SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I. GENERAL INFORMATION

Device Generic Name:	Bone Growth Stimulator
Device Trade Name:	Cervical-Stim® Model 505L Cervical Fusion System
Device Common Name:	Cervical-Stim
Applicant Name and Address:	Orthofix Inc. 1720 Bray Central Drive McKinney, TX 75069 U.S.A.
PMA Number:	P030034
Date of Panel Recommendation:	None
Date of notice of approval to applicant:	December 23, 2004

II. INDICATIONS FOR USE

The Cervical-Stim® Model 505L Cervical Fusion System is a noninvasive, pulsed electromagnetic bone growth stimulator indicated as an adjunct to cervical fusion surgery in patients at high risk for non-fusion.

III. CONTRAINDICATIONS

There are no known contraindications for the Cervical-Stim as an adjunct to cervical spine fusion surgery.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Physician Manual.

V. DEVICE DESCRIPTION

The Cervical-Stim is an external, low-level, pulsed electromagnetic field (PEMF) device. It is a single piece device that is lightweight, flexible and portable allowing freedom of movement during treatment. Colored lights and an alarm provide information during treatment (e.g. device is on, normal operation, battery low).

The Cervical-Stim is made up of a control unit and a treatment transducer. The control unit contains a microprocessor that generates the Cervical-Stim electrical signal. That signal is converted to a highly uniform, low-energy magnetic field by the treatment transducer. When the device is centered over the treatment area, the therapeutic PEMF signal is delivered directly to the fusion site.

To ensure that the device is functioning properly, the Cervical-Stim constantly monitors battery voltage and the electrical signal. If at any time during treatment, the device stops functioning properly, the red light will come on and the device will not provide treatment.

The Cervical-Stim is powered from a single 9-volt disposable battery. When the red light flashes and the alarm sounds, the battery needs to be replaced. The device will provide approximately 5 days of treatment on one battery. Orthofix will provide a supply of batteries adequate to cover the patient's treatment time.

The device is intended to be worn for 4 hours per day for 3 months or until fusion occurs. The technology and design utilized is the same as that of Orthofix's own PMA Approved Physio-Stim® bone growth stimulator (P850007 and P850007/S18).

VI. ALTERNATIVE PRACTICES OR PROCEDURES

Conventional adjunctive procedures for cervical fusion surgery include the standard of care, which is at the physician's discretion, but generally includes the following: a hospital stay of 1-3 days, appropriate medication for pain, use of a cervical collar for 1-2 weeks and appropriate levels of physical therapy with follow-up examinations and x-rays by the physician. There is currently no other commercially available adjunctive treatment for the cervical spine after fusion surgery.

VII. MARKETING HISTORY

The Cervical-Stim is marketed and commercially distributed within the European Union. The Cervical-Stim has not been withdrawn from marketing for any reason relating to the safety and effectiveness of the device.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

In a clinical study of 323 subjects in which subjects received either treatment with the Cervical-Stim device (n=163) or the standard of care (n=160) the adverse events listed in Table 1 were reported:

Table 1: Adverse Events Reported at 6 Months by Treatment Group				
	Control Group (n=160)		Cervical-Stim Group (n=163)	
Adverse Event	# (%) of Events	# (%)[1] of subjects experiencing the event	# (%) of Events*	# (%)[1] of subjects experiencing the event
Increased Neck Pain	10 (14.9)	9(5.6)	16(17.8)	15(9.2)
Shoulder/Arm Pain	10(14.9)	9(5.6)	16(17.8)	16(9.8)
Re-Injury to Cervical Spine	10(14.9)	8(5.0)	9(10.0)	9(5.5)
Adjacent level pathology	3(4.5)	3(1.9)	8(8.8)	8(4.9)
Surgical Complications	2(3.0)	2(1.3)	7(7.7)	5(3.1)
LBP/Lumbar pathology	8(11.9)	8(5.0)	5(5.5)	5(3.1)
Trauma/Injury(not cervical)	2(3.0)	2(1.3)	5(5.5)	4(2.5)
Numbness/Tingling	6(8.9)	6(3.8)	4(4.4)	4(2.5)
Headache/Migraine	2(3.0)	2(1.3)	4(4.4)	4(2.5)
Nonspecific/Unrelated Pain	2(3.0)	2(1.3)	3(3.3)	3(1.8)
Nausea	0	0	2(2.2)	2(1.2)
Dizziness/Vertigo	2(3.0)	2(1.3)	1(1.1)	1(0.6)
Rash/Discoloration	0	0	1(1.1)	1(0.6)
Rapid/Irregular Heartbeat	0	0	1(1.1)	1(0.6)
Shortness of Breath	0	0	1(1.1)	1(0.6)
Ringing in Ears	0	0	1(1.1)	1(0.6)
Neurologic Symptom/Stroke	1(1.5)	1(0.6)	1(1.1)	1(0.6)
Lump in Throat	0	0	1(1.1)	1(0.6)
Diagnosis of Diabetes	0	0	1(1.1)	1(0.6)
Diagnosis of Breast Cancer	0	0	1(1.1)	1(0.6)
Seizure	0	0	1(1.1)	1(0.6)
Death, Unrelated	0	0	1(1.1)	1(0.6)
Tenderness	1(1.5)	1(0.6)	0	0
Screw Broken	1(1.5)	1(0.6)	0	0
Graft Collapse	1(1.5)	1(0.6)	0	0
Carpal Tunnel Syndrome	2(3.0)	2(1.3)	0	0
Choking Sensation	1(1.5)	1(0.6)	0	0
Cardiac Symptoms	1(1.5)	1(0.6)	0	0
Nephrotic Syndrome	1(1.5)	1(0.6)	0	0
Suicide Attempt	1(1.5)	1(0.6)	0	0
TOTAL	**67**	**47[2]**	**90**	**58[2]**

[1] % expressed as number of subjects experiencing the event / total number of subjects in the group.

[2] Some subjects experienced multiple adverse events.

*There were several adverse events that were more frequently observed in the Cervical-Stim group than in the control group. Given the types of events, it is unlikely that these adverse events are related to the treatment.

Safety data obtained between the six-month visit and the final contact with each subject indicated that 57 adverse events were experienced by a total of 51 subjects

between both groups. The number of subjects who experienced one or more adverse events is similar in the two groups. None of the adverse events reported between the six-month visit and the final contact were severe and are similar to those reported at six months.

IX. SUMMARY OF PRECLINICAL STUDIES

ELECTRICAL SAFETY AND ELECTROMAGNETIC COMPATIBILITY

The Cervical-Stim was subjected to testing for electrical safety and electromagnetic compatibility by an independent laboratory. The Cervical-Stim was found to be fully compliant with EN 60601-1 for medical electric equipment and general requirements for safety and with EN 60601-1-2 for radiated emissions and electrostatic discharge.

BIOCOMPATIBILITY

The Cervical-Stim is an external device and has only localized, short term contact with skin. Users are instructed to wear clothing under the device strap to avoid direct skin contact. The transducer is covered in nylon with polyester seam binding and the control unit is made from ABS plastic. These materials are commonly used in consumer goods and no additional biocompatibility testing was required.

SOFTWARE VALIDATION

The Cervical-Stim is a software controlled medical device. It contains an embedded, one time programmable operating software. The operating software provides the following functions: treatment signal, self-test diagnostics, compliance data and user interface. The Cervical-Stim treatment signal is identical to the Physio-Stim treatment signal, therefore the software information was submitted for FDA review in the original clearance for the Physio-Stim (P850007). The software validation results show that the software meets the software requirements specifications and that the device performs as intended meeting all device specifications. A summary of these results are found in the Summary of Safety and Effectiveness Data for P850007.

LABORATORY AND ANIMAL STUDIES

The PEMF signal produced by the Cervical-Stim is the same signal as that of the commercially available Physio-Stim. The signal has been subjected to biological testing in cell level studies and in vivo animal studies and those results were submitted for FDA review in the original clearance for the Physio-Stim (P850007). A summary of these results are found in the Summary of Safety and Effectiveness Data for P850007.

X. SUMMARY OF CLINICAL STUDIES

Study Design

The Cervical-Stim clinical study was a controlled, randomized, parallel group study of 323 high-risk (smokers, multi-level or both and allograft) adult subjects with radiographic evidence of compressed cervical nerve roots and symptomatic radiculopathy. The purpose of the study was to evaluate the safety and effectiveness of the PEMF Cervical-Stim device as an adjunct for high risk patients who undergo cervical fusion surgery. All subjects underwent anterior cervical discectomy and

fusion using the Smith Robinson technique with the Atlantis Plate. Subjects were randomly assigned to either the control group (standard treatment, n=160) or the treatment group (standard treatment plus the Cervical-Stim, n=163). Standard treatment was at the physician's discretion but typically included the standard hospital stay, use of a soft cervical collar, appropriate medications, and physical therapy.

Subjects who met the following inclusion and exclusion criteria were eligible for participation in the study:

Inclusion Criteria
Adult male or female, 18-75 years old with radiographic evidence of compressed cervical nerve root(s), symptomatic radiculopathy, pain of 5 or greater on the visual analog scale (VAS) and/or any muscle weakness or, primary cervical spinal fusion performed using the Smith-Robinson technique with allograft bone and an anterior cervical plate. The fusion procedure must have been either multi-level (>1 fusion level) or the subject was a smoker (one pack/day or more) or both; and signed informed consent.

Exclusion Criteria:
Traumatic cervical injury, posterior approach or revision fusion, autograft or bone substitute materials for graft source, history of vascular migraine headache or prone to uncontrolled seizures or epilepsy (controlled or uncontrolled) or any neurological diseases or injury; depressed immune system, regional conditions (Spondylitis, Paget's disease, rheumatoid arthritis), infection (systemic or local) within 2 weeks prior to surgery, systemic conditions (cancer, cardiac arrhythmia, thyroid disease, uncontrolled diabetes mellitus, renal disease/dysfunction, chronic steroid use, or other conditions that may have affected bone metabolism), cardiac pacemakers, defibrillators, dorsal column stimulators, hearing aids, cochlear prostheses and cranial stimulators, subjects who were pregnant, nursing or had planned to become pregnant within 12 months, subjects that had participated in other clinical studies within the last 12 months, or had mental or physical conditions which may have precluded compliance with physician instructions.

Evaluation and Follow-Up
Follow-up visits were to have been performed at Months 1, 2, 3, 6 and 12 and annually thereafter until the last subject enrolled reached 12 months.

Device Usage
Subjects assigned to the treatment group (Cervical-Stim) were instructed to wear the device for 4 hours per day for a minimum of three months postoperative. Surgeons could, at their discretion, extend the Cervical-Stim treatment up to six months postoperative.

Demographic Data
The subjects in this study had a mean age of 46.8 years (range 24 to 73 years). Of the 323 subjects, 148 (45.8%) were female and 175 (54.2%) were male. Three hundred

one (93.2%) were Caucasian, while 17 (5.3%) were African American and 5 (1.6%) were Hispanic. One hundred fifty nine (49.2%) were nonsmokers and 164 were smokers (50.8%). Demographic data is summarized in Table 2.

Table 2: Baseline Demographic Characteristics

Variables	Number of Subjects (N = 323)	Control (n = 160)	Cervical-Stim (n = 163)	P-value[1]
Age (years)				
Mean	46.8	46.7	46.9	0.846
Range	24 – 73	26 – 72	24-73	
SD	9.3	9.2	9.4	
Gender				
Female	148 (45.8%)	75 (46.9%)	73 (44.8%)	0.706
Male	175 (54.2%)	85 (53.1%)	90 (55.2%)	
Race				
Caucasian	301 (93.2%)	150 (93.8%)	151 (92.6%)	0.703
African-American	17 (5.3%)	7 (4.4%)	10 (6.1%)	
Hispanic	5 (1.6%)	3 (1.9%)	2 (1.2%)	
Asian	0	-	-	
Others	0	-	-	
Smoking Status				
Nonsmoking	159 (49.2%)	79 (49.4%)	80 (49.1%)	0.958
Smoking				

1. P-values of comparison tests between treatment groups using Student's t-test for numerical variables and Pearson x^2 test for categorical variables.

Data Analysis and Results

The primary effectiveness endpoint was the increase in frequency of cervical fusion success by six months postoperatively as assessed by radiographic evidence. Secondary endpoints were neurological function, VAS pain assessment, and Neck Disability Index. Safety was assessed by the frequency and severity of adverse events.

Fusion was assessed by Radiographs at each visit:

Radiographic Fusion was defined as ≥ 50% bony bridging on both the superior and inferior graft interfaces between adjacent vertebral bodies AND ≤ 4° angulation (motion) between adjacent fused vertebrae on flexion/extension lateral films AND absence of radiolucency.

Radiographic Non-Fusion was defined as < 50% bony bridging at either the superior or inferior graft interface OR > 4° angulation (motion) between adjacent fused vertebrae on flexion/extension lateral films OR presence of radiolucency.

For purposes of device evaluation, all films were scanned into a central database and reviewed by two independent, blinded orthopedic surgeons and a blinded, independent radiologist following completion of the entire study. Films were viewed and scored using a common protocol. All films at each time point were evaluated for amount of radiolucency, bony bridging, and degree of motion evidenced on the flexion/extension cervical spine films. A software program was used to calculate motion. Results obtained in this fashion were reviewed and verified by the reviewing orthopedic surgeons. The radiologist's diagnosis was considered definitive in the case of a disagreement between the two orthopedic surgeons.

Effectiveness Results

Of the 323 subjects who were randomized and received surgery, 240 were evaluable for the effectiveness analysis (Cervical-Stim treatment group, n=122; control group, n=118). Subjects were deemed unevaluable for the following reasons: non-existent or non-readable x-rays, subject non-compliance, protocol violations (inclusion criteria), graft collapse, broken internal hardware, early study exits due to minor adverse experiences, and one suicide. The success or failure of these subjects is not known. These unavailable data could positively or negatively affect the overall success of the study. In order to assess the impact of the missing data, sensitivity analyses were performed. These included last observation carried forward, and all missing data imputed as non-fusion. Both of these analyses showed that the results at six months were still statistically significantly different in favor of the Cervical-Stim group.

In addition, the baseline demographic data from the evaluable population was compared to the demographic data of the missing subjects. The results of this analysis indicated there were no significant differences between the evaluable subjects and the non-evaluable subjects in 14 study variables including key demographics and clinical parameters.

Primary Effectiveness Endpoint

The primary effectiveness endpoint was evidence of radiographic fusion at the 6 month time point postoperative. At the six month time point, 102 of the 122 evaluable subjects (84%) in the Cervical-Stim treatment group were judged to be fused versus 81 of the 118 evaluable subjects (69%) in the control group (p=0.0065). Fusion outcomes are summarized on Table 3.

Table 3: Comparison of Radiographic Fusion Outcomes at Six Months

Treatment Group	Number of Subjects	Number of Subjects Fused	Fusion Rate (%)
Control	118	81	68.64
Cervical-Stim	122	102	83.61

These data show that for patients undergoing cervical fusion surgery, patients treated adjunctively with the Cervical-Stim experienced an increase in the frequency of radiographic fusion at six months when compared to the control group.

An additional analysis was performed to allow for the differences between the Cervical-Stim treatment group and the control group with respect to demographic characteristics (gender, age, diagnosis) and risk status (smoking, multilevel). The overall radiographic fusion rate at 6 months postoperative in the Cervical-Stim group remained statistically significant after adjustment for each of these variables.

Long term follow-up (12 Months) showed no statistical difference between the two groups with respect to radiographic fusion. As summarized in Table 4, one hundred sixteen of the 125 evaluable subjects (92.8%) in the Cervical-Stim treatment group were judged to be fused at the long term final endpoint, while 104 of the 120 evaluable subjects (86.7%) in the control group were judged to be fused.

Table 4: Overall Radiographic Fusion Outcomes at 12 Months

Treatment Group	Number of Subjects	Number of Subjects Fused	Fusion Rate (%)
Control	120	104	86.67
Cervical-Stim	125	116	92.80

Note: The differences in long-term success rates between treatment groups is not statistically significant per Pearson x^2 test with the available sample size ($x^2 = 2.5136$, $p = 0.1129$).

Secondary Effectiveness Endpoints

Secondary endpoints evaluated changes in clinical symptoms. A "clinical success" with regard to symptoms was defined as no worsening in neurological function, an improvement in VAS pain assessment, and no worsening in Neck Disability Index. A "clinical failure" with regard to symptoms was defined as failure for any one of these criteria. There was no statistically significant difference between the two groups with respect to the percent of subjects considered a "clinical success" at six months (p=0.8456), or at 12 months (p=0.1129).

Safety

The adverse events observed in this study are described in Table 1 (Adverse Events Report at 6 Months by Treatment Group). At six months, the numbers of subjects who experienced one or more adverse events is similar in the two groups. A total of fourteen severe events were reported in thirteen subjects; nine of the subjects were in the Cervical-Stim treatment group and five subjects were in the control group. These events included increased pain, shortness of breath, dizziness, unrelated trauma and injury, unrelated death, surgical complication, and adjacent level pathology. For the nine subjects in the Cervical-Stim treatment group, all severe adverse events were, in the judgment of the investigators, definitely or probably unrelated to the device.

Safety data obtained between the six-month visit and the final contact with each subject indicate that 57 adverse events were experienced by a total of 51 subjects between both groups. The number of subjects who experienced one or more adverse events is similar in the two groups. None of the adverse events reported between the six-month visit and the final contact were severe and are similar to those reported at six months.

XI. CONCLUSIONS DRAWN FROM THE STUDIES

The clinical data showing increased frequency of fusion at 6 months demonstrated reasonable assurance of effectiveness, especially considering the long history of use of PEMF as an adjunct to spinal fusion surgery and the low risk posed by use of the device. Safety was established by the low incidence and severity of adverse events.

XII. PANEL RECOMMENDATION

In accordance with the provisions of section 515(c)(2) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Orthopedic and Rehabilitation Devices Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XIII. CDRH DECISION

FDA issued an approval letter on December 23, 2004.

The applicants manufacturing facility was inspected and was found to be in compliance with the Quality System Regulation (21 CFR 820).

XIV. APPROVAL SPECIFICATIONS

Directions for Use: See the labeling.

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

Post Approval Requirements and Restrictions: See approval order.