DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
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November 6, 2015

SigmaGraft, Inc.
Megan Holden
R&D Manager
335 North Puente Street, Unit A
Brea, California 92821

Re: K151209
Trade/Device Name: InterOss®
Regulation Number: 21 CFR 872.3930
Regulation Name: Bone grafting material
Regulatory Class: Class II
Product Code: NPM
Dated: October 29, 2015
Received: October 29, 2015

Dear Megan Holden:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration. Please note: CDRH does not evaluate information related to contract liability warranties. We remind you, however, that device labeling must be truthful and not misleading.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Part 801); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803); good manufacturing practice requirements as set forth in

the quality systems (QS) regulation (21 CFR Part 820); and if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

If you desire specific advice for your device on our labeling regulation (21 CFR Part 801), please contact the Division of Industry and Consumer Education at its toll-free number (800) 638-2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR Part 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm for the CDRH's Office of Surveillance and Biometrics/Division of Postmarket Surveillance.

You may obtain other general information on your responsibilities under the Act from the Division of Industry and Consumer Education at its toll-free number (800) 638-2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm.

Sincerely yours,

Erin I. Keith -S

Erin I. Keith, M.S.
Director
Division of Anesthesiology,
General Hospital, Respiratory,
Infection Control, and Dental Devices
Office of Device Evaluation
Center for Devices and Radiological Health

Enclosure

Indication for Use:

InterOss® small granules are recommended for:

- Augmentation or reconstructive treatment of the alveolar ridge
- Filling of infrabony periodontal defects
- Filling of defects after root resection, apicocectomy, and cystectomy
- Filling of extraction sockets to enhance preservation of the alveolar ridge
- Elevation of the maxillary sinus floor
- Filling of periodontal defects in conjunction with products intended for Guided Tissue Regeneration (GTR) and Guided Bone Regeneration (GBR)
- Filling of peri-implant defects in conjunction with products intended for Guided Bone Regeneration (GBR)

InterOss® large granules are recommended for:

- Augmentation or reconstructive treatment of the alveolar ridge
- Elevation of the maxillary sinus floor
- Filling of periodontal defects in conjunction with products intended for Guided Tissue Regeneration (GTR) and Guided Bone Regeneration (GBR)

Prescription Use _____x_____ AND/OR Over-The-Counter _____

(Part 21 CFR 801 Subpart D) (Per 21 CFR 801 Subpart C)

(PLEASE DO NOT WRITE BELOW THIS LINE-CONTINUE ON ANOTHER PAGE IF NEEDED)

Concurrence of CDRH, Office of Device Evaluation (ODE)

510(k) Summary

Submitter and Official Correspondent
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Device Information

Trade Name: InterOss®
Common Name: Bone Grafting Material
Classification Name: Bone Grafting Material
Regulation Number: 21 CFR 872.3930
Product Code: NPM
Device Class: Class II
Date of Submission: 10/30/2015

Predicate Devices

The subject device is substantially equivalent to the following predicate device:

- Primary Predicate Device
  - Bio-Oss® (K970321) manufactured by Geistlich Pharma AG.
- Reference Predicate Device (Vial)
  - OCS-B® (K113246) manufactured by Nibec Company, Limited.
- Reference Predicate Device (Syringe)
  - GEISTLICH Bio-Oss Pen (K120601) manufactured by Geistlich Pharma AG.

General Description

InterOss® is a hydroxyapatite material derived from Australian bovine bone. The osteoconductive mineral structure is produced from bone through a multi-step purification process. Following placement in bony voids or gaps, InterOss® acts as an osteoconductive scaffold for the ingrowth of adjacent viable bone. InterOss® gradually resorbs and is replaced with bone during the healing process.

InterOss® is available in granule form and is packaged in vials or a syringe-like applicator.

InterOss®, in the vial form, will be available to the United States market in 8 versions:
Filled with 0.25g, 0.5g, 1.0g, 2.0g, or 5.0g of small granules (0.25 - 1.0mm) or filled with 0.5g, 1.0g, or 2.0g of large granules (1.0 - 2.0mm).

InterOss®, in the syringe-like applicator form, will be available to the United States market in 6 versions:
Filled with 0.25cc, 0.5cc, or 1.0cc of small granules (0.25 - 1.0mm) or filled with 0.5cc, 1.0cc, or 1.5cc of large granules (1.0mm - 2.0mm).

The syringe-like applicator was designed to deliver InterOss® granules more precisely to the intended treatment site without having to use other sterile instruments. The InterOss® granules can be wetted with either the patient's blood or sterile physiological saline solution by pulling back and then pressing down on the plunger. A removable filter cap prevents granules from falling out of the syringe-like applicator during storage and wetting.

During the manufacturing process of InterOss®, the granules are placed into a polymer syringe-like applicator or a glass vial, the vial or syringe is then capped with a rubber cap (the vial is also sealed with an aluminum cap), packaged into a polyethylene terephthalate tray, covered with a Tyvek lid, sealed, and then sterilized by gamma irradiation. The sterilized device is place in a protective package (outer box) along with its Instructions for Use and doctors notes.

All InterOss® products are supplied sterile and are intended for single use only.

Indications for Use

InterOss® small granules are recommended for:

- Augmentation or reconstructive treatment of the alveolar ridge
- Filling of infrabony periodontal defects
- Filling of defects after root resection, apicocectomy, and cystectomy
- Filling of extraction sockets to enhance preservation of the alveolar ridge
- Elevation of the maxillary sinus floor
- Filling of periodontal defects in conjunction with products intended for Guided Tissue Regeneration (GTR) and Guided Bone Regeneration (GBR)

- Filling of peri-implant defects in conjunction with products intended for Guided Bone Regeneration (GBR)

InterOss® large granules are recommended for:

- Augmentation or reconstructive treatment of the alveolar ridge
- Elevation of the maxillary sinus floor
- Filling of periodontal defects in conjunction with products intended for Guided Tissue Regeneration (GTR) and Guided Bone Regeneration (GBR)

Product Testing

a. Physical

The crystallinity ratio (106%), phase purity (100% hydroxyapatite), and Ca/P ratio (1.67) of InterOss® was assessed using X-ray diffraction. Additionally, phase analysis of InterOss® using Fourier Transform Infrared spectroscopy confirmed the presence of hydroxyapatite. The morphology (granular and porous), average granule size (568 µm and 1625 µm for small and large granules respectively), and pore interconnectivity (positive for pore interconnectivity) of InterOss® was assessed using scanning electron microscopy. Inductively coupled plasma analysis was used to confirm the absence of heavy metals in InterOss®, the elution of Ca (0.533 ± 0.016 at 3 days, 0.322 ± 0.012 at 7 days, and 0.366 ± 0.024 at 14 days) and P (3.723 ± 0.004 at 3 days, 6.277 ± 0.079 at 7 days, and 5.865 ± 0.019 at 14 days) from InterOss® small granules, and the elution of Ca (0.513 ± 0.018 at 3 days, 0.315 ± 0.009 at 7 days, and 0.351 ± 0.021 at 14 days) and P (3.640 ± 0.085 at 3 days, 6.241 ± 0.041 at 7 days, and 5.847 ± 0.019 at 14 days) from InterOss® large granules. The Barrett-Jonhner-Halenda method was used to determine the pore size (149.1660 Å for small granules and 47.3236 Å for large granules) of InterOss®. The surface area of InterOss® small (114.4452 m^2/g) and large (109.0581 m^2/g) granules was determined using the Brunauer-Emmett-Teller method. The solubility of InterOss® was found to be 74.274 ± 13.599 $\mu g/mm^3$ for small granules and 70.247 ± 12.612 $\mu g/mm^3$ for large granules and the average pH of InterOss® was found to be 7.86 ± 0.05 for small granules and 7.83 ± 0.05 for large granules. Lastly, the average compressive strength of InterOss® was found to be 1.00 MPa for small granules and 1.17 MPa for large granules.

Additionally, the physiochemical properties (pore structure, microstructure, phase structure, chemical composition, and residual organic substance) of InterOss® and Bio-Oss® were found to be comparable**.**

b. Biocompatibility

None of the tested animals exhibited abnormal clinical signs indicative of toxicity during test period for the Skin Sensitization test (LLNA; Stimulation Index = 1.03±0.26). InterOss® was determined to be non-mutagenic via the Micronucleus and AMES test. No skin reactions to InterOss® were observed for the Intracutaneous Reactivity Test. InterOss® was determined to be non-pyrogenic. The hemolysis test indicates that InterOss® does not cause a hemolytic reaction. InterOss® was determined to be non-toxic and non-cytotoxic based upon the results of the Acute Systemic Injection Test and Cytotoxicity Test, respectively. Inteross® was also considered negative for signs of systemic toxicity due to leachable compounds. Additionally, InterOss® passed sterility test and Bacterial Endotoxin (LAL) tests.

Lastly, we performed an extractables test (<0.097 mg/device ethyl ether, 0.04 mg/device bis(2-ethylhexyl) phthalate, <0.00002 mg/device Chromium, <0.000038 mg/device Copper, 0.08 mg/device Silica, and 0.0008 mg/device Zinc), a second LAL test (<0.005 EU/mL or <0.232 EU/device), and a Minimum Essential Media test on extractables from the syringe (No cell lysis, intraplasmic granules) to evaluate the biocompatibility of the syringe like adapter.

c. Animal Testing

This study was conducted for SigmaGraft, Inc., to evaluate the in-vivo performance of SigmaGraft's bone void filler, InterOss®, in a dental application. The relative performance of InterOss® was compared against the predicate device, Bio-Oss®, and an empty control in a well-documented critical sized supra-alveolar ridge defect study in beagles. Four treatment groups of beagle dogs, three groups of nine and one group of six, underwent a surgical procedure to implant the predicate or test device into critical sized defects of the right and left mandible (P3 and P4 regions) or were left empty after drilling into the remaining bone immediately after tooth extraction. The predicate or test device was implanted into the defect site on Day 0. The animals remained on study for 4, 8, or 12 weeks.

Observations for morbidity, mortality, injury, and the availability of food and water were

conducted twice daily for all animals. Clinical observations were conducted daily during Week 1 and weekly thereafter. Body weights were measured and recorded prior to surgery and weekly. Physical examinations were conducted pretest to ensure that animals were healthy prior to being placed in the study. With the exception of animal numbers 109, 129 and 131 which underwent repair surgery due to exposure of the implant site resulting from the sutures tearing out through the gingiva, there were no unexpected or noteworthy clinical observations noted during the course of this study. All animals survived to study termination in good health.

At study termination, Faxitron images were obtained and necropsy examinations were performed. The right and left hemi-mandibles (along with the implantation sites and surrounding bone) were collected and analyzed using micro-computed tomography to determine percent mineralized volume and mineralized densities of the samples. Samples were then processed for undecalcified histology and analyzed microscopically by Alizée Pathology, LLC using semi-quantitative histology scoring and histomorphometry.

By all the parameters assessed in this twelve week study, biocompatibility and healing of InterOss® treated defects were indistinguishable from those treated with the Predicate, Bio Oss® and in some cases, superior to untreated defects. Radiographic comparison of graft resorption and boney integration demonstrated similar mean scores for both the Predicate and Test Articles. Likewise, no statistical differences were observed between the Test Article and Predicate with respect to percent mineralized volume and density. Moreover, when compared to the critical sized empty controls, both InterOss® and Bio-Oss® showed statistically greater amounts of bone present within the defect sites and appeared to help preserve the mesial and distal alveolar walls of the defect. Although some migration of the Test and Predicate materials were observed, the overall loss of this material did not appear to compromise the performance of the Test Article or Predicate as compared to leaving the defect unfilled. Histomorphometry also supported the similarity in performance of the Test Article to the Predicate as no statistically significant differences were observed with regards to percent bone, percent residual implant and percent bone marrow values.

Microscopic examination of the implant slides also demonstrated equivalent performance between the Test Article and Predicate. In general, the average amount of residual implant material remaining within the defect site and surrounding soft tissue was similar for both the

Predicate and Test Article with a slight temporal decrease in value from 4 to 12 weeks (Group 3), with the exception of a slight increase in implant material at 12 weeks in the Test Article treatment over the amount found at 8 weeks. While not significantly different, InterOss® had a higher mean percent bone value as compared to Bio-Oss® at 4, 8 and 12 weeks. At 4, 8, and 12 weeks (Group 3), rare instances of polymorphonuclear cells (neutrophils) were noted and, more commonly, macrophages and multinucleated giant cells were found surrounding the implant material in the Test Article and Predicate Control treatments. The Negative Controls had a low incidence of neutrophils at 4 weeks, macrophages at 4, 8, and 12 weeks (Group 3), and a low incidence of multinucleated giant cells at 12 weeks (Group 3). The amount of inflammation present was on the low end of the spectrum and is indicative of a good biocompatibility response that would not interfere with healing. No evidence of necrosis was found in any of the treatment groups at 4, 8 or 12 weeks. Fibrosis scores tended to be equivalent or slightly higher, but not significant, in the Test Article treated sites as compared to the Predicate. No incidences of fatty infiltrate associated with fibrosis were observed for any treatment and neovascularization tended to be variable between the treatments and time points with no major differences or trends.

Basis for Substantial Equivalence

InterOss® and predicates have similar physical and chemical structures. Both are porous, biocompatible bone grafts that facilitate the formation and mineralization of new bone by the osteoblast. As both products have same source of bone (bovine source) and similar process for removal of organic compounds, the product is substantially equivalent to the predicates.

Table 1. Substantial Equivalence Comparison for vials

Item	InterOss®	Bio-Oss®	OCS-B®
Intended use	Identical to the predicate	Used as an adjective therapy in restoring bony defects	Used as an adjective therapy in restoring bony defects
Target Population	Identical to the predicate	Human Oral, Periodontal	Human Oral, Periodontal
Dosage form	Identical to the predicate	Granule contained in single	Granule contained in

		use container	single use container
Granule Sizes	0.25mm to 1mm or 1.0mm to 2.0mm granules	0.25mm to 1mm or 1.0mm to 2.0mm granules	0.2mm to 1mm or 1.0mm to 2.0mm granules
Materials	Identical to the predicate	Anorganic derived osteoconductive hydroxyapatite bone mineral	Anorganic derived osteoconductive hydroxyapatite bone mineral
Source Bone	Identical to the predicate	Bovine Bone	Bovine Bone
Physical Morphology	Identical to the predicate	Trabecular, interconnecting macro and micro pores	Trabecular, interconnecting macro and micro pores
Biocompatibility	• Genotoxicity • Intractaneous reactivity • Maximization and sensitization • Pyrogen (LAL) • Acute systemic toxicity • Cytotoxicity • Implantation • Subchronic	Biocompatible	Biocompatible
Performance	Identical to the predicate	Bone formation	Bone formation
Compatibility w/ other devices	Identical to the predicate	Can be used with GTR membrane	Can be used with GTR membrane
Sterilization Process	Identical to the predicate	Sterile by Gamma Irradiation	Sterile by Gamma Irradiation
Anatomical sites	Identical to the predicate	Similar based on chemical analysis, RD, RT-IR and ICP analysis	Similar based on chemical analysis, RD, RT-IR and ICP analysis
Non-pyrogenic	Identical to the predicate	Yes	Yes
Anatomical Sites	Identical to the predicate	Oral, Periodontal	Oral, Periodontal

Shelf Life	Identical to the predicate	Determined by Manufactures	3 Years
Risk	Non-risk as demonstrated by : -Virus inactivation process validation - Risk analysis - Cleaning Validation	-	-

Table 2. Substantial Equivalence Comparison for Syringe-like Applicator

	Subject Device	**Predicate Device**
510(k) #	N/A	K120601
Device Name	InterOss	Geistlich Bio-Oss Pen®
Manufacturer	SigmaGraft, Inc	Geistlich Parma AG
Package Type	Vial and Syringe-like Applicator	Syringe-like Applicator
Materials for Syringe-like Applicator	Identical to the predicate	Granules are placed in the polymer syringe-like applicator, packaged in a polyethylene terephthalate tray and covered with a tyvek lid, sealed and then sterilized by gamma irradiation.
Intended Use	Identical to the predicate	Geistlich Bio-Oss Pen®is intended for the following uses: - Augmentation or reconstructive treatment of the alveolar ridge - Filling of infrabony periodontal defects - Filling of defects after root resection, apicoectomy, and cystectomy - Filling of extraction sockets to enhance preservation of the alveolar ridge - Elevation of the maxillary sinus floor - Filling of periodontal defects in conjunction with products intended for Guided Tissue Regeneration (GTR) and Guided Bone Regeneration (GBR) Filling of peri-implant defects in conjunction with products intended for Guided Bone Regeneration (GBR)

Syringe-like applicator version	0.25cc, 0.5cc, or 1.0cc of small granules (0.25 - 1.0mm) or 0.5cc, 1.0cc, or 1.5cc of large granules (1.0 - 2.0mm)	0.25g, 0.5g, or 0.7g of small granules (0.25-1.0mm) or filled with 0.5g of large granules (1.0 - 2.0mm)

Summary of Data to Support Substantial Equivalence

InterOss® was the subjected to the full range of biocompatibility test recommended in the FDA's "Class II Special Controls Guidance Documents: Dental Bone Grafting Devices" and in accordance with ISO 10993. Test results confirmed product safety. Organic material has been removed from the product and product specifications have been established to limit protein content. InterOss® passed the TSE inactivation validation and virus inactivation test. Furthermore, the product is sterilized to achieve a sterility assurance level SAL 1 $X10^{-6}$.

The results of these studies confirm the substantial equivalence of InterOss® to its predicate devices.

Conclusion

InterOss® presents the same types of potential risks to consumers as the predicate device Bio-Oss® and has controlled these risks in a similar manner. Biocompatibility test show that the device meets the requirements of those standards. Chemical and physical characterization tests, as well as pre-clinical data, show that the device is substantially equivalent. Comparison with the predicate device shows that the device has similar specification and performance. Therefore, it is concluded that InterOss® is substantially equivalent to the predicate device.