SUMMARY OF SAFETY AND PROBABLE BENEFIT

I. GENERAL INFORMATION

Device Generic Name:	recombinant human Bone Morphogenetic Protein-2 (rhBMP-2) contained on an Absorbable Collagen Sponge (ACS) combined with a calcium phosphate bone void filler bulking agent
Device Trade Name:	INFUSE/MASTERGRAFT™ Posterolateral Revision Device
Applicant's Name and Address:	Medtronic Sofamor Danek USA, Inc. 1800 Pyramid Place Memphis, Tennessee 38132
Humanitarian Device Exemption (HDE) Number:	H040004
Humanitarian Use Device (HUD) Designation Number:	03-0130
Date of Humanitarian Use Device (HUD) Designation:	May 3, 2004
Date(s) of Panel Recommendation:	None
Date of Good Manufacturing Practice Inspection:	May 20, 2005 July 14, 2006 March 23, 2007 April 25, 2007
Date of Notice of Approval to Applicant:	October 10, 2008

II. INDICATIONS FOR USE

The INFUSE/MASTERGRAFT™ Posterolateral Revision 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.

III. CONTRAINDICATIONS

- The INFUSE/MASTERGRAFT™ Posterolateral Revision Device is contraindicated for patients with a known hypersensitivity to recombinant human Bone Morphogenetic Protein-2, bovine Type I collagen or to other components of the formulation.

- The INFUSE/MASTERGRAFT™ Posterolateral Revision Device should not be used in the vicinity of a resected or extant tumor, in patients with any active malignancy or patients undergoing treatment for a malignancy.

- INFUSE/MASTERGRAFT™ Posterolateral Revision Device should not be used in patients who are skeletally immature (≤ 21 years of age or no radiographic evidence of epiphyseal closure).

- The INFUSE/MASTERGRAFT™ Posterolateral Revision Device should not be used in pregnant women. The potential effects of rhBMP-2 on the human fetus have not been evaluated.

- The INFUSE/MASTERGRAFT™ Posterolateral Revision Device should not be implanted in patients with an active infection at the operative site.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the INFUSE/MASTERGRAFT™ Posterolateral Revision Device labeling (Attachment 1).

V. DEVICE DESCRIPTION

INFUSE/MASTERGRAFT™ Posterolateral Revision Device consists of a 2-part bone graft substitute (InFuse Bone Graft + MasterGraft Granules) used as part of a 3 component system (InFuse Bone Graft + MasterGraft Granules + supplemental posterior fixation system, *e.g.*, the CD HORIZON® Spinal System). A small amount of local bone may be added to the MasterGraft Granules as supplemental bulking material.

INFUSE® Bone Graft component

INFUSE® Bone Graft consists of recombinant human Bone Morphogenetic Protein-2 (rhBMP-2, known as dibotermin alfa) placed on an Absorbable Collagen Sponge (ACS). The INFUSE® Bone Graft component induces new bone tissue at the site of implantation.

rhBMP-2 is the active agent in the INFUSE® Bone Graft component. rhBMP-2 is a disulfide-linked dimeric protein molecule with two major subunit species of 114 and 131 amino acids. Each subunit is glycosylated at one site with high-mannose-type glycans. rhBMP-2 is produced by a genetically engineered Chinese hamster ovary cell line.

rhBMP-2 and excipients are lyophilized. Upon reconstitution, each milliliter of rhBMP-2 solution contains: 1.5 mg of rhBMP-2; 5.0 mg sucrose, NF; 25 mg glycine, USP; 3.7 mg L-glutamic acid, FCC; 0.1 mg sodium chloride, USP; 0.1 mg polysorbate 80, NF; and 1.0 ml of sterile water. The reconstituted rhBMP-2 solution has a pH of 4.5, and is clear, colorless and essentially free from plainly visible particulate matter.

The ACS is a soft, white, pliable, absorbent implantable matrix for rhBMP-2. ACS is made from bovine Type I collagen obtained from deep flexor (Achilles) tendon. The ACS acts as a carrier for the rhBMP-2 and acts as a scaffold for new bone formation.

The INFUSE® Bone Graft kits contain all of the components necessary to prepare the rhBMP-2/ACS:

- rhBMP-2
- Sterile Water for Injection
- Absorbable Collagen Sponge
- Syringes with needles

MasterGraft® Granules component

MasterGraft® Granules are made of medical grade combination of hydroxyapatite and β-tricalcium phosphate. MasterGraft® Granules are provided in a 15% hydroxyapatite (HA) + 85% β -tricalcium phosphate formulation. The product is supplied sterile for single patient use. MasterGraft® Granules are an osteoconductive porous implant, cleared by the FDA via the 510(k) pathway in both K012506 and K020986.

Supplemental posterior fixation system component

Because the INFUSE® Bone Graft and MasterGraft® Granules components are not capable of stabilizing the spine, it is necessary to use a supplemental posterior fixation system, such as the CD HORIZON Spinal System, in conjunction with these components. The supplemental posterior fixation system may already be in place from the initial fusion surgery or may need to be added. As a result, the supplemental posterior fixation system is not included in the INFUSE/MASTERGRAFT™ Posterolateral Revision Device kit and must be provided by the surgeon.

INFUSE/MASTERGRAFT™ Posterolateral Revision Device

One (1) INFUSE/MASTERGRAFT™ Posterolateral Revision Device size will be offered. Each kit will contain the following components:

(2) INFUSE® Bone Graft Large II kits. Each kit will consist of the following components:
- (1) 12 mg vial of rhBMP-2 (1.5 mg/ml concentration)
- (1) 10 ml vial of Sterile Water for Injection
- (1) 3" x 4" Absorbable Collagen Sponge acting as the carrier for rhBMP-2
- (2) Syringes with needles
- (1) Package Insert

(2) 10cc kits of MasterGraft® Granules. Each kit will consist of the following components:
- (1) 10 cc vial of MasterGraft® Granules
- (1) Package Insert

(1) Package Insert

(1) Instructions for Preparation

The rhBMP-2 is provided as a lyophilized powder in a vial delivering 12 mg of protein. After appropriate reconstitution, the concentration is (1.5 mg/ml) of rhBMP-2. The solution is then applied to the provided absorbable collagen sponge. The INFUSE® Bone Graft component is prepared at the time of surgery and allowed a prescribed amount of time (no less than 15 minutes) before MasterGraft® Granules are placed onto the absorbable collagen sponge The ACS should then be rolled over the MasterGraft® Granules until the ACS cannot be rolled any further. The Instructions for Preparation contain complete details on preparation of the INFUSE/MASTERGRAFT™ Posterolateral Revision Device.

All three components must be used as a system for the prescribed indication described above. The INFUSE® Bone Graft component must not be used without the MasterGraft® Granules and supplemental posterior fixation system components for the repair of symptomatic, posterolateral lumbar spine, pseudoarthrosis.

VI. ALTERNATIVE PRACTICES OR PROCEDURES

The following are possible alternatives for patients who are diabetics or smokers and require revision of a failed multi-level lumbar fusion, for whom autologous bone and bone marrow harvest are not feasible or are not expected to promote fusion:

- Allograft bone – A revision spinal fusion could be performed using bone from a donor. These types of procedures do not have the risks associated with them that autograft does. These risks include, but are not limited to new or increased pain, fracture of the donor site bone because of larger bone loss or injury to the nerves or blood vessels in the donor site area because of scar tissue from the previous surgery. Because allograft bone is from a donor, there is the risk of disease transmission.

- Bone graft substitutes – These are man-made materials that provide a guide for the formation of new bone. These devices do not have the risks associated with autograft or allograft.

- Bone Growth Stimulators - Devices that apply energy to site of the previous fusion in an attempt to promote bone formation.

- No surgical treatment – Some patients may choose to forego a second attempt at spinal fusion, in favor of pain management and non-surgical treatments.

VII. MARKETING HISTORY

The INFUSE/MASTERGRAFT™ Posterolateral Revision Device has not been marketed in the United States or any foreign country prior to this HDE. The FDA has approved and/or cleared each of the individual components that make up the prodcut for other indications. INFUSE® Bone Graft has been marketed for both a spine and trauma indication. INFUSE® Bone Graft with an Interbody Fusion Device is indicated for lumbar interbody spinal fusion procedures (P000058).

INFUSE® Bone Graft alone is indicated for treating acute, open tibial shaft fractures that have been stabilized with intramedullary (IM) nail fixation (P000054). Separately, MasterGraft® Granules has been cleared for bony voids or gaps that are not intrinsic to the stability of the bony structure (K012506).

The INFUSE® Bone Graft Device is currently being sold in the following countries: United States, Australia, Canada, Costa Rica/Panama, Hong Kong, India, Israel, Mexico, European Union. (In the EU, it is approved under the trade name InductOs).

MasterGraft® Granules are currently being marketed in the following countries: United States, Australia, Canada, New Zealand, Singapore.

None of these products have been withdrawn from marketing for any reason.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

The product approved in this HDE has not been studied in human clinical trials. However, several studies involving other products containing rhBMP-2, the signaling molecule present in this HDE product, have been performed. Although these devices and indications differ from the product configuration and indication approved in this HDE, these data were used to support safety. As a result, all adverse event data described below were from uses of products that are different from the HDE product and implanted in patients that were not identical to the HDE target population.

ADVERSE EVENTS:

INFUSE® Bone Graft/ LT-CAGE Lumbar Tapered Fusion Device

The active ingredient in the INFUSE® Bone Graft kit is rhBMP-2, provided in a concentration of 1.5mg/mL. This formulation of INFUSE® Bone Graft has been used in previous studies. Adverse events observed in two studies which utilized this formulation of INFUSE® Bone Graft are outlined below.

Adverse event rates presented are based on the number of patients having at least one occurrence for a particular adverse event divided by the total number of patients in that treatment group.

The INFUSE® Bone Graft/LT-CAGE Lumbar Tapered Fusion Device was implanted in 288 investigational patients and compared to 139 control patients who received an LT-CAGE Lumbar Tapered Fusion Device filled with iliac crest autograft. The investigational patients were implanted with the device via either an open anterior surgical approach or a laparoscopic anterior surgical approach. The control patients were implanted only via the open anterior surgical approach.

INFUSE® BONE GRAFT/LT-CAGE® LUMBAR TAPERED FUSION DEVICE

ADVERSE EVENTS

	IDE Phase																				Post-Approval Phase					
																					48 Months			72 Months		
	Surgery		Postoperative 1 day – <4 Weeks		6 Weeks ≥4 Weeks – <9 Weeks		3 Months ≥9 Weeks – <5 Months		6 Months ≥5 Months – <9 Months		12 Months ≥9 Months – <19 Months		24 Months ≥19 Months – <30 Months		Total Adverse Events		Total # of Patients Reporting #(% of N)				≥30 Months – <60 Months # of Patients Reporting			≥60 Months – <84 Months # of Patients Reporting		
Complication	Invest.	Control	Invest.	Control	Invest.	Control	Invest.	Control	Invest.	Control	Invest.	Control	Invest.	Control	Invest.	Control	Invest. #	(% of 288)	Control #	(% of 139)	Total	Total #	(% of 134)	Total	Total #	(% of 140)
Anatomical/Technical Difficulty	11	3	0	0	0	0	0	0	0	0	0	0	0	0	11	3	11	3.8%	3	2.2%	0	0	0.0%	0	0	0.0%
Back and/or Leg Pain	0	0	12	4	11	5	12	5	15	4	20	7	8	1[1]	78	36	70	24.3%	32	23.0%	23	22	16.4%	21	18	12.9%
Cancer	0	0	0	0	0	0	0	1	0	0	1	0	1	0	2	1	2	0.7%	1	0.7%	4	4	3.0%	1	1	0.7%
Cardio/Vascular	1	0	6	5	5	2	1	3	2	1	4	2	1	1	20	14	17	5.9%	12	8.6%	7	7	5.2%	4	4	2.9%
Death	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	1	0	0.0%	1	0.7%	2	2	1.5%	0	0	0.0%
Dural Injury	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	1	0	0.0%	1	0.7%	0	0	0.0%	0	0	0.0%
Gastrointestinal	1	0	40	22	2	0	5	1	7	1	10	3	7	5	72	32	56	19.4%	27	19.4%	17	14	10.4%	8	6	4.3%
Graft Site Related	0	0	0	8	0	0	0	0	0	0	0	0	0	0	0	8	0	0.0%	8	5.8%	0	0	0.0%	0	0	0.0%
Implant Displacement/ Loosening	0	0	1	1	3	0	1	0	0	0	0	0	0	0	5	1	5	1.7%	1	0.7%	0	0	0.0%	0	0	0.0%
Infection	0	0	19	9	8	4	5	1	5	1	3	0	0	2	40	17	36	12.5%	16	11.5%	4	4	3.0%	3	3	2.1%
Malpositioned Implant	5	0	0	0	0	0	0	0	0	0	0	0	0	0	5	0	5	1.7%	0	0.0%	0	0	0.0%	0	0	0.0%
Neurological	0	0	8	5	7	3	5	2	6	2	13	4	6	8	45	24	39	13.5%	23	16.5%	12	12	9.0%	5	5	3.6%
Non-Union (OUTCOME PENDING)	0	0	0	0	0	0	0	0	1	2	4	0	1	1	6	3	6	2.1%	3	2.2%	0	0	0.0%	0	0	0.0%
Non-Union	0	0	0	1	0	1	2	0	3	4	4	6	1	1	16	13	10	3.5%	13	9.4%	0	0	0.0%	0	0	0.0%
Other	5	6	18	11	9	2	3	4	11	4	15	6	20	7	81	42	64	22.2%	37	26.6%	29	22	16.4%	18	17	12.1%
Other Pain	0	0	3	1	2	1	4	2	5	1	11	8	10	3	36	16	31	10.8%	14	10.1%	19	14	10.4%	13	12	8.6%
Respiratory	0	0	3	2	1	0	0	0	1	0	0	1	0	1	5	4	5	1.7%	4	2.9%	1	1	0.7%	1	1	0.7%
Retrograde Ejaculation	0	0	5	1	4	0	1	0	0	0	2	0	0	0	12	1	11	3.8%	1	0.7%	0	0	0.0%	0	0	0.0%
Spinal Event	0	0	1	2	1	0	6	2	10	4	10	8	9	2	37	18	30	10.4%	17	12.2%	9	9	6.7%	8	8	5.7%
Subsidence	0	0	3	2	2	0	1	0	1	0	0	0	0	0	7	2	7	2.4%	2	1.4%	0	0	0.0%	0	0	0.0%
Trauma	0	0	4	5	5	3	11	7	14	5	28	11	18	8	81	39	69	24.0%	34	24.5%	23	21	15.7%	22	20	14.3%
Urogenital	0	0	24	5	3	0	2	3	5	3	3	1	7	2	45	14	41	14.2%	13	9.4%	2	2	1.5%	3	3	2.1%
Vascular Intra-Op	5	5	0	0	0	0	0	0	0	0	0	0	0	0	15	5	14	4.9%	5	3.6%	1	1	0.7%	0	0	0.0%
Vertebral Fracture	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1	0	1	0.3%	0	0.0%	0	0	0.0%	0	0	0.0%
Any Adverse Event																	235	81.6%	121	87.1%		84	62.7%		64	45.7%

[1] Percent for 140 males

[2] Percent for 70 males

In the IDE portion of the clinical study, the reported rates of several adverse events were high, but similar, in both the investigational and control groups. These events included back and leg pain, gastrointestinal events, neurological events, infection, and spinal events.

Urogenital events occurred with greater frequency in the investigational groups (14.2%) compared to the control group (9.4%). Retrograde ejaculation rates were greater in the investigational groups (11 subjects) compared to the control group (1 subject) with the majority of events occurring in the early postoperative period.

In the post-approval portion of the study, only investigational patients were followed at the 48 and 72 month timepoints. Patients continued to be monitored for all adverse events types. All adverse event rates, including those that were previously reported as high, did decrease throughout the extended follow-up periods.

Some of the reported adverse events required surgical interventions subsequent to the initial surgery. The number of subjects requiring a second surgical intervention was 8.7% (25/288) in the investigational groups and 10.8% (15/139) in the control group during the IDE phase of the trial. The majority of supplemental fixations were due to painful non-union.

The incidence of adverse events that were considered device related, including implant displacement/loosening, implant malposition and subsidence were all greater in the investigational groups compared to the control group. The rates of these events were low, however, and may be partially attributed to a learning curve associated with the laparoscopic surgical approach. The rate of non-union requiring secondary surgery in the investigational groups was comparable to that of the control group.

During the course of the study, 10 pregnancies were reported – one (1) in the control group and nine (9) in the investigational groups. There were seven (7) pregnancies in the laparoscopic approach group. Two (2) pregnancies in the IDE phase of the laparoscopic approach group resulted in first trimester miscarriages. The other five (5) pregnancies in the laparoscopic approach group resulted in live births with no reported complications. Two (2) of the five (5) pregnancies occurred during the post-approval phase of the study and were second pregnancies for both patients. There were two (2) pregnancies in the IDE phase of the open approach group that resulted in live births with no reported complications. There were no pregnancies reported in the post-approval phase of the open approach group. None of the pregnant subjects had antibody responses to rhBMP-2 or Type I collagen (bovine or human), that were detectable to the limits of the sensitivity of the assay. One (1) pregnancy was reported in the control group, resulting in a live birth with complications at approximately 24 months post-operatively. Control patients were not followed throughout the post-approval phase of the study.

Three (3) cases of cancer were diagnosed during the course of the IDE phase – two (2) in an investigational group (breast and pancreatic) and one (1) in the control group (breast). Five (5) additional cases of cancer were reported in the post-approval phase of the study (thyroid, melanoma of the leg, testicular, breast, squamous cell carcinoma of the scalp). No additional information is available on these subjects, *e.g.*, BMP-2 receptor expression.

One (1) death was reported in a control group subject with cardiovascular disease during the IDE phase of the trial. No investigational patients expired during the IDE phase. Two (2) investigational patient deaths were reported during the post-approval phase of the trial due to respiratory failure in a patient with diabetes mellitus and a patient with pancreatic cancer.

INFUSE® Bone Graft/MASTERGRAFT™ Granules/CD HORIZON® Spinal System Pilot Clinical Trial

The active ingredient in the INFUSE® Bone Graft kit is rhBMP-2, provided in a concentration of 1.5mg/mL. This formulation of INFUSE® Bone Graft has been used in previous studies. Adverse events observed in one study, which utilized this formulation of INFUSE® Bone Graft with MASTERGRAFT™ Granules, are outlined below.

Adverse event rates presented are based on the number of patients having at least one occurrence for a particular adverse event divided by the total number of patients in that treatment group.

The INFUSE® Bone Graft/ MASTERGRAFT™ Granules/ CD HORIZON® Spinal System was implanted in 25 investigational patients and compared to 21 control patients who received iliac crest autograft used in conjunction with the CD HORIZON® Spinal System. All patients were implanted with the device via posterolateral surgical approach.

INFUSE® Bone Graft/ MASTERGRAFT™ Granules/ CD HORIZON® Spinal System Pilot Clinical Trial

Adverse Event	Operative		Postop 1 Day-<1 Month		6 Weeks (≥1-<2 Months)		3 Months (≥2-<5 Months)		6 Months (≥5-<9 Months)		12 Months (≥9-<18 Months)		24 Months (≥18-<30 Months)		36 Months (≥30-<42 Months)		Total Adverse Events		Total # Patients Reporting #(% of N)			
	Inv N=25	Ctrl N=21	Inv N=25	Ctrl N=21	Inv N=25	Ctrl N=21	Inv N=25	Ctrl N=21	Inv N=25	Ctrl N=21	Inv N=25	Ctrl N=21	Inv N=25	Ctrl N=21	Inv N=25	Ctrl N=21	Inv N=25	Ctrl N=21	Inv N=25	%	Ctrl N=21	%
Accidental Injury/Muscle Strain	0	0	1	0	2	1	2	1	0	1	2	0	5	1	0	0	12	4	10	40.0	4	19.0
Allergic Reaction	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1	0	1	4.0	0	0.0
Back &/or Leg Pain	0	0	1	1	1	0	2	0	2	2	2	1	1	1	0	0	9	5	8	32.0	5	23.8
Cancer	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1	4.0	0	0.0
Cardiovascular	0	0	0	1	1	0	0	1	0	1	1	1	0	1	0	0	2	5	2	8.0	3	14.3
Cervical Spinal Event	0	0	0	0	0	0	1	1	0	0	0	0	0	0	0	0	1	1	1	4.0	1	4.8
Dural Injury	1	1	0	0	0	0	0	0	0	0	0	1	1	0	0	0	2	2	2	8.0	2	9.5
Electrolyte Imbalance	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	1	0	0.0	1	4.8
Endocrine	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1	0	0.0	1	4.8
Gastrointestinal	0	0	1	4	0	1	1	1	0	0	1	4	1	0	0	1	4	11	3	12.0	8	38.1
Graft Site Related	0	0	0	1	0	0	0	0	0	1	0	1	0	1	0	0	0	4	0	0.0	4	19.0
Implant Displacement/ Loosening/ Breaking	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	1	0	1	4.0	0	0.0
Incision Related	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	4.0	1	4.8
Infection	0	0	1	1	0	1	0	0	0	2	2	1	1	0	1	1	5	6	4	16.0	5	23.8
Lower Extremity Pain Not of Back Etiology	0	0	1	1	0	0	0	0	1	1	4	0	0	0	1	0	7	2	6	24.0	2	9.5
Malpositioned Implant	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1	4.0	0	0.0
Neck &/or Arm Pain	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1	0	0.0	1	4.8
Neurological	0	0	2	2	0	0	3	0	0	1	0	1	0	0	0	0	5	4	4	16.0	3	14.3
Non-Union (Pending)	0	0	0	0	0	0	0	0	0	1	0	1	0	0	0	0	0	2	0	0.0	2	9.5
Non-Union (Failure)	0	0	0	0	0	0	0	1	0	0	1	1	0	0	0	0	1	2	1	4.0	2	9.5
Other	0	0	1	3	0	0	0	0	1	0	0	0	2	2	0	1	4	6	3	12.0	6	28.6
Other Pain	0	0	1	0	0	0	2	0	0	0	2	0	0	0	1	0	6	0	4	16.0	0	0.0
Respiratory	0	0	0	1	0	0	0	0	0	1	1	0	1	0	0	0	2	2	2	8.0	2	9.5
Skin Disorder	0	0	0	1	0	0	0	1	0	0	0	0	0	0	0	0	0	2	0	0.0	2	9.5
Spinal Event at Other Lumbar Level(s)	0	0	0	0	0	0	0	0	1	1	0	0	0	0	1	1	2	2	2	8.0	2	9.5
Spinal Event at Target Level	0	0	0	0	0	0	0	0	0	0	2	0	0	0	0	0	2	0	2	8.0	0	0.0
Spinal Event at Thoracic Level	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	1	0	0.0	1	4.8
Trauma	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1	0	1	4.0	0	0.0
Upper Extremity Pain Not of Neck Etiology	0	0	0	0	0	0	1	0	1	0	0	0	0	1	0	1	2	2	2	8.0	1	4.8
Urogenital	0	0	1	0	0	0	0	0	1	1	0	1	0	0	0	0	2	2	2	8.0	2	9.5
Any Adverse Event																	74	69	22	88.0	18	85.7

The reported rates of several adverse events were high, but similar, in both the investigational and control groups. These events included back and leg pain, infection, and neurological events.

Some of the reported adverse events required surgical interventions subsequent to the initial surgery which includes revisions and removals. The number of subjects requiring a second surgical intervention was 12.0% (3/25) in the investigational group and 9.5% (2/21) in the control group.

Gastrointestinal events occurred with greater frequency in the control group (38.1%) compared to the investigational group (12.0%). Lower extremity pain, not of back etiology, events occurred with greater frequency in the investigational group (24.0%) compared to the control group (9.5%).
The incidence of adverse events that were considered device or device/surgical procedure related were similar between the investigational and control group. The rate of non-union requiring secondary surgery in the investigational group (4.0%) was less than that of the control group (9.5%).

During the course of the study, there were no reported pregnancies.

One case of cancer was diagnosed during the course of the study. An investigational subject was found to have pancreatic cancer. No additional information is available on this subject, *e.g.*, BMP-2 receptor expression. One death was reported (4.0%). This occurred in an investigational patient secondary to pancreatic cancer.

rhBMP-2/Compression Resistant Matrix (CRM)/CD HORIZON® Spinal System
The active ingredient in the rhBMP-2/Compression Resistant Matrix (CRM)/CD HORIZON® Spinal System is rhBMP-2, provided in a concentration of 2.0mg/mL. This formulation of rhBMP-2 has not been used in previous studies. Adverse events observed in one pivotal study, which utilized this formulation of rhBMP-2/Compression Resistant Matrix (CRM)/CD HORIZON® Spinal System, is outlined below.

Adverse event rates presented are based on the number of patients having at least one occurrence for a particular adverse event divided by the total number of patients in that treatment group.

The rhBMP-2/Compression Resistant Matrix (CRM)/CD HORIZON® Spinal System was implanted in 239 investigational patients and compared to 224 control patients who received iliac crest autograft used in conjunction with the CD HORIZON® Spinal System. All patients were implanted with the device via posterolateral surgical approach.

rhBMP-2/Compression Resistant Matrix (CRM)/CD HORIZON® Spinal System

EVENT	Operative		Postop 1 Day-<1 Month		6 Weeks (≥1-<2 Months)		3 Months (≥2-<5 Months)		6 Months (≥5-<9 Months)		12 Months (≥9-<19 Months)		24 Months (≥19-<30 Months)		Total Adverse Events		Total # Patients Reporting #(% of N)			
	Inv N=239	Ctrl N=224	Inv N=239	Ctrl N=224	Inv N=239	Ctrl N=224	Inv N=239	Ctrl N=224	Inv N=239	Ctrl N=224	Inv N=239	Ctrl N=224	Inv N=239	Ctrl N=224	Inv N=239	Ctrl N=224	Inv N=239	%	Ctrl N=224	%
Anatomical/Technical Difficulty	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1	0.4	0	0
Arthritis/Bursitis	0	0	3	1	1	1	7	2	4	3	6	6	1	6	23	19	22	9.2	19	8.5
Back &/or Leg Pain	0	0	19	7	10	5	15	13	19	29	33	29	31	23	135	111	127	53.1	106	47.3
Cancer	0	0	0	0	0	0	1	0	2	1	3	1	2	0	8	2	8	3.3	2	0.9
Cardiovascular	2	0	37	39	0	2	4	3	2	7	13	6	2	6	69	68	60	25.1	63	28.1
Carpal Tunnel Syndrome	0	0	0	0	0	0	0	0	2	1	4	3	3	2	9	7	9	3.8	6	2.7
Death	0	0	0	0	1	0	0	0	1	2	1	1	0	1	3	4	3	1.3	4	1.8
Dural Injury	13	18	1	0	0	0	0	0	0	0	0	0	0	0	14	18	14	5.9	18	8
Gastrointestinal	0	0	17	15	0	2	4	3	5	2	9	7	6	7	42	42	41	17.2	36	16.1
Graft Site Related	0	0	0	4	0	3	0	5	0	3	0	2	0	0	0	17	0	0	17	7.6
Implant Displacement / Loosening	0	1	0	0	0	0	0	1	0	0	1	1	0	0	1	3	1	0.4	3	1.3
Infection	0	0	19	24	3	6	4	2	4	1	11	9	6	6	52	51	47	19.7	46	21.4
Malpositioned Implant	1	0	3	1	0	1	1	0	0	0	0	0	0	0	5	2	5	2.1	2	0.9
Neurological	0	0	9	6	2	6	17	14	19	17	18	14	15	12	86	75	80	33.5	69	30.8
Non-Union Failure	0	0	0	0	0	0	1	7	0	4	5	5	0	1	6	17	6	2.5	17	7.6
Non-Union Outcome (Pending)	0	0	0	0	0	0	0	1	0	2	4	1	1	2	5	6	5	2.1	6	2.7
Other	1	0	35	26	7	3	6	8	5	10	14	11	16	15	99	92	84	35.1	73	32.6
Other Pain	0	0	2	3	2	0	1	1	6	5	12	4	8	16	31	30	31	13	29	12.9
Respiratory	0	0	8	7	0	1	1	1	0	1	4	3	2	0	16	13	15	6.3	13	5.8
Spinal Event	0	0	1	0	0	1	3	3	5	2	5	11	4	2	18	20	18	7.5	19	8.5
Trauma	0	0	3	3	2	8	8	7	11	15	33	16	23	18	87	70	80	33.5	67	29.9
Urogenital	0	0	10	6	2	2	5	3	4	3	5	4	1	5	27	24	27	11.3	23	10.3
Vertebral Fracture	3	3	0	0	0	0	0	0	0	1	0	0	0	1	3	5	3	1.3	5	2.2
Any Adverse Event															740	696	217	90.8	207	92.4

The incidence of adverse events that were considered device or device/surgical procedure related were similar between the investigational and control group. The rate of non-union requiring secondary surgery in the investigational group (2.5%) was less to that of the control group (7.6%). Seven deaths were reported (1.5%). Three deaths occurred in investigational treatment subjects (2 cancer events, 1 stroke) and four deaths occurred in control treatment subjects (2 cardiovascular events, 1 cancer event, 1 trauma). Ten cases of cancer were diagnosed during the course of this study – eight subjects in the investigational group and two in the control group. Cancers in the investigational group included basal cell carcinoma, laryngeal, lung, lymphatic, ovarian, pancreatic, prostate, squamous cell carcinoma, and breast. Cancers in the control group included colon and lymphatic.

Some of the reported adverse events required surgical interventions subsequent to the initial surgery which includes revisions and removals. The number of subjects requiring a second surgical intervention was 17.2% (41/239) in the investigational group and 25.4% (57/224) in the control group. Secondary surgical intervention information for investigational and control treatment groups is summarized in the Table below.

rhBMP-2/Compression Resistant Matrix (CRM)/CD HORIZON® Spinal System						
EVENT	**Total Events through 24 Month Time point**		**# of Patients Reporting**			
	Inv N=239	**Ctrl N=224**	**Inv N=239**		**Ctrl N=224**	
Revisions	4	4	4	1.7%	3	1.3%
Removals	13	29	13	5.4%	28	12.5%
Supplemental Fixations	6	9	6	2.5%	9	4.0%
Reoperations	13	13	12	5.0%	11	4.9%

During the course of the study, three pregnancies were reported – one in the control group (reported 25 months postoperatively) and two in the investigational groups (reported 6 months and 24 months postoperatively). All pregnancies resulted in healthy births and there were no delivery or post-delivery complications. None of the pregnant subjects had antibody responses to rhBMP-2 or Type I collagen (bovine or human) that were detectable to the limits of the sensitivity of the assay.

POTENTIAL ADVERSE EVENTS

The following is a list of potential adverse events that may occur with spinal fusion surgery with the INFUSE/MASTERGRAFT™ Posterolateral Revision Device. Some of these adverse events may have been previously reported in the adverse events tables or have been reported to the manufacturer:

- Allergic reaction
- Anaphylactic reaction
- Bone fracture
- Bowel or bladder problems
- Cessation of any potential growth of the operated portion of the spine.
- Change in mental status

- Damage to blood vessels and cardiovascular system compromise
- Damage to internal organs and connective tissue
- Death
- Development of respiratory problems
- Disassembly, bending, breakage, loosening, and/or migration of components
- Dural tears
- Ectopic and/or exuberant bone formation
- Edema (swelling)
- Elevated erythrocyte sedimentation rate
- Erythematous tissue
- Fetal development complications
- Fluid–filled cysts, fluid collection, seromas
- Foreign body (allergic) reaction
- Gastrointestinal complications
- Hematoma
- Incisional complications
- Infection
- Inflammation
- Itching
- Loss of spinal mobility or function
- Neurological system compromise
- Non-union (or pseudoarthrosis), delayed union, mal-union
- Pain
- Postoperative change in spinal curvature, loss of correction, height, and/or reduction
- Scar formation
- Seroma
- Tissue or nerve damage

Note: Additional surgery may be necessary to correct some of these potential adverse events.

IX. SUMMARY OF PRECLINICAL STUDIES

Pre-clinical testing of the INFUSE/MASTERGRAFT™ Posterolateral Revision Device consisted of biocompatibility testing and animal testing. Three sets of pre-clinical laboratory studies were performed – those related to the INFUSE® Bone Graft (rhBMP-2/ACS) component alone, those related to the bone void filler (MasterGraft® Granules) alone, and those related to the combination of INFUSE® Bone Graft rolled around the bone void filler.

Tests assessing the characteristics of the rhBMP-2 alone, the ACS alone or the INFUSE® Bone Graft (rhBMP-2/ACS) component were previously described in Section IX. "Summary of Nonclinical Laboratory Studies" of the Summary of Safety and Effectiveness Data for P000058 (http://www.fda.gov/cdrh/pdf/P000058b.pdf). Please refer to this document for those data.

Two additional sets of studies related to exposure to rhBMP-2 were performed after approval of P000058. The first set of studies evaluated the potential for rhBMP-2 to promote tumorigenesis via *in vitro* cell proliferation and cell receptor assessments, and *in vivo* tumor promotion analyses. The second set of studies assessed the potential of a pre-existing anti-rhBMP-2 immune response to cause abnormalities to fetuses in animals

that subsequent to immunization, became pregnant.

Tumor promotion studies

Three studies were performed – receptor expression, *in vitro* cell growth and *in vivo* cell growth to assess the potential of rhBMP-2 to promote the growth of tumor cells in patients implanted with the product. In initial evaluations, tumor cell lines were evaluated for BMP type I and type II receptor expression status. Cell proliferation evaluations were then conducted to see if cells expressing receptors were positively or negatively influenced by the addition of rhBMP-2. Expression of receptor mRNA was not correlated with a positive or negative cell proliferative response. Cell lines found to express BMP type I and II receptors were then evaluated in the nude mouse xenograft model to observe whether rhBMP-2 administered to mice implanted with the tumor cells might promote *in vivo* growth and tumor cell metastasis. Mice received a subcutaneous injection of the tumor cell lines in one limb and one of four treatments in the contralateral limb (sham control surgery, placement of ACS without rhBMP-2 or placement of one of two concentrations of rhBMP-2/ACS – 0.422 or 4.22mg/ml). Cell lines expressing BMP receptors were not stimulated to proliferate in the athymic nude mouse xenograft model, nor did rhBMP-2 increase the incidence of tumor cell metastases in the mice.

Reproductive toxicity

BMP-2 knockout mice experiments had previously demonstrated that deletion of the BMP-2 gene during embryogenesis was a lethal mutation. If women of child-bearing age, exposed to rhBMP-2, developed anti-rhBMP-2 antibodies, and the antibodies crossed the placental barrier, potential fetal toxicities could result. To evaluate for this potential safety issue, female NZW rabbits were immunized with rhBMP-2. Those animals raising an anti-rhBMP-2 titer were then mated. All animals were sacrificed 29 days after mating (GD 29). Maternal assessment included mortality, clinical observations, abortion rate, body weight, food consumption, gravid uterine weight, and hysteroscopy findings on GD 29. Hysteroscopy included: corpora lutea, litter size embryo/fetal mortality, and serum anti-BMP2, as well as determination of antibody neutralizing character. Fetal/embryo postmortem assessments consisted of sex, weight, determination of external, palatal, visceral and skeletal anomalies as well as placental appearance and serum anti-BMP2 neutralizing antibody formation.

Antibody analysis

Pregnancy did not increase the maternal anti-BMP-2 antibody titers. Antibody levels in the fetuses were similar to those of the naively immunized mothers. Anti-BMP-2 antibody levels were similar in the fetuses and the mothers, indicative of the ability of these antibodies to cross the placenta. Mothers that had detectable levels of neutralizing anti-BMP-2 antibodies were noted to have offspring with neutralizing anti-BMP-2 antibody titers, again indicating that antibodies were able to cross the placenta.

Skeletal analysis

Reduced ossification of the frontal and parietal bones of the skull were observed. Data are not available to indicate whether or not these effects were reversible since studies were not carried out sufficiently long enough. Although these anomalies were greater in the treated than control animals, there did not appear to be a direct one-to-one correlation between anti-BMP-2 antibody titer and the presence of decreased ossification. Other skeletal abnormalities, which appeared to be within historical control rates, included -

bipartite sternebrae and vertebral centrum; reduced ossification of caudal vertebrae, pelvic girdle, hyoid, frontal and parietal bones; reduced numbers of ossified front phalanges, metacarpals and sternebrae, and unossified talus.

Data describing the characteristics of the MasterGraft® Granules component alone and the complete INFUSE/MASTERGRAFT™ Posterolateral Revision Device are outlined below.

Biocompatibility Studies for MasterGraft® Granules

The safety of MasterGraft® Granules was evaluated in a series of biocompatibility tests. Under the conditions of these studies, there was no mortality or evidence of significant systemic toxicity in the mouse, no intracutaneous toxicity or significant dermal irritation in the rabbit, no evidence of cell lysis or toxicity in the extract and overlay cytotoxicity tests, and no evidence of hemolysis.

Study Type: Species	Groups/ No. Animals/ Sex	Route	Relevant Findings
Cytoxicity/ in vitro agarose overlay: L-929 mouse fibroblast cell line	n/a	n/a	The test article extracts showed no evidence of causing cell lysis or toxicity.
Intracutaneous toxicity: rabbit: New Zealand white	1/3	IC	The test article extracts showed no evidence of causing significant irritation or toxicity.
In vitro hemolysis: rabbit whole blood	n/a	n/a	The test article extracts were not considered hemolytic.
Systemic toxicity study/mouse	4/20/M	IV IP	The test article extracts were not considered systemically toxic to the mouse at the prescribed USP dosage.

Osteoconductive Studies for MasterGraft® Granules

A 12-week animal study comparing the *in vivo* performance of MasterGraft® Granules to a commercially available bone void filler and an empty control group was performed. Twelve skeletally mature sheep were used in a study in which defects were drilled into the femoral condyles and the MasterGraft® Granule and the other material were implanted.

Radiographs were obtained on all animals at regular intervals to evaluate bone development. At the end of the evaluation period the animals were sacrificed and histological evaluation of the defect sites were performed. The study found that bone growth within the MasterGraft® Granules group was 30.78%. By comparison, bone growth in the bone void filler group was 31.40%, while the empty control group had 20.39% bone growth. The results indicate that the MasterGraft® Granules are substantially equivalent to the commercially available bone void filler, which establishes MasterGraft® Granules as an osteoconductive bone void filler.

Biocompatibility Studies for Combined Components

As documented above, biocompatibility studies were conducted on the separate components of the INFUSEMASTERGRAFT™ Posterolateral Revision Device (INFUSE® Bone Graft alone and MasterGraft® Granules alone). Additionally, the safety of the combined components (INFUSE® Bone Graft and MasterGraft® Granules) was evaluated in a series of biocompatibility tests.

Under the conditions of these studies, the devices were classified as non-cytotoxic; no sensitization; being negligible irritants; having no evidence of systemic toxicity, pyrogenicity, or mutagenicity (AMES Assay); and being hemocompatible.

Study Type: Species	Groups/ No. Animals/ Sex	Route	Relevant Findings
Cytoxicity/L-929 MEM Elution Test	n/a	n/a	No biological reactivity was observed. The device is considered non-cytotixic.
Sensitization – Kligman Maximization Test (Hartley guinea pigs)	30	Intradur-mal Injection and Topical Applica-tion	The test article elicited no reaction (0% sensitization, Kligman Grade I).
Irritation or Intracutaneous Injection Test (New Zealand White Rabbit)	1/sex	Intra-cutaneous Injection	The test article sites did not show a significantly greater biological reaction than the sites injected with the control article. The test article is considered a negligible irritant.
Systemic Toxicity Test (Albino Swiss Mouse)	4/5	Systemic Injection	The test for systemic toxicity is considered negative for the device.
Systemic Toxicity Test (New Zealand White Rabbit)	2/sex	Rabbit Pyrogen (Intra-venous Injection)	The device is considered non-pyrogenic.
Genotoxicity Test (AMES Assay)	n/a	n/a	The test article is not mutagenic in the test species.
in vitro hemocompatibility test	n/a	n/a	The test article did not have any adverse effects on any of the hematological parameters tested and passes the test for *in vitro* hemocompatibility.

Animal Testing of Combined Components

Monkey posterolateral model

A nonhuman primate lumbar intertransverse process arthrodesis study was used to evaluate the effectiveness of the combination of rhBMP-2/ACS wrapped around MasterGraft® Granules. Skeletally mature, rhesus macaque monkeys underwent single level posterolateral arthrodesis at L4-L5. Monkeys received the rhBMP-2 delivered on an ACS, which was then wrapped around the dry MasterGraft® Granules used as a bulking agent. The monkeys were euthanized at 24 weeks after surgery. Manual palpation, plain radiographs, computerized tomography, and nondecalcified histology were used to evaluate fusion in a blinded fashion.

All monkeys with rhBMP-2/ACS wrapped around MasterGraft® Granules achieved solid spine fusions. Histologic analysis of the bone induced by these combinations showed normal trabecular bone and bone marrow elements. Adding MasterGraft® Granules to the existing rhBMP-2/ACS formulation made the implant more compression resistant and

improved the radiographic visualization of implant and new bone. This study supported the ability of the combination to induce bone formation in a nonhuman primate posterolateral fusion model.

X. SUMMARY OF CLINICAL INFORMATION

Currently there have been no prospective clinical studies of the INFUSE/MASTERGRAFT™ Posterolateral Revision Device. The clinical data for the two studies summarized below describing the use of the HDE product in the HDE target population were derived from retrospective analyses of pre-existing data describing the use of the various components of the HDE product under the practice of medicine. While these studies were not specifically designed to evaluate the use of the HDE product in the HDE population, a retrospective analysis of the data revealed that a small number of patients met the definition of the HDE target population. Their outcome data could be used to provide insight into the probable behavior of the HDE product in the HDE population.

The second set of clinical data describes the use of rhBMP-2 as a constituent of several different products to treat populations different from the HDE population (last three studies). These datasets are only provided as additional clinical information to supplement the relative safety and probable benefit of the HDE product. Because of differences in product constituents and target populations, the clinical results of these studies would not be indicative of the expected clinical results from the use of the HDE product in the HDE population.

Retrospective data describing the use of the HDE product in the HDE population

INFUSE® Bone Graft/MASTERGRAFT™ Resorbable Ceramic Granules plus a supplemental posterior fixation device

Clinical data to support the safety and probable benefit of the INFUSE/MASTERGRAFT™ Posterolateral Revision Device in the indicated patient population was collected in a retrospective manner. All patients had a compromising condition (diabetes or smokers) and were treated with INFUSE® Bone Graft and MASTERGRAFT® Granules in a multi-level, posterolateral revision procedure. No autograft bone was used to supplement the INFUSE/MASTERGRAFT™ Device. Supplemental posterior fixation was used in all cases.

Fusion status and clinical outcomes were obtained. Collection of patient outcome measures in a retrospective manner did not allow for success criteria to be defined prospectively. Chart reviews were used to determine patient outcomes. A radiographic success was defined as any patient stated to have fusion. A clinical success was defined as patients reported to be doing well or having improved pain. A clinical failure is defined as a patient continuing to have pain.

Primary Outcome Variable	INFUSE® Bone Graft/MASTERGRAFT™ Resorbable Ceramic Granules plus a supplemental posterior fixation device	
	Fusion Outcome	Clinical Outcome
Success	3/3	1/2
Failure	0/0	1/2
Not reported	1	2

INFUSE® Bone Graft with MASTERGRAFT® Resorbable Ceramic Granules
"Retrospective Study of INFUSE® Bone Graft in Clinical Practice"
"Retrospective Study of INFUSE® Bone Graft in Clinical Practice" was a retrospective study conducted to collect data on the clinical experience with INFUSE® Bone Graft when it is implanted as a substitute for or as a supplement to autogenous bone graft. Data was collected from the medical records on patients at least one year from the index surgery. The success of the surgical procedure was determined at the last available evaluation documented in the medical record. This retrospective study was conducted at multiple sites and all patients treated with INFUSE® Bone Graft were eligible for inclusion. For the purposes of the Humanitarian Device Exemption (HDE), a search of the database of these patients was performed to find patients meeting the HDE indications for use. The following clinical data are the result of this database query.

There were three (3) men and two (2) women ages 52 to 63 years old that met the HDE indications for use. There were three (3) two-level and two (2) three-level, revision surgeries. All patients were diabetics or smokers. While these patients may have had other co-morbidities that could have altered their ability to form a solid fusion mass, including osteoporosis/osteopenia and rheumatoid arthritis requiring chronic use of corticosteroids and NSAIDs, there was not sufficient information to add these conditions to the description of the HDE target population. These patients underwent these multi-level lumbar posterolateral fusions using INFUSE® Bone Graft and MASTERGRAFT® Resorbable Ceramic Granules and posterior instrumentation. As would be expected, surgeons did not discard any local bone graft that was available to them from the surgical approach and exposure, and thus local bone graft was used in all cases. Surgeons used this local bone graft in order to add volume to the grafting materials ("void" or "space filling") and did not consider local bone graft alone to be sufficient to promote a successful fusion. The local bone alone would not be expected to stimulate spinal fusion in these patients and would be expected to function only as an osteoconductive material.

Latest documented assessment of patient outcomes and fusion success ranged from 2-48 months from the index revision procedure. Four out of five (4/5) patients had a successful fusion at the final evaluation. The final evaluation available for the patient whose fusion status was undetermined occurred at two (2) months postoperative, which was too early for a definitive fusion assessment. Thus, for those patients with sufficient follow-up to determine fusion, 4/4 patients were successfully fused.

The goal of pain relief was assessed in all five (5) patients. For this criteria, two (2) patients were graded as complete successes, two (2) were graded as partial successes, and one (1) patient was graded as unsuccessful at the 2-month time period. The goal of bone healing was assessed in three (3) patients. Two (2) patients were graded as complete successes, and one (1) was unsuccessful at 2 months postoperative. The goal of relief of neurological symptoms was assessed in one (1) patient and was graded as a complete success. There was only one adverse event reported. This patient had a revision surgery at the involved levels 2 months postoperatively. The reason for the revision surgery is unknown.

INFUSE® Bone Graft/MASTERGRAFT™ Resorbable Ceramic Granules plus autograft bone and a supplemental posterior fixation device			
Fusion Measures	**Fusion Outcomes**	**Pain Relief Measures**	**Pain Relief Outcomes**
Success	4/5	Complete Success	2/5
Failure	0/5	Partial Success	2/5
Undetermined	1/5	Unsuccessful	1/5

Prospective data describing the use of rhBMP-2 as a constituent of several different products to treat populations different from the HDE population

Three clinical studies have been conducted to support the safety and effectiveness of rhBMP-2 used in the lumbar spine evaluating both anterior interbody and posterolateral fusions. In these studies, neither the investigators nor the subjects were blinded to the treatment. Subject blinding was not possible due to the second surgical site resulting from the need to collect the iliac crest grafts in control subjects. The potential for investigator bias in the clinical outcome parameters was reduced by having the subjects rate their outcome using objective self-assessments. The radiographic outcome parameters were performed by independent radiologists who were blinded to treatment. These were the only radiographic evaluations used for determining radiographic success.

Clinical and radiographic effectiveness parameters

Patients were evaluated preoperatively (within 6 months of surgery), intraoperatively, and postoperatively at 6 weeks, 3, 6, 12 and 24 months, and biennially thereafter until the last subject enrolled in the study had been seen for their 24 month evaluation. Complications and adverse events, device-related or not, were evaluated over the course of the clinical trial. At each evaluation time point, the primary and secondary clinical and radiographic outcome parameters were evaluated. Success was determined from data collected during the initial 12 or 24 months of follow-up.

Primary and secondary clinical and radiographic effectiveness outcome parameters were evaluated for all treated subjects at all follow-up evaluation time points identified above. The primary clinical parameters assessed were of pain, function, and neurological status or pain/disability status. The secondary clinical outcome parameters assessed were general health status, back and leg pain, donor site pain (control subjects only), patient satisfaction, and patient global perceived effect of the treatment. The primary radiographic outcome parameter consisted of evaluations of fusion.

In the anterior interbody study, fusion was evaluated at 6, 12 and 24 months post-op using plain radiographs (AP, lateral and flexion/extension films) and high resolution thin-slice CT scans. Fusion was defined as the presence of bridging bone connecting the inferior and superior vertebral bodies; a lack of motion on flexion/extension ($\leq$ 3mm of translation and $< 5°$ of angulation); and no evidence of radiolucencies over more than 50% of either implant. Fusion success was defined as the presence of all of these parameters plus the lack of a second surgical intervention resulting from a non-union. All assessments were made from the plain films except for the assessment of bridging bone, which was made using the CT scans only if bridging bone could not be visualized on the plain film.

In the posterolateral studies, fusion was assessed at 6, 12, and 24 months postoperatively using plain radiographs (AP, lateral and flexion/extension films) and

high resolution thin-slice CT scans. Fusion was defined as evidence of bridging trabecular bone defined as bony continuous connection from the superior transverse process to the inferior transverse process on both sides; no evidence of motion (≤ 3mm of translation and < 5° of angulation between flexion and extension as seen on lateral flexion/extension radiographs), and the absence of cracking, as evidenced by radiolucent lines completely through the fusion mass. All assessments were made from the plain films except for the assessment of bridging bone, which was made using the CT scans only if bridging bone could not be visualized on the plain film.

Pain and function were measured in all studies using the Oswestry Low Back Pain Disability Questionnaire. Success was defined as a 15 point improvement in the Oswestry score from the pre-op baseline score.

Neurological status consisted of measurements of four parameters - motor, sensory, reflexes, and straight leg raise (SLR). Neurological status success was defined as maintenance or improvement of the pre-op baseline score for each parameter. Overall neurological status success required that each individual parameter be a success for that subject to be counted as a success.

Clinical and radiographic effectiveness evaluation
Individual subject success was defined as success in each of the primary clinical and radiographic outcome parameters. Success for these parameters included:

1. The presence of radiographic fusion;
2. An improvement of at least 15 points from the baseline Oswestry score;
3. Maintenance or improvement in neurological status;
4. The presence of no serious adverse event classified as implant-associated or implant/surgical procedure-associated; and
5. No additional surgical procedure classified as "Failure."

Success rate was expressed as the number of individual subjects categorized as a success divided by the total number of subjects evaluated. The summaries below describes the success rates for the individual primary outcome parameters and/or overall success. In completed pivotal studies, all success rates were based on the data from the 24 month follow-up evaluation and posterior probabilities of success were calculated using Bayesian statistical methods. In pilot studies or pivotal studies that are not yet complete, success rates were presented as general summary statistics.

INFUSE® Bone Graft/LT CAGE® Lumbar Tapered Fusion Device - Pilot and Pivotal Studies Results
A summary of these clinical data was provided in Section X. "Summary of Clinical Studies" of the Summary of Safety and Effectiveness Data for P000058 (http://www.fda.gov/cdrh/pdf/P000058b.pdf). Please refer to this document for those data.

INFUSE® Bone Graft/ MASTERGRAFT™ Granules/ CD HORIZON® Spinal System - Pilot Study Results
Clinical data to support the safety and effectiveness of the INFUSE® Bone Graft/ MASTERGRAFT™ Granules/ CD HORIZON® Spinal System were collected as part of a prospective, multi-center pilot, randomized study. The active ingredient in the

INFUSE® Bone Graft kit is rhBMP-2, provided in a concentration of 1.5mg/mL. The investigational patients were implanted with the INFUSE® Bone Graft with MASTERGRAFT® Granules and the CD HORIZON® Spinal System. The control patients received iliac crest autograft used in conjunction with the CD HORIZON® Spinal System. Both arms were completed via a posterolateral fusion approach in which the implant was placed bilaterally across two adjacent transverse processes.

The indication studied was degenerative disc disease (DDD) accompanied by back pain, with or without leg pain, at a single level between L1 and S1 confirmed by history and radiographic studies.

A total of 25 investigational and 21 control patients were enrolled in the study and received the device. For the majority of the demographic parameters, there were no significant differences between the investigational and control groups.

Success rate was expressed as the number of individual subjects categorized as a success divided by the total number of subjects evaluated. The table below describes the success rates for the individual primary outcome parameters at 24 months postoperative.

INFUSE® Bone Graft/ MASTERGRAFT® Granules/ CD HORIZON® Spinal System – Summary of Pilot Study Success at 24 Months

Primary Outcome Variable	Investigational		Control	
	Success	Failure	Success	Failure
Fusion	18 (94.7%)	1 (5.3%)	14 (70.0%)	6 (30.0%)
Oswestry Pain	22 (95.7%)	1 (4.3%)	15 (75.0%)	5 (25.0%)
Neurological	22 (95.7%)	1 (4.3%)	18 (90.0%)	2 (10.0%)
Overall Success	17 (81.0%)	4 (19.0%)	11 (55.0%)	9 (45.0%)

rhBMP-2/CRM/CD HORIZON® Spinal System - Pivotal Study Results

Clinical data to support the safety and effectiveness of the rhBMP-2/CRM/CD HORIZON® Spinal System were collected as part of a prospective, multi-center, randomized, pivotal study that consisted of two groups, one investigational and one control. The active ingredient in the rhBMP-2/Compression Resistant Matrix (CRM)/CD HORIZON® Spinal System is rhBMP-2, provided in a concentration of 2.0mg/mL. The investigational group was implanted with the rhBMP-2/CRM/CD HORIZON® Spinal System, while the control group received surgical treatment utilizing the CD HORIZON® Spinal System with autogenous bone derived from the iliac crest. Both arms were completed via a posterolateral fusion approach in which the implant was placed bilaterally across two adjacent transverse processes.

The indication studied was degenerative disc disease (DDD) at a single level between L1 and S1 accompanied by back pain, with or without leg pain, confirmed by subject history and radiographic studies.

As of October, 2006, a total of 463 patients were enrolled and treated in the study, 239 investigational and 224 control patients. There were no significant differences in

demographics and preoperative evaluations between the two treatment groups. The patients were of an average age of 53 years.

Success rate was expressed as the number of individual subjects categorized as a success divided by the total number of subjects evaluated. The table below describes the success rates for the individual primary outcome parameters at 12 and 24 months postoperative.

rhBMP-2/CRM/CD HORIZON® Spinal System – Summary of Study Success at 12 and 24 Months

	12 Months				24 Months			
	Investigational		Control		Investigational		Control	
Primary Outcome Variable	Success	Failure	Success	Failure	Success	Failure	Success	Failure
Fusion	182 (87.5%)	26 (12.5%)	150 (82.4%)	32 (17.6%)	186 (95.9%)	8 (4.1%)	150 (89.3%)	18 (10.7%)
Oswestry Pain	159 (71.3%)	64 (28.7%)	150 (73.9%)	53 (26.1%)	152 (73.1%)	56 (26.9%)	133 (72.7%)	50 (27.3%)
Neurological	197 (87.6%)	28 (12.4%)	180 (88.7%)	23 (11.3%)	180 (87.0%)	27 (13.0%)	154 (84.2%)	29 (15.8%)
Overall Success	117 (54.7%)	97 (45.3%)	106 (53.8%)	91 (46.2%)	121 (60.5%)	79 (39.5%)	101 (55.5%)	81 (44.5%)

XI. RISK PROBABLE BENEFIT ANALYSIS

The results of the preclinical studies in animals demonstrate that INFUSE® Bone Graft and INFUSE® Bone Graft with MasterGraft® Granules are osteoinductive and:

- capable of inducing solid fusion in the posterolateral spine following primary treatment;
- induce bone formation in a variety of animal species; and
- generate bone that is mechanically and histologically normal

As described in Section X above, a small amount of clinical data exist describing the clinical behavior of the INFUSE/MASTERGRAFT™ Posterolateral Revision Device in the HDE population. These data lend support to the relative safety and probable benefit to health of the use of this product in the identified target population.

Based on clinical studies, INFUSE® Bone Graft has demonstrated relative safety and probable benefit as an alternative to autograft in patients who required a primary fusion utilizing an interbody fusion device for the treatment of degenerative disc disease. While these data cannot be directly extrapolated to the expected performance of INFUSE/MASTERGRAFT™ Posterolateral Revision Device in revision posterolateral spinal fusions in the compromised population, *i.e.*, diabetics and smokers, there is reason to believe that INFUSE/MASTERGRAFT™ Posterolateral Revision Device could have a probable benefit in this population.

When revision of a failed fusion is required, most patients are limited to either living

with pain and altered function or repeating the original procedure with additional autologous bone, which may result in depletion of the bone stock and further risk to the patient. Allograft bone and bone graft substitutes are not considered feasible alternatives to autograft in revision surgery due to their lack of osteogenic potential. For certain patients, *e.g.*, those with implanted leads, bone growth stimulators would not be considered as feasible options. INFUSE/MASTERGRAFT™ Posterolateral Revision Device has the potential to eliminate the risks and complications associated with these treatment alternatives while providing a feasible and beneficial alternative treatment.

Therefore, it is reasonable to conclude that the probable benefit to health from using the product for the target population outweighs the risk of illness or injury, taking into account the probable risks and benefits of currently available devices or alternative forms of treatment when used as indicated in accordance with the directions for use.

XII. PANEL RECOMMENDATION

This HDE was not taken to a meeting of the Orthopedics and Rehabilitation Devices Advisory Committee (the Panel). The Panel has reviewed similar products containing recombinant human growth factors. The review of this HDE was done collaboratively between scientists in the Center for Devices and Radiological Health and the Center for Drug Evaluation and Research.

XIII. CDRH DECISION

CDRH has determined that, based on the data submitted in this HDE application, the INFUSE/MASTERGRAFT™ Posterolateral Revision Device will not expose patients to an unreasonable or significant risk of illness or injury and the probable benefit to health from using the product outweighs the risk of illness or injury, and issued an approval order on October 10, 2008.

XIV. APPROVAL SPECIFICATIONS

Directions for use: See the Physician's Labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions and Adverse Events in the labeling.

Postapproval Requirements and Restrictions: See Approval Order.

XV. REFERENCES

None