the report and include the following information required by 21 CFR 814.126(b)(1):

1. An update of the information required under §814.102(a) in a separately bound volume;

2. An update of the information required under §814.104(b)(2), (b)(3), and (b)(5);

3. The number of devices that have been shipped or sold and, if the number shipped or sold exceeds 4,000, an explanation and estimate of the number of devices used per patient. If a single device is used on multiple patients, an estimate of the number of patients treated or diagnosed using the device together with an explanation of the basis for the estimate;

4. Information describing the applicant's clinical experience with the device. This shall include safety information that is known or reasonably should be known to the applicant, a summary of medical device reports made pursuant to 21 CFR 803, any data generated from postmarketing studies, and information (whether published or unpublished) that is known or reasonably expected to be known by the applicant that may affect an evaluation of the safety of the device or that may affect the statement of contraindications, warnings, precautions, and adverse reactions in the device labeling; and

5. A summary of any changes made to the device in accordance with supplements submitted under §814.108 and any changes required to be reported to FDA under §814.39(b).

B. **ADVERSE REACTION AND DEVICE DEFECT REPORTING**

As provided by 21 CFR 814.82(a)(9), FDA has determined that in order to provide continued reasonable assurance of the safety and probable benefit of the device, the holder shall submit three copies of a written report identified, as applicable, as an "Adverse Reaction Report" or "Device Defect Report" to the Document Mail Center (HFZ-401), Office of Device Evaluation, Center for Devices and Radiological Health, Food and Drug Administration, 9200 Corporate Blvd., Rockville, Maryland 20850. Such reports should be submitted within 10 days after the HDE holder receives or has knowledge of information concerning:

(1) A mixup of the device or its labeling with another article.

(2) Any adverse reaction, side effect, injury, toxicity, or sensitivity reaction that is attributable to the device and

(a) has not been addressed by the device's labeling or

(b) has been addressed by the device's labeling, but is occurring with unexpected severity or frequency.

(3) Any significant chemical, physical or other change or deterioration in the device or any failure of the device to meet the specifications established in the approved HDE that could not cause or contribute to death or serious injury but are not correctable by adjustments or other maintenance procedures described in the approved labeling. The report shall include a discussion of the HDE holder's assessment of the change, deterioration or failure and any proposed or implemented corrective action by the firm. When such events are correctable by adjustments or other maintenance procedures described in the approved labeling, all such events known to the holder shall be included in the "Annual Report" described under "Postapproval Reports" above unless otherwise specified in the conditions of approval for this HDE. This postapproval report shall appropriately categorize these events and include the number of reported and otherwise known instances of occurrence for each category during the reporting period. Additional information regarding the events discussed above shall be submitted by the HDE holder when determined by FDA to be necessary to provide continued reasonable assurance of the safety and probable benefit of the device for its intended use.

C. **REPORTING UNDER THE MEDICAL DEVICE REPORTING REGULATION**

The Medical Device Reporting regulation (MDR) (21 CFR 803) became effective on July 31, 1996 and requires that all manufacturers and importers of medical devices, including in vitro diagnostic devices, report to FDA whenever they receive or otherwise became aware of information that reasonably suggests that one of its marketed devices:

(1) may have caused or contributed to a death or serious injury; or

(2) has malfunctioned and that the device or a similar device marketed by the manufacturer or importer would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.

The same events subject to reporting under the MDR Regulation may also be subject to the above "Adverse Reaction and Device Defect Reporting" requirements in the "Conditions of Approval" for this HDE. FDA has determined that such duplicative reporting is unnecessary. Whenever an event involving a device is subject to reporting under both the MDR Regulation and the "Conditions of Approval" for a HDE, the manufacturer shall submit the appropriate reports required by the MDR Regulation within the time frames as identified in 21 CFR 803.10(c) using FDA Form 3500A, i.e., 30 days after becoming aware of a reportable death, serious injury, or malfunction as described in 21 CFR 803.50 and 21 CFR 803.52 and 5 days after becoming aware that a reportable MDR event requires remedial action to prevent an unreasonable risk of substantial harm to the public health. The manufacturer is responsible for submitting a baseline report on FDA Form 3417 for a device when the device model is first reported under 21 CFR 803.50. This baseline report

is to include the HDE reference number. Any written report and its envelope is to be specifically identified, e.g., "Manufacturer Report," "5-Day Report," "Baseline Report," etc.

Any written report is to be submitted to:

Food and Drug Administration
Center for Devices and Radiological Health
Medical Device Reporting
PO Box 3002
Rockville, Maryland 20847-3002

Additional information on MDR is available at http://www.fda.gov/cdrh/devadvice/351.html.

CDRH Consumer Information

New Humanitarian Device Approval

Picture of Device

FDA approved this device under the Humanitarian Device Exemption (HDE) program http://www.fda.gov/cdrh/ode/hdeinfo.html. See the links below to the Summary of Safety and Probable Benefit (SSPB) and other sites for more complete information on this product, its indications for use, and the basis for FDA's approval.

Product Name: INFUSE/MASTERGRAFT™ Posterolateral Revision Device
Manufacturer: Medtronic Sofamor Danek USA, Inc.
Address: 1800 Pyramid Place Memphis, Tennessee 31832
Approval Date: October 10, 2008
Approval Letter: A link to web for the approval letter

What is it?

The INFUSE/MASTERGRAFT™ Posterolateral Revision Device is used to produce a posterolateral spinal fusion in patients who already have a failed spinal fusion. It is made from a manufactured (genetically engineered) human protein powder that is mixed with a sterile saline solution (salt water) and soaked into bovine (cow) collagen sponge. Granules of calcium phosphate (a ceramic similar to materials normally found in bone) are placed onto the sponge and the combination is rolled up. If desired, the surgeon may also mix a small amount of local bone with the calcium phosphate granules as a supplemental bulking material. During surgery, the rolled up sponge is then placed on each side of the spinal level that needs to be fused. Metallic spinal fixation hardware is used to stabilize the spine while a new spinal fusion is forming.

How does it work?

The INFUSE/MASTERGRAFT™ Posterolateral Revision Device may help to form new bone by imitating the body's own method of bone healing and growth. The INFUSE/MASTERGRAFT™ Posterolateral Revision Device also gives a physical platform to support any new bone that forms.

When is it used?

The INFUSE/MASTERGRAFT™ Posterolateral Revision Device can be used in patients with a failed spinal fusion surgery at two or more spinal levels who are not able to provide their own bone or bone marrow or have a condition where these tissues are not expected to help in the formation of a new spinal fusion. These conditions are smoking and diabetes.

What will it accomplish?

It may help form a spinal fusion in patients that have already failed a previous spinal fusion surgery and have diabetes or smoke.

When should it not be used?

The device should not be used if :

- you are pregnant or suspect that you might be pregnant,
- if you are sensitive to titanium, titanium alloy, bovine (cow) Type I collagen or recombinant human Bone Morphogenetic Protein-2,
- if you have an infection near the area of the surgical incision, or

- if you had a tumor removed from the area of the implantation site or currently have a tumor in that area.

Precautions and Warnings:
This device has not been tested in patients:
- who did not have diabetes or were smokers;
- who are women of child-bearing age;
- who are nursing mothers;
- who have the device implanted more than once;
- with liver or kidney problems (this might be important because these organs are involved in removing any byproducts of the device.);
- with metabolic bone diseases, such as osteoporosis;
- with autoimmune or immunosuppressive disease, such as AIDS or lupus; or
- with an immune deficiency due to other treatments, such as radiation therapy, chemotherapy or steroid therapy.

Sufficient numbers of patients 65 years and older have not been studied to determine whether they respond differently from younger subjects.

Although not seen in any studies performed by the manufacturer, there is a possibility that too much bone may form at the implantation site, bone may form at a location away from the implantation site or the bone that is formed may be abnormal.

Some patients may have an allergic reaction to the InFUSE™ Bone Graft component.

Please talk with your doctor about any of the above warnings and precautions.

Additional information:
SSPB and Labeling: The SSPB is not yet available and that a link will be established when the SSPB is posted to the web.