

Petition

I. Specification of the Type of Device [860.123(a)(1)]

The petitioner seeks to reclassify the Non-invasive Bone Growth Simulator from Class III (Premarket Approval) to Class II (Special Controls) due to the ability of the General and Special Controls to provide a reasonable assurance of safety and effectiveness. This petition also presents evidence that the devices that would be reclassified as a result of this action are themselves safe and effective for their intended use.

Section I of the petition:

- presents a proposed classification regulation;
- describes the generic type of device covered by this petition, including technological characteristics; and,
- identifies the commercially marketed devices and one new device manufactured by the petitioner that would be reclassified from Class III to Class II as result of this petition.

A. Proposed Classification Regulation

The Non-invasive Bone Growth Simulator is a post-Amendments device identified by the product code LOF in the Physical Medicine medical specialty. A proposed classification regulation follows. It identifies the device name, intended use, and technological features of this generic type of device. This proposed classification regulation describes only those technological characteristics that are needed for a specific device to fit within the type. There may be numerous variations in other technological characteristics in the immediate devices to be reclassified and in any new device found to be substantially equivalent.

§ 8XX.XXXX Non-invasive Bone Growth Simulator

(a) *Identification.* A Non-invasive Bone Growth Simulator provides stimulation through electrical and/or magnetic fields to promote osteogenesis to facilitate the healing of nonunion fractures and lumbar spinal fusions. The stimulation may be delivered through capacitive coupling with electrodes placed directly over the treatment site, through pulsed electromagnetic fields (PEMF) with treatment coils placed into a brace or over a cast at the treatment site, or through combined magnetic fields with treatment coils applied to the site. The device is intended for use for 1) the treatment of established nonunion fractures acquired secondary to trauma (excluding vertebrae and flat bone), and 2) as an adjunct to the treatment of lumbar spinal fusion surgery for one or two levels. The device consists of an output waveform generator, either battery-powered or AC-powered, a user interface with visual and/or

audible alarms, and electrodes or coils to deliver the stimulation. Accessories may include additional electrodes or coils, electrode accessories, electrode gel, positioning guides, connectors, batteries, battery chargers, belts and/or belt clips, carrying case, physician test meter, and others.

(b) *Classification.* Class II (Special Controls). Non-invasive Bone Growth Stimulators must comply with the following special controls:

- (i) FDA Guidance Document “Class II Special Controls Guidance Document: Contents of Premarket Notifications [510(k)s] for Non-invasive Bone Growth Stimulators”;
- (ii) 21 CFR Part 898 Performance Standards for Electrode Lead Wires and Patient Cables;
- (iii) ISO 10993: Biological Evaluation of Medical Devices: Part 1: Evaluation and Testing;
- (iv) IEC 60601-1: Medical Electrical Equipment, Part 1: General Requirements for Safety;
- (v) IEC 60601-1-2: Electromagnetic Compatibility for Medical Equipment: Requirements and Tests; and,
- (vi) Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices.

As is implied by the language of the proposed classification regulation, this petition proposes the development of a guidance document for the Non-invasive Bone Growth Stimulator as one of the Special Controls. **Attachment I** provides a draft of this guidance document. It addresses issues associated with device design, labeling requirements, and the recommended preclinical, animal and clinical testing requirements based upon the product’s design.

B. Attributes of this Generic Type of Device

The petitioner seeks to reclassify a generic type of post-Amendments device, the Non-invasive Bone Growth Stimulator. A generic type of device is defined in 21 CFR § 860.3(i) as follows:

“...a grouping of devices that do not differ significantly in purpose, design, materials, energy source, function, or any other feature related to safety and effectiveness, and for which similar regulatory controls are sufficient to provide reasonable assurance of safety and effectiveness.”

A further description of the attributes of this proposed generic type of device follows. The petitioner has proposed a classification regulation which limits the generic type of device to three fundamental, overlapping technologies because of the similarities in the device design, use, principles of operation, and the ability of

the same Special Controls to provide a reasonable assurance of safety and effectiveness.

1. Purpose and Intended Use

The purpose of the devices within this proposed generic type is the same; namely, to provide stimulation through electrical and/or magnetic fields to promote osteogenesis to facilitate the healing of nonunion fractures and spinal fusions.

2. Design and Operation

All devices within this proposed generic type share certain design characteristics, including a non-invasive design where externally applied coils (sometimes referred to as transducers) or electrodes (sometimes referred to as capacitor plates) are used to deliver stimulation, either electrical or magnetic, to the immediate treatment area.

All devices within this type rely upon an electrical component to produce an output waveform that is delivered to the patient through either coils or electrodes.

The devices also incorporate internal means to monitor the output waveform and delivery of treatment, and to provide visual and/or audible alarms to alert the user of improper device function.

3. Function

Devices within this proposed generic type function by generating either electrical and/or magnetic fields within the body to induce osteogenesis and facilitate healing. The devices rely upon three fundamental technologies to produce these electrical and/or magnetic fields: 1) capacitive coupling, 2) pulsed electromagnetic fields and 3) combined magnetic fields. A summary of each technology follows, including those characteristics relevant to its performance.

Capacitive Coupling - Capacitive coupling produces electrical fields within the tissue between the electrodes. The induced field is driven by an oscillating electrical current, which combines low amperage, very low voltage and high frequency (Brighton and Pollack, 1985). For these devices, “coupling” refers to the transfer of the output signal from the source to the fracture site, or the transfer of power from one system to another. The coupling between the signal generator and the fracture site is vectorally capacitive, thus leading to the term “capacitive coupling.”

In capacitive coupling, the electrical field that is produced in the tissue between the electrodes depends upon the voltage drop across the electrode-dermal junction and the frequency of the signal. Typically, a dielectric material is interposed between the metallic electrodes and the skin, resulting in a large drop in voltage across the dielectric material. For Non-invasive Bone Growth Stimulators, the dielectric properties of the skin can be used at 60 kilohertz to avoid this voltage drop, thereby permitting the use of lower voltage amplitudes. When a conductive gel is placed between the electrode and the skin, the voltage drop across the electrode-dermal junction is even further reduced, resulting in an increase in the electrical field within the tissue for any given output.

In capacitive coupling, a tissue electrical field of 0.1 to 20 mV/cm (current density of 300 $\mu\text{A}/\text{cm}^2$) is desired to promote osteogenesis and facilitate the healing of nonunion fractures and spinal fusion (Nelson et al., 2003).

Pulsed Electromagnetic Field (PEMF) – PEMF was originally developed to simulate in magnitude and time course the endogenous electrical fields produced *in vivo* in response to strain. The device converts electrical pulses into PEMFs through the use of magnetic coils to produce time varying magnetic and electrical fields within the body between two opposing treatment coils. The two opposing treatment coils are positioned facing each other at 180 degrees with the cast or extremity between them. The pulsing electromagnetic fields (B fields) expand outward at right angles from the faces of the coils. The distance between the coils should be equal to or less than the diameter of the coil to produce reasonably uniform B fields.

The pulsed electrical current results in a magnetic flux density of approximately 0.1 to 18 gauss (G) in the form of a pulse train with a 15 Hz or sinusoidal 76 Hz frequency (Nelson et al., 2003). A pulse train is a rapid sequence, typically consisting of 20, 220 μsecond (μsec) repeating spikes. PEMF devices can also deliver a modified output of an average of 790 mG field of a burst of 21, 260 μsec pulses repeated at 15 Hz. This modified output reduces energy requirements, allowing the modified PEMF devices to be battery-operated.

A tissue electrical field of approximately 1.5 mV/cm and 10 $\mu\text{A}/\text{cm}^2$ at the nonunion site for the PEMF device or 4 mV/cm peak to peak for the modified PEMF devices is desired to promote osteogenesis (Bassett and Pollack, 1985; Nelson et al., 2003).

Combined Magnetic Field: Combined magnetic field stimulators use both dynamic and static low energy magnetic fields to induce bone growth. The dynamic magnetic field is superimposed upon the static

magnetic field. A pair of copper wire coils converts the electrical signal into magnetic fields. The coils are positioned facing each other and are arranged so that a uniform magnetic field is produced between them. The coils are provided in a brace or housing unit designed for an anatomical location. A magnetic field sensor may be located between the coils to monitor the static field to maintain it at 200 mG. The dynamic field is a 76.6 Hz sinusoidal 40 μ T (400 mG) peak to peak AC magnetic field superimposed on a 20 μ T direct current (DC) static magnetic field.

4. Output Waveform

Table 1 summarizes the established waveform and tissue effects for each technology.

Table 1: Summary of the Waveform and Tissue Effects for Each of the Three Technologies for Non-invasive Bone Growth Stimulators

Technology	Waveform	Tissue Electrical Field
Capacitive Coupling	60 kHz, 10 μ A (rms), 6 V peak to peak	0.1 to 20 mV/cm 300 μ A/cm ²
Pulsed Electromagnetic Fields	4.5 msec long bursts of 20, 220 μ sec 18 G pulses repeated at 15 Hz	1.5 mV/cm 10 μ A/cm ²
	790 mG field of a burst of 21, 260 μ sec pulses repeated at 15 Hz	4 mV/cm peak to peak
Combined Magnetic Fields	76.6 Hz sinusoidal 40 μ T (400 mG) peak to peak AC magnetic field superimposed on 20 μ T DC magnetic field	Magnetic field effect

Adapted from Nelson et al., 2003.

5. Operational Use

Products within this type are prescription devices, intended for use by the patient in a home environment. The physician typically prescribes the device for a patient either with a nonunion fracture or as an adjunct for lumbar spinal fusion.

The three technologies share many similar operational features. In all cases, a physician determines that the patient might benefit from using the device. A health care professional selects the appropriate device, and determines the electrode or coil position. A health care professional instructs the patient or primary care giver on the use and care of the device. The different technologies do have some slight variations in their use, such as duration of stimulation. The similarities and differences for each follow.

Capacitive Coupling – For nonunion fractures acquired secondary to trauma, two small openings are cut into the cast to allow for the application of the electrodes to deliver the stimulation to the fracture site. For lumbar spinal fusion, the electrode application sites are exposed. The health care professional initially positions the electrodes across the approximate site of the nonunion fracture or fusion, and moistens the electrode pads with gel before application. The patient or a primary care giver is provided instructions on how to care for the device, including how to replace the electrodes and electrode pads. The battery-operated stimulator is housed in a small, plastic case. The device is prescribed for use for 24 hours a day until healing occurs, or up to a maximum of 270 days (9 months). Electrodes typically last up to 1 week without requiring reapplication of the gel. When the electrode pads become dry during use, the device detects the loss of contact and triggers an alarm, indicating the need to remoisten the electrode pads with gel.

PEMF – The health care professional selects the appropriate positioning guide, block or brace for the patient depending upon the anatomical site of the fracture and patient size to properly position the treatment coils to deliver stimulation to the site. The health care professional initially positions the treatment coils and provides instructions to the patient or the primary care giver on how to use and care for the device. The PEMF devices require a standard domestic 110-volt alternating current power supply or a rechargeable battery. The modified PEMF devices operate from a 9-volt battery. PEMF devices are prescribed for use for approximately 10 hours per day and may be used up to 270 days (9 months). The modified PEMF devices are prescribed for use for 2-3 hours per day until healing occurs or up to 270 days (9 months).

Combined Magnetic Fields – The health care professional selects the appropriate positioning guide or brace for the patient depending upon the anatomical site of the fracture and patient size to properly position the treatment coils to deliver the stimulation to the site. The health care professional instructs the patient or primary care giver on how to use and care for the device. The brace also contains the electronics to generate the output signal and is battery-operated. The device is prescribed for use for 30 minutes a day until healing occurs or up to 270 days (9 months).

6. Materials

The electrodes and treatment coils must be constructed of conductive metals to deliver the stimulation to the treatment site and must be biocompatible for skin contact. Other device components with patient skin contact must also be biocompatible.

7. Energy Source

The devices may be either battery-operated (such as a 9 volt battery or rechargeable battery) or operated from a standard domestic 110-volt alternating current power supply. The power supply depends upon the energy source needed to generate the output waveform.

C. Devices Covered by the Reclassification Petition

The petitioner proposes that seven commercially available devices and one new device, manufactured by the petitioner, be reclassified as a result of this petition. The commercially available devices are all identified in the FDA PMA databases by the product code LOF - Non-invasive Bone Growth Simulator. Table 2 provides a summary of the devices which will be reclassified as a result of this petition and which could serve as predicate devices for future 510(k) submissions. The intended use for the Non-invasive Bone Growth Simulator provided in this petition represents a consensus of the specific indications for use for the commercially available devices with two exceptions.

First, one of the Non-invasive Bone Growth Stimulators listed under product code LOF in the FDA PMA database (P790002) includes the treatment of congenital pseudarthrosis. The petition seeks only to reclassify devices that promote osteogenesis at the endplates of a fracture created secondarily due to trauma (either accidental or surgical in nature). Congenital pseudarthrosis is a rare malformation, present at birth, whose etiology and treatment are not well known. It is believed to involve the failure of the ossification centers to unite during fetal development, subsequently causing a nonunion in the bone that is typically diagnosed either during infancy or during the first 2 years of life. Because of these etiological differences, the petitioner did not include this use in the reclassification effort.

Second, the petition excluded the use as an adjunct to cervical fusion surgery in patients at high risk for nonfusion to simplify the reclassification process. Only one device has recently been approved for this specific indication for use (P030034). Nonetheless, the same General and Special Controls for the Non-invasive Bone Growth Simulator identified in this petition would provide a reasonable assurance of device safety and effectiveness for use as an adjunct to cervical fusion surgery. For all uses, the device functions the same by providing stimulation through electrical and/or magnetic fields to promote osteogenesis to facilitate healing of a nonunion fracture site caused by trauma, either accidental or surgical in nature.

The reclassification petition specifically excluded two other products identified by unique product codes in the FDA databases because of the inability of the same Special Controls to provide a reasonable assurance of safety and effectiveness.

This petition excludes Invasive Bone Growth Stimulators identified by product code LOE because the inherent risks of these devices are different due to their invasive nature and would, consequently, require the application of different Special Controls. The petition also excludes Non-invasive Bone Growth Stimulators identified by the product code LPQ – Stimulator, Ultrasound and Muscle, For Use Other Than Applying Therapeutic Deep Heat. The devices sought for reclassification use a common mechanism of action; they deliver electrical and/or magnetic fields to cause a piezoelectric effect. Ultrasound devices use sonic waves to produce a mechanical stress, resulting in a piezoelectric effect - a different mechanism of action. Based upon the different mechanisms of action and technological features, the same Special Controls proposed in this petition for Non-invasive Bone Growth Stimulators identified by product code LOF would likely not be sufficient for products identified by product code LPQ.

Table 2: Summary of the Non-invasive Bone Growth Stimulators for Reclassification

Manufacturer	Trade Name	Intended Use	Stimulation Type	Output Waveform Parameters	Duration of Use
Bioelectron	OrthoPak® Bone Growth Stimulator	Treatment of an established nonunion secondary to trauma	Capacitive Coupling	60 kHz, 3 to 6.3 Volts (V) peak to peak	24 hours per day (hrs/day) Up to 200 days
Bioelectron	SpinalPak® Fusion Stimulator	Adjunct electrical treatment to primary lumbar spinal fusion surgery at one or two levels	Capacitive Coupling	60 kHz, 3 to 6.3 V peak to peak	24 hrs/day Up to 270 days
Electro-Biology (EBI), L.P.	EBI Bone Healing System®	Treatment of fracture nonunions, failed fusion and congenital pseudarthroses	PEMF	2.5 msec long bursts of 250 to 400 µsec 20 G pulses repeated at 5-20 Hz	10 hrs/day Up to healing
Orthofix	Physio-Stim® Lite	Treatment of established nonunion acquired secondary to trauma	PEMF	260 µsec, 20 G pulses repeated at 15 Hz	Minimum of 3 hrs/day Up to 180 days
Orthofix	Spinal-Stim® Lite	Fusion adjunct to increase the probability of fusion success and as a nonoperative treatment of failed fusion surgery	PEMF	260 µsec, 20 G pulses repeated at 15 Hz	Minimum of 2 hrs/day Up to 270 days
OrthoLogic	OrthoLogic™ 1000	Treatment of an established nonunion secondary to trauma	Combined Magnetic Fields	76.6 Hz sinusoidal 40 µT (400 mG) peak to peak AC magnetic field superimposed on 20 µT DC magnetic field	30 minutes per day (min/day) Up to 270 days
OrthoLogic	SpinaLogic™	Adjunct treatment to primary lumbar spinal fusion surgery for one or two levels	Combined Magnetic Fields	76.6 Hz sinusoidal 40 µT (400 mG) peak to peak AC magnetic field superimposed on 20 µT DC magnetic field	30 min/day Up to 270 days
RS Medical	To be determined	Treatment of established nonunion fractures acquired secondary to trauma and as an adjunct to the treatment of lumbar spinal fusion surgery	Capacitive Coupling	60 kHz, 3 to 6.3 V peak to peak	24 hrs/day Up to 270 days

II. Statement of Requested Action [860.123(a)(2)]

Although electrical stimulation has been known to induce osteogenesis since the 1950s, the Non-invasive Bone Growth Stimulator is a post-Amendments device; i.e., the Agency determined that such devices did not fit within any pre-Amendments type of device that the Agency had identified during the pre-Amendments device classification process. As a result, this type of device was automatically classified by Section 513(f)(1) of the Food, Drug, and Cosmetic Act (FDCA) into Class III, and no specific device within the type can be marketed unless it has received premarket approval, or unless this type of device is reclassified into Class I or II.

The automatic classification of a post-Amendments device into Class III under 513(f) was meant to provide a temporary classification for a new device unless the device in question conformed to the definition of a Class III device found in Section 513(a)(1)(C) of the FDCA. Falling outside the definition of an existing type of device, or being not substantially equivalent to a device within an existing type, does not mean that a device poses risks, or safety and effectiveness questions, worthy of FDA's highest regulatory class. This petition presents evidence that the Non-invasive Bone Growth Stimulator does not conform to the criteria for Class III describe in Section 513(a)(1)(C) of the FDCA, but conforms to the criteria described in 513(a)(1)(B) for Class II devices.

Given that the device was classified under Section 513(f)(1), it is eligible for reclassification under Section 513(f)(2). Section 513(f)(2), however, is reserved for petitions submitted by persons who have previously submitted 510(k)s for a device within the type to be reclassified. [Please refer to Section 513(f)(2) of the FDCA and 21 CFR §860.134(b)(1).]

In this case, the petitioner has not submitted a 510(k) for any device within the type to be reclassified. Thus, this petition is being submitted in accordance with Section 513(e) of the FDCA and 21 CFR § 860.130 and § 860.123. Section 513(e) of the FDCA allows any interested person to petition for the reclassification of any type of device based upon new information respecting the device. Consequently, the petitioner, in the absence of having submitted a 510(k), is able to use this Section of the FDCA to seek the reclassification of Non-invasive Bone Growth Stimulators, provided there is new information. The "new information" provided in this petition is described in Section IX, entitled "Summary of the New Information."

The petitioner is aware that reclassification under Section 513(e) of the FDCA requires "rulemaking" by FDA. The petitioner is also aware that the Agency may ask for a recommendation from a classification panel respecting this proposed action. The petitioner believes the rule making process, with or without advisory panel involvement, will be advantageous for all parties interested in the proposed action. There are numerous approved premarket approval applications for specific devices within this type, and a number of the companies that hold such approvals presumably will have an interest in the reclassification process. The rule making process, with or without advisory panel

involvement, will ensure that all interested persons have the appropriate opportunity to provide comments on any action considered by FDA.

Table 2 in Section I.C identifies those products approved by FDA under the product code LOF that are included in this proposed reclassification action.

III. Supplemental Data Sheet [21 CFR § 860.123(a)(3)]

Attachment 2 provides a completed Supplemental Data Sheet as specified in 21 CFR § 860.123 (a)(3).

IV. Classification Questionnaire [21 CFR § 860.123(a)(4)]

Attachment 3 provides a completed Classification Questionnaire as specified in 21 CFR § 860.123 (a)(4).

V. Statement for the Reasons for Disagreement with the Current Classification [21 CFR § 860.123(a)(5)]

The Non-invasive Bone Growth Stimulator is a post-Amendments device; i.e., the Agency determined that this device did not fit within any pre-Amendments type of device, resulting in the automatic classification of these devices as Class III by Section 513(f)(1) of the FDCA. As noted above, the automatic classification of a post-Amendments device into Class III under 513(f) was meant to provide a temporary classification for a new device unless the device in question conforms to the definition of a Class III device found in Section 513(a)(1)(C) of the FDCA. Section 513(a)(1)(C) of the FDCA defines a Class III medical device as follows:

*“(C) Class III, PREMARKET APPROVAL. —A device which because—
(i) it (I) cannot be classified as a class I device because insufficient information exists to determine that the application of general controls are sufficient to provide reasonable assurance of the safety and effectiveness of the device, and (II) cannot be classified as a class II device because insufficient information exists to determine that the special controls described in subparagraph (B) would provide reasonable assurance of its safety and effectiveness, and
(ii)(I) is purported or represented to be for a use in supporting or sustaining human life or for a use which is of substantial importance in preventing impairment of human health, or
(II) presents a potential unreasonable risk of illness or injury, is to be subject, in accordance with section 515, to premarket approval to provide reasonable assurance of its safety and effectiveness.”*

This petition presents evidence that the Non-invasive Bone Growth Stimulator does not conform to either of the criterion for Class III described in Section 513(a)(1)(C) of the FDCA, but conforms to the criteria described in 513(a)(1)(B) for Class II devices.

As quoted above in its statutory format, there are two criteria for retaining a post-Amendments device in Class III.

One criterion is that the device presents a potential unreasonable risk of illness or injury. Published literature clearly demonstrates that devices within this type do not pose an unreasonable risk of illness or injury. Section VI.C of this petition identifies the type and expected occurrence of the risks posed by the device. Information from well-controlled clinical studies and the Medical Device Reporting database show that the adverse events associated with these devices are minor and transient, and can be addressed by either terminating or modifying usage of the device. The risks are not “unreasonable,” by any standard.

The second criterion is that the device is life sustaining or life supporting or of substantial importance in preventing impairment to health, and there is insufficient information to determine that the application of General and Special Controls are sufficient to provide reasonable assurance of the safety and effectiveness of the device.

This device promotes osteogenesis to facilitate the healing of nonunion fractures and lumbar spinal fusions. It does not support or sustain human life. Given that nonunion fractures and unsuccessful spinal fusions are associated with continued patient disabilities, and this device treats such conditions, it can be considered of substantial importance in preventing impairment of human health. But a device that is of substantial importance in preventing the impairment of health is meant to be in Class III only if the application of Special and General Controls will not provide for provide for reasonable assurance of its safety and effectiveness; and the extensive preclinical and clinical research with the Non-invasive Bone Growth Stimulator has demonstrated that a combination of General and Special Controls will provide sufficient regulatory oversight to provide a reasonable assurance of safety and effectiveness. Section VI.D of this petition details how the application of General and Special Controls, such as a guidance document; conformance to recognized safety standards (IEC 60601-1 and 60601-1-2); compliance with the Quality System Regulation (21 CFR Part 820); and, conformance to already established performance standards for electrodes and cables (21 CFR Part 898) will provide for a reasonable assurance of safety and effectiveness.

VI. Statement of the Reasons for How the New Class Will Provide Reasonable Assurance of Safety and Effectiveness [21 CFR § 860.123(a)(6)]

The petitioner contends that the Non-invasive Bone Growth Stimulator should be in Class II. The criteria for Class II appear in Section 513(a)(1)(B) of the FDCA:

“(B) Class II, Special Controls.—A device which cannot be classified as a class I device because the general controls by themselves are insufficient to provide reasonable assurance of the safety and effectiveness of the device, and for which there is sufficient information to establish special controls to provide such assurance, including the promulgation of

performance standards, postmarket surveillance, patient registries, development and dissemination of guidelines (including guidelines for the submission of clinical data in premarket notification submissions in accordance with section 510(k)), recommendations, and other appropriate actions as the Secretary deems necessary to provide such assurance. For a device that is purported or represented to be for a use in supporting or sustaining human life, the Secretary shall examine and identify the special controls, if any, that are necessary to provide adequate assurance of safety and effectiveness and describe how such controls provide such assurance.”

Section VI.D of this petition details how the application of General and Special Controls, such as a guidance document; conformance to recognized safety standards (IEC 60601-1 and 60601-1-2); compliance with the Quality System Regulation (21 CFR Part 820); and, conformance to already established performance standards for electrodes and cables (21 CFR Part 898) will provide for a reasonable assurance of safety and effectiveness. Thus, this type of device should be in Class II.

In order to evaluate whether the Non-invasive Bone Growth Stimulator presents an unreasonable risk (Section VI.D), and to identify the failure modes to determine if General and Special Controls will provide a reasonable assurance of safety and effectiveness (Section VI.D), the petitioner conducted an extensive search of the published literature, using the PubMed database. This published literature includes reports of well-controlled and partially-controlled clinical studies meeting the definition of valid, scientific evidence (21 CFR § 860.7).

This literature review resulted in the identification of over 50 articles. The identified articles are being included in support of this reclassification petition. **Attachment 4** describes the methodology for obtaining the aforementioned literature articles. **Attachments 5, 6 and 8** provide a copy of each article.

The petitioner is aware that it cannot rely upon data submitted in the premarket approval (PMA) applications related to devices within this type, including the Summary of Safety and Effectiveness (SSE) published with each PMA, for purposes of supporting this reclassification. Nonetheless, there are numerous published literature articles on the currently approved devices which provide data regarding the risks and benefits of these devices. Sometimes these publications result from the same clinical studies which supported approval of the device, and sometimes they resulted from different clinical studies. It is these data published in the literature which support this petition.

A. Summary of Risks and Off-setting Special Controls

The risks associated with this type of device include electrical shock, burn, skin irritation and/or allergic reaction, and inconsistent or ineffective treatment. These are described in more detail in Section VI.C. The off-setting Special Controls include Design Controls (21 CFR § 820.3), software verification and validation,

labeling requirements (21 CFR § 801), conformance with FDA guidance documents, and conformance with IEC, ISO and FDA standards. These are described in more detail in Section VI.D.

B. Detailed Description of the Benefits/Effectiveness with Supporting Data

The literature available on the Non-invasive Bone Growth Stimulator is comprehensive and describes the benefits of its use for both nonunion fractures and as an adjunct to spinal fusion. This literature demonstrates that devices within this type facilitate osteogenesis and promote bone growth through the application of electrical and/or magnetic fields.

Following a discussion of how the literature review was conducted and the outcome of the process, the literature review is organized into two sections: the benefits of stimulation for nonunions and the benefits of stimulation for lumbar spinal fusion.

In summary, over 6,700 patients have been evaluated in these studies combined. The majority of these studies (29) are prospective in nature and demonstrate that stimulation results in osteogenesis and bone growth at the fracture site created by trauma (either accidental or surgical in nature). These findings are supported by the retrospective studies as well. Evidence from the clinical studies presented here demonstrates that: the devices are effective for a variety of fracture sites and locations; devices using different output waveforms are effective at promoting osteogenesis and bone growth; and, devices are effective in patients who have suffered long-term disability and for whom other treatments have not been successful.

1. Literature Search Details

The literature searches conducted for this reclassification petition resulted ultimately in the identification of 56 articles for which detailed review and discussion are provided. Forty-two of these articles are included in the discussion of effectiveness information in this section of the petition. The remainder of the unique articles were obtained from information associated with legally marketed Non-invasive Bone Growth Stimulators, and are discussed later in Section VII of this petition.

Initially, 12 journal articles were selected by the petitioner based upon their relevance to the therapeutic applications of capacitive coupling or pulsed electromagnetic field bone growth stimulators. Subsequently, a search of the PubMed database, a service of the National Library of Medicine which provides access to over 12 million MEDLINE citations and life science journals, was conducted using key words obtained from the initial 12 articles. The following combinations of keywords were used in this search:

- Adverse Event
- Adverse Events
- Bone Graft
- Bone Graft Stimulator
- Bone Growth
- Bone Growth Stimulator
- Capacitive Coupling
- Capacitively Coupled
- Clinical
- Electrical Stimulation
- Fusion
- PEMF
- Pulsed Electromagnetic Field
- Pulsed Electromagnetic Fields
- Safety
- Stimulation
- Study
- Studies
- Trial
- Trials

Searches were conducted for the time period ranging from 1950 through mid-2004. A total of 2,289 non-duplicated citations were identified from the search and all 12 initial articles were located among these. Initially, no limits were imposed on the search. Using ProCite and EndNote 7 bibliographic citation programs, the following Boolean filters were applied to limit the search:

Title = “combined magnetic AND Title= “spine”
OR (Title = “lumbar fusion” AND Title = “nonsurgical”
OR (Title = “capacitive coupl*”, “capacitively coupl*”, “pulsing
electromagnetic*”, “pulsed electromagnetic”)

The above filters resulted in the identification of 166 articles from the original 2,289. Each abstract was reviewed for relevance to include in the petition. Of these 166 articles, 58 were selected for in-depth analysis following abstract review. Forty-two of those articles were determined to be applicable to the effectiveness discussion within this petition.

In addition, the petitioner conducted a separate search of the literature used in support of marketing applications for the Non-invasive Bone Growth Stimulators currently in commercial distribution in the United States. This search included a review of available and appropriate Summaries of Safety and Effectiveness (SSEs), labeling for legally

marketed devices at the time of their approval, and other sources. Articles that were used in support of marketing applications for those devices and had not appeared in the previous literature search were obtained and reviewed. Fourteen articles were identified as a result and their relevance is discussed in Section VII of this petition.

Subsequent to the initial citation and abstract review, complete articles were reviewed and separated according to the device use: nonunion fractures and lumbar spinal fusion. Thirty-three of the articles describe studies pertaining to stimulation of nonunion fractures and nine articles are related to the use of stimulation as an adjunct to lumbar spinal fusion. These were reviewed in-depth and the effectiveness information extracted from these published studies is summarized in the tables that follow. **Attachment 4** summarizes the literature search methodology.

2. Benefits for Nonunion Fractures

The literature provides ample evidence from multiple clinical studies that devices within this type promote osteogenesis and the healing of nonunion fractures. This includes the results from 33 controlled prospective and retrospective clinical studies in which over 5,600 subjects have been treated and evaluated. Many of the clinical studies utilized the same design in which each subject served as his/her control. The patients enrolled in the studies had established nonunions and failed to achieve union using conventional therapies. Thus, this study design is scientifically valid for this intended use.

During the in-depth review of these articles, certain information was extracted in order to summarize the data in a tabular form. Information pertaining to the type of study (prospective or retrospective), control group and treatment, fracture site, and length of follow-up is noted. To permit logical discussion of the extensive information obtained, articles have been categorized according to the type stimulation – either capacitive coupling or PEMF. Characteristics of the various patient populations are further delineated according to the number of subjects enrolled and evaluated, number of fractures, location of fractures, and previous or concomitant treatments. Treatment variables include stimulation type, device manufacturer, output waveform parameters, treatment regimen, and time between fracture and stimulation treatment. Effectiveness outcomes were evaluated radiographically and clinically. Serial radiographs were examined for evidence of trabecular bridging across the gap, increased radiographic density, and disappearance of the gap. Clinical parameters included disappearance of pain, no movement at the fracture site, and no pain on stress at the fracture site. **Attachment 5** provides a copy of each cited literature article for further review.

a) Overview of the Clinical Studies for Nonunion Fractures

Thirty-three articles regarding Non-invasive Bone Growth Stimulators and nonunion fractures were identified in the review. This body of work spans the last 27 years. For clarity, these articles were separated according to the type of electrical stimulation employed: capacitive coupling (5 studies) and pulsed electromagnetic fields (28 studies). The literature search did not identify any specific article concerning the effectiveness of combined magnetic fields for nonunion fractures. Section VII presents other publicly available information on the benefits of combined magnetic field stimulation for nonunion fractures.

Tables 3 and 4 provide an overview of the studies cited in the literature. In these tables, each study is described according to study type, stimulation type, control group, fracture site, length of follow-up, and country of origin. Twenty-two of the studies are prospective and 11 are retrospective. Studies were conducted in the United States as well as internationally. The majority of studies use the subject as his/her own control. In three studies, subjects are compared to a concurrent control group (Dhawan et al., 2004; Scott and King, 1994; and, Sharrard, 1990). Two retrospective studies used either a surgical and/or invasive stimulator control group (Brighton and Pollack, 1985; and, Gossling et al., 1992). Highlights and details of these studies will be discussed in the text that follows.

There are five studies which investigated capacitive coupling as the electrical stimulus to promote osteogenesis and fracture healing. Table 3 summarizes these five studies. Mostly long bones were treated; however, cases involving the navicular, metatarsal, clavicle, and scaphoid are also included. Follow-up periods range from at least 6 weeks to 27 months in these studies. Two of the studies employing controls, either sham or another stimulus, are within this set (Brighton et al., 1995 and Scott and King, 1994).

Table 3. Overview of the Literature Citations Regarding the Use of Capacitive Coupling Non-invasive Bone Growth Stimulators for Nonunion Fractures

Reference (Author/Year)	Type of Study	Stimulation Type	Control Group	Fracture Site	Length of Follow-up	Country of Origin
Abeed et al., 1998	Prospective	Capacitive Coupling	Subject as Own	Long Bone	30 weeks	Britain
Benazzo et al., 1995	Prospective	Capacitive Coupling	Subject as Own	Tibia, Fibula, Navicular, Metatarsal, Talus	At least 6 weeks	Italy
Brighton and Pollack, 1985	Prospective	Capacitive Coupling	Subject as Own	Long Bone, Clavicle, Scaphoid	Up to 27 months	United States
Brighton et al., 1995	Retrospective	Capacitive Coupling	Direct Current Bone Graft	Tibia	3 months	United States
Scott and King, 1994	Prospective, Randomized, Double-Blind	Capacitive Coupling	Sham Unit	Tibia, Femur, Ulna	12 months	Britain

Table 4 summarizes the 28 studies in which PEMF provided the electrical stimulus for treatment. In all studies except two (Sharrard, 1990; and, Gossling et al., 1992), subjects serve as their own control. Sharrard compares PEMF treatment to a sham control group, whereas Gossling and coworkers review cohorts treated with stimulation and compare these to cohorts receiving surgical treatment. Follow-up varies from 62 days (Madroñero et al., 1988) up to 9 years (Meskens et al., 1990). Eighteen of the studies are of prospective design and 10 are retrospective. In the majority of the reports (24), long bones are included in the sets of fractures treated with PEMF. The tibia is the focus of six of these studies (Bassett, 1981; Caullay and Mann, 1982; Gossling et al., 1992; Ito and Shirai, 2001; Meskens et al., 1988; and, Sharrard, 1990). Treatment of other fracture sites is also reported including: hip, shoulder/scapula/clavicle, knee, wrist, and bones of the foot and ankle. Smaller bones of the hand and foot are the focus of treatment in 4 studies (Adams et al, 1992; Dhawan et al., 2004; Frykman et al., 1986; and Holmes, 1994).

Table 4. Overview of the Literature Citations Regarding PEMF Non-invasive Bone Growth Stimulators for Nonunion Fractures

Reference (Author/Year)	Type of Study	Stimulation Type	Control Group	Fracture Site	Length of Follow-up	Country of Origin
Adams et al., 1992	Retrospective	PEMF ¹	Subject as Own	Scaphoid	Mean of 8.5 months Range 4-33 months	United States
Bassett et al., 1982	Prospective	PEMF	Subject as Own	Long Bone, Hip, Shoulder, Scapula, Knee	NR ²	United States and Others
Bassett et al., 1982	Retrospective	PEMF	Subject as Own	Long Bone	Mean of 21 months Range 4-52 months	United States
Bassett et al., 1977	Prospective	PEMF	Subject as Own	Long Bone, Shoulder	Range 4 months - 3 years	United States
Bassett et al., 1978	Prospective	PEMF	Subject as Own	Long Bone, Shoulder, Wrist, Ankle	Up to 5 years	United States and Others
Bassett, 1981	Prospective	PEMF	Subject as Own	Tibia	Up to 5 years	United States
Caullay and Mann, 1982	Prospective	PEMF	Subject as Own	Tibia	Range 9 months – 3.5 years	Britain
Cheng et al., 1985	Prospective	PEMF	Subject as Own	Long Bone	Range 4-12 months	Belgium
Colson et al., 1988	Prospective	PEMF	Subject as Own	Long Bone	1 year	Britain
Delima and Tanna, 1989	Prospective, Randomized	PEMF	Subject as Own	Long Bone	Range 6 months – 5 years	India
Dhawan et al., 2004	Prospective	PEMF	Surgical	Foot	27 weeks or until radiographic union	United States
Fontanesi et al., 1983	Prospective	PEMF	Subject as Own	Long Bone, Clavicle, Navicular	At least 6 months	Italy
Frykman et al., 1986	Retrospective	PEMF	Subject as Own	Scaphoid	Mean of 8.4 months	United States
Garland, et al., 1991	Prospective	PEMF	Subject as Own	Long Bone, Short Bone, Failed Fusion	Mean of 4.1 years Range 3.6 – 5.4 years	United States

¹ PEMF – Pulsed electromagnetic fields

² NR – Not reported

Table 4. Overview of the Literature Citations Regarding PEMF Non-invasive Bone Growth Stimulators for Nonunion Fractures (Continued)

Reference (Author/Year)	Type of Study	Stimulation Type	Control Group	Fracture Site	Length of Follow-up	Country of Origin
Gossling et al., 1992	Retrospective	PEMF	Surgical	Tibia	NR	United States
Heckman et al., 1981	Retrospective	PEMF	Subject as Own	Long Bones, Ischium, Carpals, Metatarsals	Range 3 months – 1 year	United States
Hinsenkamp et al., 1985	Retrospective	PEMF	Subject as Own	Tibia, Femur, Humerus, Ulna, Other	NR	Belgium
Holmes, 1994	Retrospective	PEMF	Subject as Own	Metatarsal	Mean of 39 months Range 24-60 months	United States
Ito and Shirai, 2001	Prospective	PEMF	Subject as Own	Tibia	Mean of 8.6 months	Japan
Madroñero et al., 1988	Prospective	PEMF	Subject as Own	Radius	At least 62 days	Spain
Marcet et al., 1984	Retrospective	PEMF	Subject as Own	Tibia, Femur, Humerus	At least 7 months	United States
Meskens et al., 1990	Retrospective	PEMF	Subject as Own	Tibia, Femur, Humerus, Ulna, Radius, Fibula	Mean of 5.7 years Range 24 months – 9 years	Belgium
Meskens et al., 1988	Retrospective	PEMF	Subject as Own	Tibia	At least 6 months	Belgium
O'Connor, 1985	Prospective	PEMF	Subject as Own	Tibia, Humerus, Femur, Radius, Ulna, Congenital Nonunion	12 months	Britain
Sedel et al., 1982	Prospective	PEMF	Subject as Own	Tibia, Humerus, Radius/Ulna, Ulna, Clavicle	Mean of 6 months Range 1 month – 1 year	France

Table 4. Overview of the Literature Citations Regarding PEMF Non-invasive Bone Growth Stimulators for Nonunion Fractures (Continued)

Reference (Author/Year)	Type of Study	Stimulation Type	Control Group	Fracture Site	Length of Follow-up	Country of Origin
Sharrard, 1990	Prospective	PEMF	Sham stimulation	Tibial Shaft	12 weeks	Britain
Sharrard et al., 1982	Prospective	PEMF	Subject as Own	Tibia, Femur, Radius/Ulna, Knee, Ankle, Humerus, Capitellum	1 year	Britain
Simonis et al., 1984	Prospective	PEMF	Subject as Own	Tibia, Radius, Ulna, Knee	At least 6 months	Britain

b) Description of the Study Populations

Tables 5-8 further describe the study populations, including the number and location of fractures, previous treatments, number of subjects receiving stimulation, and concomitant treatments. In its entirety, this information describes the treatment of over 5,600 subjects with fractures of mainly long bones, various other areas, and smaller bones. Please note that some articles distinguish between nonunion and delayed union. Historically, nonunion was defined as no demonstrated healing on serial radiographs over a 3-month period, whereas delayed union was defined as slower than anticipated fracture healing with no expectancy of either eventual healing or eventual nonunion. More recently, however, the definition of nonunion has been refined and modified as failure to exhibit visibly progressive signs of healing; alleviating the need to differentiate these subjects (Nelson et al., 2003). In some studies, populations include subjects with failed arthrodeses (Bassett et al., 1982; and, Simonis et al., 1984) and congenital or acquired pseudarthroses (Bassett et al., 1977; Bassett et al., 1978; Caullay and Mann, 1982; Cheng et al., 1985; Fontanesi et al., 1983; and, Sedel et al., 1982).

In most of the studies, the subjects have undergone at least 1 surgical attempt at repair and other procedures. Many had multiple procedures prior to trying electrical stimulation. Generally, subjects were immobilized in a cast and, at least initially, directed to be non-weight-bearing. In some cases, bone grafts were implanted or other surgical procedures performed concomitantly (Bassett et al., 1982; Bassett et al., 1982; Bassett et al., 1977; Caullay and Mann, 1982; Dhawan et al., 2004; Fontanesi et al., 1983; O'Connor, 1985; Sharrard, 1990; and, Simonis et al., 1984), while in other cases stimulation was offered several months after surgery (Colson et al., 1988; Heckman et al., 1981; and, O'Connor, 1985). The populations in this reported literature also include subjects whose next option for treatment could be amputation of the affected limb.

Table 5 summarizes the study populations treated with capacitive coupling devices. These five studies represent experience with 351 patients, 327 of who had experienced at least 1 previous surgical treatment. Of the 355 fractures treated, 332 were fractures of the long bone with 304 of the tibia specifically. Two studies provide a comparison to another type of stimulation or treatment or a sham group (Brighton et al., 1995 and Scott and King, 1994). The table shows the number of subjects enrolled and the number of

nonunions evaluated for each study. The effectiveness results, described later, are typically presented for the number of nonunions evaluated.

Table 5. Description of the Study Populations with Nonunion Fractures Treated with Capacitive Coupling Non-invasive Bone Growth Stimulators

Reference	Number of Subjects Enrolled	Number of Nonunions Evaluated	Location of Fractures	Percentage of Subjects with Previous Treatment and Mean Number of Treatments ¹	Number of Subjects with Concomitant Surgery	Number of Subjects with Stimulation	Number of Subjects with Sham or No Stimulation
Abeed et al., 1998	16	16	Radius/Ulna: 7; Tibia: 6; Femur: 3	81.3% (13/16) Range 1-9	0	16	NA ²
Benazzo et al., 1995	21	25	Tibia: 2; Fibula: 2; Navicular: 13; Talus: 1; Metatarsal: 7	19.0% (4/21)	0	21	NA
Brighton and Pollack, 1985	20	22	Tibia: 10; Radius: 3; Femur: 3; Ulna: 2; Humerus: 2; Clavicle: 1; Scaphoid: 1	85.0% (17/20) Mean of 3.7	0	20	NA
Brighton et al., 1995	271	271	Tibia: 271	100% (271/271)	Bone Graft ³ : 48	Capacitive Coupling: 56 Direct Current: 167	NA
Scott and King, 1994	Total: 23	Total: 21 Active: 10 Sham: 11	Tibia: 15; Femur: 4; Ulna: 2	95.6% (22/23) At least 1	0	10	11

¹ Percentages are calculated based upon the numbers provided in parentheses, which were obtained from the references. Any noted differences between the percentages reported in this table and the reference are slight and the result of rounding differences.

² NA - Not applicable

³ These subjects received bone grafts but did not receive stimulation concurrently.

Tables 6-8 summarize the use of PEMF to treat nonunion fractures. This represents 28 studies with over 5,300 subjects. The majority of the nonunion fractures result from injuries, but some subjects had congenital pseudarthroses (Bassett et al., 1977; Bassett et al., 1978; Caullay and Mann, 1982; Cheng et al., 1985; O'Connor, 1985; and, Sedel et al., 1982), failed arthrodeses (Bassett et al., 1982; Cheng et al., 1985; and, Simonis et al., 1984) and acquired pseudarthroses (Bassett et al., 1978; Caullay and Mann, 1982). In all but 2 of these studies (Fontanesi et al., 1985; Sharrard, 1990), the populations include subjects who have had at least one previous surgical operation to repair the fracture. In many cases, subjects had a mean of 2-3 previous operations, highlighting that many of these subjects have few remaining treatment options and may have been disabled for an extended period.

Table 6 describes the study populations for studies focusing solely on the treatment of nonunions of the tibia. One publication is a review article which compares published studies on stimulation and surgical treatment of nonunions (Gossling et al., 1992). One study provides a comparison of PEMF to sham stimulation for the treatment of nonunions of the tibia (Sharrard, 1990).

Table 6. Description of the Study Populations with Nonunion Fractures of the Tibia Treated with PEMF Non-invasive Bone Growth Stimulators

Reference	Number of Subjects Enrolled	Number of Nonunions Evaluated	Location of Fractures	Percentage of Subjects with Previous Treatment and Mean Number of Treatments ¹	Number of Subjects with Concomitant Surgery	Number of Subjects with Stimulation	Number of Subjects with Sham or No Stimulation
Bassett et al., 1981	125	127	Tibia: 127	Mean of 2.4	2	125	NA ²
Caulley and Mann, 1982	4	Total: 6 Nonunion: 4 Pseudarthrosis: 2	Tibia: 4; Fibula: 2	100% (4/4)	1	4	NA
Gossling et al., 1992	Total: 2,287 PEMF ³ : 1,718 Surgery: 569	Total: 2,287 PEMF: 1,718 Surgery: 569	Tibia: 2,287	PEMF Group: Most >1	569	1,718	NA
Ito and Shirai, 2001	30	30	Tibia: 30	76.7% (23/30) Mean of 1.8 Range 1–5	0	30	NA
Meskens et al., 1988	57	57	Tibia: 57	Mean of 2.3	0	57	NA
Sharrard, 1990	45	45	Tibial Shaft: 45	0	0	20	25

¹ Percentages are calculated based upon the numbers provided in parentheses, which were obtained from the references. Any noted differences between the percentages reported in this table and the references are slight and the result of rounding differences.

² NA – Not applicable

³ PEMF – Pulsed electromagnetic fields

Table 7 describes the study populations for studies where multiple long bones, including the tibia, fibula, femur, radius, ulna, humerus and clavicle are treated. In addition, there are cases of nonunion fractures of the scapula/shoulder, navicular, knee, ankle and wrist. While immobilization is generally part of the standard treatment protocol, some populations also underwent concomitant surgery, such as bone grafts or external fixation (Bassett et al., 1982; Bassett et al., 1977; Fontanesi et al., 1983; and, Simonis et al., 1984).

Table 7. Description of the Study Populations with Nonunion Fractures of the Long Bones and Others Treated with PEMF Non-invasive Bone Growth Stimulators

Reference	Number of Subjects Enrolled	Number of Nonunions Evaluated	Location of Fractures	Percentage of Subjects with Previous Treatment and Mean Number of Treatments ¹	Number of Subjects with Concomitant Surgery	Number of Subjects with Stimulation	Number of Subjects with Sham or No Stimulation
Bassett et al., 1982	Total: 1,078 ² Columbia: 220 Other U.S.: 625 International: 233	1,078 Total 1,007 Nonunion 71 Failed Arthrodeses	Tibia: 657; Femur: 189; Humerus: 52; Radius/Ulna: 77; Scapula: 19; Miscellaneous: 13; Hip: 5; Knee: 27; Ankle: 30; Shoulder: 1; Wrist: 9	Mean of 2.2	U.S.: 38 International: NR ³	1,078	NA ⁴
Bassett et al., 1982	Total: 83 Group A (Large Gap, Mal-alignment): 38 Group B (Previous Failure with PEMF Alone): 45	Total: 83 Group A: 38 Group B: 45	Group A Tibia: 18; Femur: 12; Humerus: 4; Radius/Ulna: 2; Miscellaneous: 2 Group B Tibia: 27; Femur: 13; Humerus: 4; Radius/Ulna: 0; Miscellaneous: 1	Mean of 2.4	Bone Graft: 83	83	NA

¹ Percentages are calculated based upon the numbers provided in parentheses, which were obtained from the references. Any noted differences between the percentages reported in this table and the references are slight and the result of rounding differences.

² In the Brighton article, the total the number of tibial nonunions is reported differently at 657 and 658. Using either of these subtotals, the overall total fracture number adds to 1,079 or 1,080, which also differs from their report of 1,078.

³ NR – Not reported

⁴ NA – Not applicable

Table 7. Description of the Study Populations with Nonunion Fractures of the Long Bones and Others Treated with PEMF Non-invasive Bone Growth Stimulators (Continued)

Reference	Number of Subjects Enrolled	Number of Nonunions Evaluated	Location of Fractures	Percentage of Subjects with Previous Treatment and Mean Number of Treatments	Number of Subjects with Concomitant Surgery	Number of Subjects with Stimulation	Number of Subjects with Sham or No Stimulation
Bassett et al., 1977	Total: 26 Congenital Nonunion: 12 Acquired Nonunion: 14	Total: 26 Congenital Nonunion: 12 Acquired Nonunion: 14	Tibia: 17; Femur: 1; Fibula: 2; Radius/Ulna: 3; Navicular: 1; Shoulder Fusion: 1; Ankle: 1	Congenital: 91.7% (11/12) Mean of 3.4 Range 0-10 Acquired: 78.6% (11/14) Mean of 2.2 Range 0-8	5	26	NA
Bassett et al., 1978	220 ⁵	Total: 108 Acquired Nonunion: 73 Congenital Nonunion: 35	Tibia: 84; Femur: 10; Radius/Ulna: 8; Humerus: 3; Wrist: 1; Ankle: 1; Shoulder: 1	54.0% (119/220) Mean of 4	NR	108	NA
Cheng et al., 1985	Total: 63 Nonunion: 54 Congenital Nonunion: 3 Benign Cystic Lesion: 3 Failed Arthrodeses: 2 Failed Synostosis: 1	Total: 63 Nonunion: 54 Congenital Nonunion: 3 Benign Cystic Lesion: 3 Failed Arthrodeses: 2 Failed Synostosis: 1	Tibia: 33; Femur: 11; Humerus: 8; Radius: 2; Ulna: 3; Knee: 2; Radius/Ulna: 1	Mean of 2.2	0	63	NA

⁵ The article reports 220 subjects enrolled in the study, but only end results for 108 subjects are available.

Table 7. Description of the Study Populations with Nonunion Fractures of the Long Bones and Others Treated with PEMF Non-invasive Bone Growth Stimulators (Continued)

Reference	Number of Subjects Enrolled	Number of Nonunions Evaluated	Location of Fractures	Percentage of Subjects with Previous Treatment and Mean Number of Treatments	Number of Subjects with Concomitant Surgery	Number of Subjects with Stimulation	Number of Subjects with Sham or No Stimulation
Colson et al., 1988	32	33	Tibia: 22; Femur: 4; Ulna: 1; Radius/Ulna: 1; Radius: 2; Humerus: 3	59.4% (19/32) Range 0-6	NR	32	NA
Delima and Tanna, 1989	Total: 29 Nonunion: 28 Resected Osteoclastoma: 1	Total: 29 Nonunion: 28 Resected Osteoclastoma: 1	Humerus: 7; Tibia: 15; Femur: 6; Radius/Ulna: 1	89.7% (26/29) Range 0-6	0	29	NA
Fontanesi et al., 1983	33	Total: 35 Nonunion: 11 Pseudarthrosis: 24	Tibia: 9; Femur: 6; Humerus: 4; Radius: 3; Ulna: 4; Clavicle: 2; Carponavicular: 2; Unspecified: 5	NR	6	33	NA
Garland, et al., 1991	181	193	Long Bones: 130; Short Bones: 35; Failed Fusion: 28	81.3% (157/193) ⁶ Mean of 2	181	181	NA
Heckman et al., 1981	174	149	Tibia: 94; Femoral Shaft: 31; Humerus: 9; Ulna: 4; Radius/Ulna: 4; Radius: 2; Carponavicular: 2; Ischium: 1; Femoral Neck: 1; Metatarsal: 1	12.6% (22/174)	0	149	NA
Hinsenkamp et al., 1985	308	272	Tibia: 148; Femur: 55; Humerus: 19; Ulna: 16; Other: 34	80.6% (248/308)	NR	267	NA
Madroffero et al., 1988	11	10	Radius: 11	100% (11/11)	0	11	NA

⁶ This figure reflects the number of previous fractures receiving prior treatment, not the number of subjects, as indicated by the column heading.

Table 7. Description of the Study Populations with Nonunion Fractures of the Long Bones and Others Treated with PEMF Non-invasive Bone Growth Stimulators (Continued)

Reference	Number of Subjects Enrolled	Number of Nonunions Evaluated	Location of Fractures	Percentage of Subjects with Previous Treatment and Mean Number of Treatments	Number of Subjects with Concomitant Surgery	Number of Subjects with Stimulation	Number of Subjects with Sham or No Stimulation
Marcer et al., 1984	147	147	Tibia: 102; Femur: 32; Humerus: 13	Mean of 3.3	0	147	NA
Meskens et al., 1990	34	34	Tibia: 15; Femur: 9; Humerus: 5; Ulna: 2; Radius: 2; Fibula: 1	Mean of 3	0	34	NA
O'Connor, 1985	Total: 54 Nonunion: 53 Congenital Nonunion: 1	Total: 54 Nonunion: 53 Congenital Nonunion: 1	Tibia: 30; Humerus: 7; Femoral Shaft: 7; Radius: 6; Femoral Neck: 2; Ulna: 1; Congenital Tibial Nonunion: 1	89.0% (48/54) At least 1	11	54	NA
Sedel et al., 1982	Total: 39 Nonunion: 35 Congenital Nonunion: 4	Total: 39 Nonunion: 35 Congenital Nonunion: 4	Tibia: 20; Femur: 11; Humerus: 4; Radius/Ulna: 2; Ulna: 1; Clavicle: 1	Mean of 2 Range 0-6	0	39	NA
Sharrard et al., 1982	52	53	Tibia: 30; Femur: 7; Ulna: 6; Radius: 4; Knee: 2; Ankle: 2; Humerus: 1; Capitellum: 1	100% (52/52) Mean of 2.9	0	53	NA
Simonis et al., 1984	Total: 15 Nonunion: 14 Failed Arthrodesis: 1	Total: 15 Nonunion: 14 Failed Arthrodesis: 1	Tibia: 11; Radius/Ulna: 2; Ulna: 1; Knee: 1	Mean of 3	11	15	NA

Table 8 describes the study populations for studies focusing on the treatment of the foot and hand with PEMF devices. This includes over 180 subjects with nonunions of the foot or hand.

Table 8. Description of the Study Populations with Nonunions Fractures of the Foot and Hand Treated with PEMF Non-invasive Bone Growth Stimulators

Reference	Number of Subjects Enrolled	Number of Nonunions Evaluated	Location of Fractures	Percentage of Subjects with Previous Treatment and Mean Number of Treatments ¹	Number of Subjects with Concomitant Surgery	Number of Subjects with Stimulation	Number of Subjects with Sham or No Stimulation
Adams et al., 1992	62	54	Scaphoid: 54	22.2% (14/62)	0	54	NA ²
Dhawan et al., 2004	70	70	Subtalar: 64; Talonavicular: 42; Calcaneocuboid: 41	20.0% (14/70)	70	32	38
Frykman et al., 1986	50	44	Scaphoid: 50	26.0% (13/50)	0	50	NA
Holmes, 1994	9	9	Proximal Fifth Metatarsal: 9	11.1% (1/9)	0	9	NA

¹ Percentages are calculated based upon the numbers provided in parentheses, which were obtained from the references. Any noted differences between the percentages reported in this table and the references are slight and the result of rounding differences.

² NA - Not applicable

c) Stimulation Variables and Regimens

Tables 9-12 describe the treatment variables and regimens for subjects in these studies. Treatment regimens for all types of stimulation involved extended periods of daily usage starting at 3 hours per day. Treatments were typically prescribed for several months to achieve healing. Overall, the timeframe between the occurrence of fracture and the onset of stimulation treatment ranges from 7 days (Benazzo et al., 1995) to 42 years (Garland et al., 1991), highlighting that the majority of subjects in these studies have been disabled and immobilized as a result of the nonunions for as long as many months to years.

Table 9 provides the treatment variables and regimens from studies in which capacitive coupling was employed. Table 9 identifies the stimulation type, the device manufacturer, and the output waveform parameters of the device for each article when provided. The output waveform parameters for the stimulators are similar, consisting of a sinusoid waveform with an amplitude of approximately 3-6 volts peak to peak at a frequency of 60 – 63 kHz (Abeed et al., 1998; Brighton and Pollack, 1985; Brighton and Pollack, 1995; Benazzo et al., 1995, and Scott and King, 1994). The treatment regimens range from 7 – 24 hours per day for several months, up to 30 weeks to achieve healing. In four of the five studies, subjects had been disabled for at least 5 months prior to the attempt at stimulation therapy.

Table 9. Summary of the Stimulation Treatment Variables for Capacitive Coupling Non-invasive Bone Growth Stimulators for Nonunion Fractures

Reference	Stimulation Type	Device Manufacturer	Output Waveform Parameters	Treatment Regimen	Time Between Fracture and Stimulation Treatment
Abeed et al., 1998	Capacitive Coupling	NR ¹	63 kHz sinusoid wave, 6 V peak to peak	7-8 hrs for 12-30 weeks	9 months – 6.3 years
Benazzo et al., 1995	Capacitive Coupling	Bioelectron	60 kHz sinusoid wave, amplitude 3-6.3 V	24 hrs/day for mean of 52 days	Mean of 147.5 days Range 7-730 days
Brighton and Pollack, 1985	Capacitive Coupling	Bioelectron	60 kHz sinusoid wave, 5 V peak to peak	Mean of 22.5 weeks	Mean of 3.3 years Range 10 months – > 14 years
Brighton et al., 1995	Capacitive Coupling	NR	Capacitive Coupling: 60 kHz sinusoid wave, 5 V peak to peak Direct Current: Implantable 10 μ A	Capacitive Coupling: 24 hrs/day for 12-24 weeks Direct Current: Implanted 24 hrs/day for 12 weeks	23.5 months Range 5 – >70 months
Scott and King, 1994	Capacitive Coupling	Bioelectron	Active: 60 kHz sinusoid wave, 5-10 V peak to peak	24 hrs/day for mean of 22.5 weeks	Active: Mean of 31 months Range 11-83 months Sham: Mean of 26 months Range 12-43 months

¹ NR – Not reported

Tables 10-12 describe the treatment variables and regimens for subjects in studies in which PEMF stimulation was used. The tables identify the stimulation type, the device manufacturer, and the output waveform parameters of the device for each article when provided. The authors describe the output waveform parameters in a variety of ways. The information provided in the tables is the authors' descriptions. In some cases, the authors report the desired tissue effects rather than the output waveform parameters. In such cases, the table presents the desired tissue effects in parentheses. Twenty-seven of these studies report using the output waveform parameters which this petition seeks to reclassify.

Subjects were treated for various timeframes although there are common patterns. The treatment regimens range from 8 to 16 hours per day for 2 months (Frykman et al., 1986; Holmes, 1994; Ito and Shirai, 2001) to 43 months (Meskens et al., 1990).

Table 10 provides the stimulation treatment variables for nonunions of the tibia. Table 11 provides the same information for nonunion fractures of long bones, with Table 12 providing information for nonunion fractures of the foot and hand.

Table 10. A Summary of the Stimulation Treatment Variables of PEMF Non-invasive Bone Growth Stimulators for Subjects with Nonunions of the Tibia

Reference	Stimulation Type	Device Manufacturer	Output Waveform Parameters ¹ (Tissue Effect)	Treatment Regimen	Time Between Fracture and Stimulation Treatment
Bassett, 1981	PEMF ²	EBI, L.P.	NR ³ (1.5 mV/cm at tibial axis)	10 hrs/day Mean of 5.2 months	Mean of 28 months Range 4 months – 18 years
Caullay and Mann, 1982	PEMF	EBI, L.P.	NR ⁴	12-16 hrs/day for 1600 hrs	Range 3-5 years
Gossling et al., 1992	PEMF	NR	Various designs and regimens until healed	Various	PEMF group: Range 4 months – 37 years Surgery group: Range 4 months – 5 years
Ito and Shirai, 2001	PEMF	NR	5 msec square wave at 15 Hz	8 hrs/day	Mean of 18 months Range 6 months – >8 years
Meskens et al., 1988	PEMF	EBI, L.P.	NR	14 hrs/day for 3 months, then 10 hrs/day for 3 months, then only at night Mean of 10 months	Mean of 1.9 years
Sharrard, 1990	PEMF	NR	20 balanced pulses of an asymmetric waveform in a pulse train at 15 Hz	12 hrs/day for 12 weeks	Range 16-32 weeks

¹ As described by the authors in the cited reference

² PEMF – Pulsed electromagnetic fields

³ NR – Not reported

⁴ EBI, L.P. reports an output waveform parameter of 2.5 msec long bursts of 250-400 µsec 20 G pulses, repeated at a frequency of 5-20 Hz.

Table 11. A Summary of the Stimulation Treatment Variables of PEMF Non-invasive Bone Growth Stimulators for Subjects with Long Bones and Other Nonunions

Reference	Stimulation Type	Device Manufacturer	Output Waveform Parameters (Tissue Effects) ¹	Treatment Regimen	Time Between Fracture and Stimulation Treatment
Bassett et al., 1982	PEMF ²	EBI, L.P.	NR ^{3,4} (1.5 mV/cm along tibial axis)	10-12 hrs/day Mean of 5.5 months	Mean of 4.7 years
Bassett et al., 1982	PEMF	EBI, L.P.	5 msec wide burst of 200 µsec-wide pulses at 15 Hz	10 hrs/day for 2-12 months	Group A: Median 16 months Group B: Median 17 months
Bassett et al., 1977	PEMF	EBI, L.P.	300 µsec pulse at 75 Hz (peak current density of 10 µA in tissue 2-3 mV/cm bone)	12-16 hrs/day for 3-6 months	Congenital Nonunion Group: Mean of 4.9 years Acquired Nonunion Group: Mean of 2.5 years
Bassett et al., 1978	PEMF	EBI, L.P.	200 µsec pulse width in 5 msec trains at 10-15 Hz	12-16 hrs/day	NR
Cheng et al., 1985	PEMF	NR	NR (1.0 – 1.5 mV/cm)	14 hrs/day until healed	Mean of 2.5 years
Colson et al., 1988	PEMF	NR	Train of 5 pulses, each 300 µsec duration, separated by 1500 µsec, at 50 Hz	12-15 hrs/day for up to 1 year	PEMF Alone: 2-93 months Mean of 25 months Median of 12 months PEMF & Surgery: 3-120 months Mean of 27 months Median of 15 months
Delima and Tanna, 1989	PEMF	NR	Continuous pulse train at 40 Hz	16-18 hrs/day for 3-6 months	Range <3 months – 25 months

¹ As described by the authors in the cited reference

² PEMF – Pulsed electromagnetic fields

³ NR – Not reported

⁴ EBI, L.P. reports an output waveform parameter of 2.5 msec long bursts of 250-400 µsec 20 G pulses repeated at 5-20 Hz.

Table 11. A Summary of the Stimulation Treatment Variables of PEMF Non-invasive Bone Growth Stimulators for Subjects with Long Bones and Other Nonunions (Continued)

Reference	Stimulation Type	Device Manufacturer	Output Waveform Parameters (Tissue Effects) ⁵	Treatment Regimen	Time Between Fracture and Stimulation Treatment
Fontanesi et al., 1983	PEMF	NR	1.3 msec pulse at 75 Hz	12 hrs/day for at least 60 days	Mean of 15 months Range 5 months – 2 years
Garland, et al., 1991	PEMF	Orthofix	260 µsec 20 G pulses repeated at 15 Hz	Greater than or equal to 3 hrs/day for 3 months	Range 9 months – 42 years
Heckman et al., 1981	PEMF	EBI, L.P.	NR	Minimum 12 hrs/day for 3-4 months	Mean of 30.2 months Range 6 months – 37 years
Hinsenkamp et al., 1985	PEMF	EBI, L.P.	Train of pulses at 15 Hz	12 hrs/day	Mean of 36.2 months
Madroñero et al., 1988	PEMF	NR	NR	For mean of 104 days Range 62-178 days	Mean of 171 days Range 130-262 days
Marcet et al., 1984	PEMF	EBI, L.P.	Repeating 5 msec wide burst of 200 µs-wide pulses at 15 Hz	10 hrs/day Mean of 7 months	Mean of 13.8 months
Meskens, et al., 1990	PEMF	NR	NR	14 hrs /day for 3 months, 10 hrs /day for 3 months, then only at night Mean of 11.5 months Range 3-43 months	Mean of 38.8 months Range 24-124 months
O'Connor, 1985	PEMF	EBI, L.P.	Train of 20-22, 200 µsec long positive waveforms, burst lasting 5 msec at 15 Hz	For ≥ 12 hrs/day for 4-9 months	Range < 9 months – > 5 years
Sedel et al., 1982	PEMF	EBI, L.P.	NR (1-1.5 mV/cm)	12-14 hrs/day for ≥ 2 months	Mean of 11 months Range 2 months – 14 years
Sharrard et al., 1982	PEMF	EBI, L.P.	5 msec train of asymmetrical pulses at 15 Hz (1-1.5 mV)	12-16 hrs/day until healed	Median 28 months
Simonis et al., 1984	PEMF	NR	236 µsec period combined in a pulse train of 3 msec repeated at 25 Hz	12-16 hrs/day for 3-8 months	Mean of 27 months Range 10-55 months

⁵ As described by the authors in the cited reference

Table 12. A Summary of the Stimulation Treatment Variables of PEMF Non-invasive Bone Growth Stimulators for Subjects with Foot and Hand Nonunions

Reference	Stimulation Type	Device Manufacturer	Output Waveform Parameters ¹	Treatment Regimen	Time Between Fracture and Stimulation Treatment
Adams et al., 1992	PEMF ²	EBI, L.P.	NR ^{3,4}	Until healed or at least 3 months	Mean of 35 months Range 6-241 months
Dhawan et al., 2004	PEMF	EBI, L.P.	NR	12 hrs/day until healed	NA ⁵
Frykman et al., 1986	PEMF	EBI, L.P.	NR	8-10 hrs/day for mean of 4.3 months	Mean of 40 months Range 6-241 months
Holmes, 1994	PEMF	NR	4.5 msec bursts at 15 Hz (20 pulses per burst with an increasing phase of 200 µsec duration and a decreasing phase of 20µsec followed by a 5 µsec pause)	8-10 hrs/day	Mean of 2.8 months Range 1-5 months

¹ As described by the authors in the cited reference

² PEMF – Pulsed electromagnetic fields

³ NR – Not reported

⁴ EBI, L.P. reports an output waveform parameter of 2.5 msec long bursts of 250-400 µsec 20 G pulses, repeated at 5-20 Hz.

⁵ NA – Not applicable

d) Effectiveness Assessments

The articles report that radiological and clinical assessments are the key effectiveness measurements, or benefits of the devices (Tables 13-16.) Serial radiographs are reviewed for bone trabeculae crossing the fracture line (or gap) in all radiographic views. Clinical assessment of union is based upon disappearance of pain, absence of movement at the fracture site, and a diminished need for pain medications. In some studies, both radiologic and clinical results are presented. Most often, the main effectiveness variable is from serial radiographs given the well-established risks and complications of nonunion fractures. This information is presented according to the type of electrical stimulation treatment – capacitive coupling or PEMF.

Table 13 presents the results from five studies investigating capacitive coupling. The table identifies the definitions of radiological and clinical success and the percentage of subjects who achieved a successful outcome.

In the first three studies, the subject serves as his/her own control. Serial radiographs showed that union occurred in 68.8% (11/16) of subjects with nonunions of long bones (Abeed et al., 1998). Thirteen of these subjects had undergone 1-9 previous surgical interventions in an attempt to heal their fractures, but had not achieved union with these other treatments. A union rate of 77.3% (17/22) is reported for mostly long bones in patients who had undergone an average of 3.7 previous procedures (Brighton and Pollack, 1985). In a series of subjects with fractures of mostly smaller foot bones, successful union was reported in 88% (22/25) (Benazzo et al., 1995).

Two studies include control groups in their assessment. Sixty percent of those who were treated with capacitive coupling stimulation achieved union, whereas no one in the sham-stimulated group achieved union (Scott and King, 1994). Brighton et al. (1995) compared three treatment regimens – direct current (DC), capacitive coupling, and bone grafts. This article focused on identifying the risk factors for nonunion for the various treatments. Overall, union was achieved in 73.1% (198/271) of the population using the three methods. Individual group results are not provided for the stimulated groups. Based upon a logistic regression analysis that adjusted for risk factors, the union rates were calculated for all three groups and were similar in the absence of

any risk factors (99%, 96%, and 99%). Inclusion of possible risk factors altered that outcome, however. For instance, a patient who had failed previous bone graft surgery would not be likely to achieve success with subsequent bone graft surgery, but direct current or capacitive coupling would more likely be successful in such a patient.

Table 13. Benefits of Capacitive Coupling Non-invasive Bone Growth Stimulators for Nonunion Fractures

Reference	Radiological Definition of Union	Clinical Definition of Union	Radiological Success ¹ (%)	Clinical Success ¹ (%)	Overall Success (Radiographic and Clinical) ¹ (%)
Abeed et al., 1998	Serial radiographs Bone trabeculae observed across full width of fracture line in all views	NR ²	68.8% (11/16)	NR	68.8% (11/16)
Benazzo et al., 1995	Biweekly radiographs, scintigraphy, and computerized tomography	Time of pain disappearance, return to sports	NR	NR	88.0% (22/25)
Brighton and Pollack, 1985	Serial radiographs Bone trabeculae cross full width of fracture line on all radiographs	NR	77.3% (17/22)	NR	77.3% (17/22)
Brighton et al., 1995	Serial radiographs All 4 radiographic views showed bony trabeculae spanning full width of non-union gap	NR	Overall: 73.1% (198/271) Bone Graft: 58.3% (28/48) Capacitive Coupling: NR Direct Current: NR	NR	NR
Scott and King, 1994	Serial radiographs Trabecular bridging seen on all 4 radiographs	No apparent movement at fracture site and no pain on stress	NR	NR	Active: 60.0% (6/10) Sham: 0.0% (0/11) SD³

¹ Percentages are calculated based upon the numbers provided in parentheses, which were obtained from the references. Any noted differences between the percentages reported in this table and the references are slight and the result of rounding differences.

² NR – Not reported

³ SD – Statistically significant difference

Tables 14-16 present the results for PEMF stimulation. PEMF has been used not only to treat various long bones in the body, but also the hip and smaller bones in the hand (scaphoid) and foot. Twenty-eight reports describe the use of PEMF in the repair of nonunions in all of these areas. These studies will be discussed in terms of the specific areas treated to present the information in a more simplified manner. First, the use of PEMF exclusively in the tibia will be presented followed by those studies including more diverse populations, but mainly long bones. Third, details for studies in which smaller bones were treated exclusively will be outlined.

Six articles report results from PEMF-treated nonunion fractures of the tibia with the rate of achieving successful unions similar over the 20-year period covered by these studies, as shown in Table 14. The outcomes from 127 tibial nonunion fractures treated with PEMF show an 86.6% success rate in achieving union (Bassett, 1981). Serial radiographs were taken and evaluated to determine successful union. Over seventy-five percent of a group of 57 nonunions of the tibia showed fusion when assessed radiographically and clinically (Meskens et al., 1988). Gossling et al. (1992) performed a retrospective analysis of studies involving 2,287 tibial nonunions. A group of 1,718 subjects were treated with PEMF and compared to a control group of 569 subjects who were treated surgically. PEMF was shown to be at least as effective (81%) as surgical management (81.9%), demonstrating that it provides a viable, less invasive alternative to surgical treatment. In fact, the more surgeries a patient has undergone, the less effective subsequent surgical procedures become, so PEMF offers an effective noninvasive treatment. In 1990, 45 tibial shaft nonunions were evaluated both radiologically and clinically (Sharrard, 1990). Twenty subjects received PEMF and were compared to 25 who received sham stimulation. The results demonstrate that the PEMF group exhibited a higher union rate (45%) compared to the sham stimulation group (12.0%), the difference being statistically significant. More recently, similar results have been confirmed in 30 tibial nonunion fractures (Ito and Shirai, 2001). Subjects were evaluated using serial radiographs and clinical assessment every 6 weeks. Successful fusion was observed in 83.3% of these people, 80% of who had undergone at least one previous attempt at surgical repair. In a small set of 6 subjects, 100% were successfully treated after all of them had failed previous surgical attempts (Caullay and Mann, 1982).

Table 14. Benefits of PEMF Non-invasive Bone Growth Stimulators for Nonunion Fractures of the Tibia

Reference	Radiological Definition of Union	Clinical Definition of Union	Radiological Success ¹ (%)	Clinical Success ¹ (%)	Overall Success (Radiographic and Clinical) ¹ (%)
Bassett, 1981	Serial radiographs	NR ²	NR	NR	86.6% (110/127)
Caulley and Mann, 1982	Serial radiographs	NR	NR	NR	100% (4/4)
Gossling et al., 1992	Not specified	NR	NR	NR	PEMF ³ : 81.0% (1392/1718) Surgery: 81.9% (466/569)
Ito and Shirai, 2001	Serial radiographs Bony trabecular crossing at least half the width of the defect on 2 planes	Absence of mobility at site, pain on stress, tenderness over fracture site	83.3% (25/30)	NR	83.3% (25/30)

¹ Percentages are calculated based upon the numbers provided in parentheses, which were obtained from the references. Any noted differences between the percentages reported in this table and the references are slight and the result of rounding differences.

² NR – Not reported

³ PEMF – Pulsed electromagnetic fields

Table 14. Benefits of PEMF Non-invasive Bone Growth Stimulators for Nonunion Fractures of the Tibia (Continued)

Reference	Radiological Definition of Union	Clinical Definition of Union	Radiological Success (%)		Clinical Success (%)		Overall Success (Radiographic and Clinical) (%)	
Meskens et al., 1988	Serial radiographs Increase in radiographic density, bone stress lines bridging the gap, remodeling, obliteration of fracture gap	Mechanical stability, absence of local tenderness	NR		NR		75.4% (43/57)	
Sharrard, 1990	Radiographs initially and at 12 weeks	Absence of movement in mediolateral and anteroposterior planes, pain, tenderness	Stim: ⁴ No Progress: 10 Progress to Union: 5 Probable Union: 2 Full Union: 3 SD ⁵ OS ⁶ : United: 9 Improved: 2 No Progress: 9 SD	Sham ⁷ No Progress: 23 Progress to Union: 1 Probable Union: 1 Full Union: 0 OS: United: 3 Improved: 5 No Progress: 17	Stim: ML Movement Nil: 13 Slight: 5 Moderate: 1 Marked: 1 AP Movement Nil: 12 Slight: 6 Moderate: 1 Marked: 1 NSD ⁸ Pain: 0.9 ± 1.2 Tenderness: 1.6 ± 2.4 SD from initial	Sham: ML Movement Nil: 12 Slight: 10 Moderate: 3 Marked: 0 AP Movement Nil: 13 Slight: 9 Moderate: 2 Marked: 1 Pain: 1.5 ± 2.1 Tenderness: 2.7 ± 3.1	Stim: 45.0% (9/20) OS assessment SD 50.0% (10/20) Radiologist SD	Sham: 12.0% (3/25) OS assessment 8.0% (2/25) Radiologist

⁴ STIM - Stimulator

⁵ SD - Statistically significant difference

⁶ OS - Orthopedic surgeon

⁷ SHAM - Sham stimulator

⁸ NSD - No statistically significant difference

Table 15 summarizes eighteen studies from the literature, providing reports of successful union rates varying from 58.7% (Cheng et al., 1985) to 93.9% (Colson et al., 1988) for the treatment of long bones with PEMF. In a prospective study, Cheng treated 54 nonunions (45 long bones and 9 others) with PEMF (Cheng et al., 1985). He observed a 58.7% union rate with a 78.6% union rate for the tibia alone. Madroñero treated 10 nonunions of the radius with PEMF and reported a similar success rate of 60% (Madroñero et al., 1988). Experience in a population of 149 nonunions, which included mainly tibias (94) and femurs (31), long bones in the arm (humerus, radius and ulna) as well as 5 in the ischium, femoral neck, and foot is reported retrospectively (Heckman et al., 1981). Overall, successful fusions were achieved in 64.4% of the subjects. Higher healing rates were observed in the tibia (71.3%) than with the femur and humerus. Half of the failures could be attributed to lack of patient compliance with the protocol related to immobilization and weight-bearing. Similar success rates (67.6%) were observed by Meskens and colleagues who treated 34 nonunions involving the tibia (15), femur (9), humerus (5), ulna (2), radius (2), and fibula (1). Looking at the tibia and femur exclusively, success rates improved to 73.3% and 77.8%, respectively. These fractures can be more easily immobilized which contributes to the success, in contrast to nonunions of the humerus that are difficult to immobilize. In these groups representing more diverse locations of fractures, the rate of union is reproducible.

Table 15. Benefits of PEMF Non-invasive Bone Growth Stimulators for Nonunion of Long Bones and Others

Reference	Radiological Definition of Union	Clinical Definition of Union	Radiological Success ¹ (%)	Clinical Success ¹ (%)	Overall Success (Radiographic and Clinical) ¹ (%)
Bassett et al., 1982	Serial radiographs Cortical or trabecular bridging or both with major modifications of the radiolucent gap	No motion on stress at fracture site, no local tenderness, no pain on ambulation, no further plaster immobilization	NR ²	NR	Overall: 77.4% (834/1078) Columbia: 80.9% (178/220) U.S.: 75.7% (473/625) International: 78.5% (183/233) Tibia at each Investigational Site: 81.9% (538/657) Overall Failed Arthrodeses: 81.7% (58/71) Columbia: 87.0 % (20/23) U.S.: 78.6% (33/42) International: 83.3% (5/6)
Bassett et al., 1982	Serial radiographs (monthly) Osseous bridging of the gap defect	No motion or tenderness on physical exam, no pain on weight-bearing, no requirement for external support	Group A: 87.0% (33/38) Group B: 93.0% (42/45)	NR	Overall: 90.4% (75/83)
Bassett et al., 1977	Serial radiographs (monthly)	NR	73.0% (19/26)	NR	73.0% (19/26)

¹ Percentages are calculated based upon the numbers provided in the parentheses, which were obtained from the references. Any noted differences between the percentages reported in this table and the references are slight and the result of rounding differences.

² NR – Not reported

Table 15. Benefits of PEMF Non-invasive Bone Growth Stimulators for Nonunion of Long Bones and Others (Continued)

Reference	Radiological Definition of Union	Clinical Definition of Union	Radiological Success (%)	Clinical Success (%)	Overall Success (Radiographic and Clinical) (%)
Bassett et al., 1978	Serial radiographs Obliteration of radiolucent lines, bony bridging	Mechanical stability, no local tenderness, function without local protective splint	NR	NR	80.6% (87/108)
Cheng et al., 1985	Serial radiographs	NR	NR	NR	Overall: 58.7% (37/63) Tibia: 78.6% (22/28) Femur: 60.0% (6/10) Humerus: 25.0% (2/8) Radii: 50.0% (1/2) Ulna: 0.0% (0/2)
Colson et al., 1988	Serial radiographs every 4 –6 weeks Defined as sound bony bridging on x-ray	NR	PEMF ³ : 85.7% (12/14) PEMF with surgery: 100% (19/19)	NR	93.9% (31/33)
Delima and Tanna, 1989	Serial radiographs at 8 weeks and 3 months Mature lamellar bone bridging fracture gap	NR	79.3% (23/29) ⁴	NR	79.3% (23/29)
Fontanesi et al., 1983	Serial radiographs	NR	NR	NR	88.6% (31/35)

³ PEMF – Pulsed electromagnetic fields

⁴ The reference states 82.5% in the abstract and 82.14% in the text without explanation. According to calculations based on the data, 79.3% appears to be the correct percentage.

Table 15. Benefits of PEMF Non-invasive Bone Growth Stimulators for Nonunion of Long Bones and Others (Continued)

Reference	Radiological Definition of Union	Clinical Definition of Union	Radiological Success (%)	Clinical Success (%)	Overall Success (Radiographic and Clinical) (%)
Garland et al., 1991	Serial radiographs Cortical and/or trabecular bridging with major modifications of the radiolucent gap on any view Overall callus showing progression from baseline	Evaluation of motion, tenderness, pain, requirement for casting Healed: non-casted, without motion at the fracture site, absent or minimal pain at the nonunion site	NR	NR	PEMF: 80.0% (108/135) > 3/hrs/day PEMF: 35.7% (5/14) < 3/hrs/day SD Long Bones Overall: 82.7% (81/98) Tibia: 74.0% (37/50) Short Bones Overall: 81.0% (17/21) Scaphoids: 76.9% (10/13)
Heckman et al., 1981	Serial radiographs Trabecular bridging of fracture gap re-medullarization of bone	Evaluation of motion and pain	64.4% (96/149)	Decreased motion and pain	Overall: 64.4% (96/149) Tibia: 71.3% (67/94) Femur: 51.6% (16/31) Humerus: 44.0% (4/9)
Hinsenkamp et al., 1985	NR	NR	NR	NR	72.3% (193/267)
Madroñero, et al., 1988	Presence of bone callus	Absence of pain, mobility on focus	60.0% (6/10)	NR	60.0% (6/10)
Marcer et al., 1984	NR	NR	NR	NR	72.8% (107/147)
Meskens et al., 1990	Serial radiographs Bridging and disappearance of gap on x-ray	Disappearance of mobility on stress and pain on percussion	NR	NR	67.6% (23/34)
O'Connor, 1985	Serial radiographs Bony bridging	Clinically stable	NR	NR	83.3% (25/30)

Table 15. Benefits of PEMF Non-invasive Bone Growth Stimulators for Nonunion of Long Bones and Others (Continued)

Reference	Radiological Definition of Union	Clinical Definition of Union	Radiological Success (%)	Clinical Success (%)	Overall Success (Radiographic and Clinical) (%)
Sedel et al., 1982	NR	NR	NR	NR	83.7% (31/37)
Sharrard et al., 1982	Serial radiographs Increase in density in the gap, trabecular bridging, cortical continuity	Absence of movement at fracture site, pain on stressing, tenderness at site	Tibia: 86.7% (26/30) Femur: 57.1% (4/7) Ulna: 50.0% (3/6) Radius: 75.0% (3/4) Humerus: 0.0% (0/1) Capitellum: 0.0% (0/1) Knee: 50.0% (1/2) Ankle: 50.0% (1/2)	NR	71.7% (38/53)
Simonis et al., 1984	Monthly radiographs Fracture line filled in	NR	86.7% (13/15)	NR	86.7% (13/15)

In six studies, successful fusions were observed in 70% of the populations in which greater than half of the nonunions were in the tibia, but fractures of other long bones, foot, wrist, and shoulder were also included. In a large study of 1,078 nonunions conducted both here and internationally, the overall success rate was 77.4% (Bassett et al., 1982). Hinsenkamp et al. (1985) reported similar results in a retrospective review of 267 nonunions (72.3%). Similar results of 71.7% (Sharrard et al., 1982) and 79.3% (Delima and Tanna, 1989) were observed in study populations with various origins of nonunions. Lower union rates could be attributed consistently to wider fracture gaps and insecure fixation or instability (Marcer et al., 1984; Sharrard et al., 1982; Delima and Tanna, 1989; and Bassett et al., 1982). Anatomical variation, attention to immobilization protocols, and patient compliance also affected the success rate.

Higher success rates (80 – 100%) were reported in other series, consisting mainly of long bones and various other fracture sites. This indicates some evolution of the technique and experience of the investigators. As investigation continued with Bassett and colleagues (Bassett et al., 1978), and an 80.6% success rate was observed. In a subsequent 1982 report by Bassett, fractures with large gaps and pseudarthrosis (Group A) were compared to subjects who had previously failed PEMF treatment alone (Group B). All subjects received concomitant bone grafts. Success rates were 87% and 93%, respectively. Simonis et al. (1984) observed success in 13 of 15 subjects (86.7%). Rates of 83.3 and 88.6% were observed in two separate studies, respectively (O'Connor, 1985 and Fontanesi et al., 1983). Similarly, Sedel observed a union rate of 83.7% in 39 subjects. Over ninety-three percent of the 33 subjects treated for nonunions had united fractures after PEMF treatment (Colson et al., 1988).

In studies of subjects with various fractures of the hand and foot, success rates similar to those discussed above are reported, as shown in Table 16. Forty-four subjects with scaphoid fractures were treated with PEMF (Frykman et al., 1986), and successful union was achieved in 79.5% (35/44) of the treated subjects. Another study of scaphoid fractures showed a 68.5% rate of union (Adams et al, 1992). Although not as successful as their previous work, the range falls within that discussed above with regards to long bones. PEMF treatment after primary foot joint arthrodesis was compared to the control group that received the surgery alone (Dhawan et al., 2004). There was an increased rate and speed of

union when PEMF was included (100% versus 89%). Holmes (1994) reported a 100% union rate of the proximal fifth metatarsal in nine subjects.

Table 16. Benefits of PEMF Non-invasive Bone Growth Stimulators for Nonunion Fractures of the Foot and Hands

Reference	Radiological Definition of Union	Clinical Definition of Union	Radiological Success ¹ (%)	Clinical Success ¹ (%)	Overall Success (Radiographic and Clinical) ¹ (%)
Adams et al, 1992	Serial radiographs	NR	68.5% (37/54)	NR	68.5% (37/54)
Dhawan et al., 2004	Serial radiographs Joint apposition, quality of bone, stages of graft incorporation and maturation, time to fusion, presence/absence of fusion, bone density	NR	PEMF: 100% (22/22) Control: 89.0% (33/37)	NR	Rate and Speed of Fusion Increased with PEMF
Frykman et al., 1986	Radiographs	Wrist extension, flexion, radial deviation, ulnar deviation, grip strength	79.5% (35/44)	Compared to normal: Wrist Extension: 84.1% (37/44) Flexion: 92.2% (41/44) Radial Deviation: 84.1% (37/44) Ulnar Deviation: 90.9% (40/44) Grip Strength: 83.0% (36/44)	79.5% (35/44)
Holmes 1994	Pre-treatment and post-treatment radiographs Trabecular bridging over the fracture line	Pain-free gait, ambulation without cast, boot, wooden shoe	100% (9/9)	100% (9/9)	100% (9/9)

¹ Percentages are calculated based upon the numbers provided in the parentheses, which were obtained from the references. Any noted differences between the percentages reported in this table and the references are slight and the result of rounding differences.

e) Conclusions

These studies demonstrate that Non-invasive Bone Growth Stimulators are an effective treatment for healing nonunions. With nonunions associated with significant disability and pain, being able to treat a variety of fracture locations and sites with these devices provides well-established benefits to patients by achieving a successful union.

Some of the output waveform parameters reported in the literature are produced by the FDA-approved devices being sought for reclassification, and other output waveform parameters were novel, therapeutic signals. Nonetheless, all of the output waveform parameters used in the clinical studies resulted in the delivery of therapeutic signals as evidenced by the establishment of unions.

3. Benefits as an Adjunct for Spinal Fusion

The literature provides ample evidence from multiple clinical studies that the Non-invasive Bone Growth Stimulator promotes spinal fusion in the presence or absence of instrumentation. A discussion of nine studies is presented here, which represents data from over 1,100 subjects. During the in-depth review of these articles, certain information was extracted in order to summarize the data in a tabular form. Information pertaining to the type of study (prospective or retrospective), control group, type and site of fusion, length of follow-up, number of subjects, and country of origin are noted. Characteristics of the various study populations are further delineated according to the number of subjects, fusions evaluated, type of fusion, previous treatment, concomitant surgery, and presence or absence of stimulation. In seven of the studies, concomitant treatments were performed (i.e., lumbar fusion surgery), with stimulation administered post-operatively. In the remaining two studies, stimulation was used at least 9 months after surgery in a non-operative attempt to salvage failed surgery. Treatment variables include stimulation type, output waveform parameters, and treatment regimens.

Effectiveness outcomes were assessed radiographically and clinically. Radiographs provide evidence of the formation of bridging, bony masses and assimilation. Clinically, subjects were evaluated for evidence of pain, use of pain medication, physical activity levels, and occupational status.

Attachment 6 provides a copy of each cited literature article for further review.

a) Overview of the Clinical Studies for Spinal Fusion

The nine articles obtained through this literature search represent studies spanning the last 20 years, with the majority being published within the past 6 years. Table 17 provides an overview of these studies. Each study is described according to study type, treatment plan, control group, fusion site, length of follow-up, and country of origin. All but one study were conducted in the United States, and seven of the nine studies were prospective. Further, five of the prospective studies had concurrent control groups (Goodwin et al., 1999; Jenis et al., 2000; Linovitz, et al., 2002; Mooney, 1990; Simmons, 1985; and, Simmons et al., 2004) with three of those being randomized, double-blind studies (Goodwin et al., 1999; Linovitz et al., 2002; and Mooney, 1990). The other studies used either historical controls or the subject as his/her own control (DiSilvestre and Savini, 1992; Simmons, 1985; and Simmons et al., 2004). There are two retrospective studies (Bose et al., 2001 and Marks, 2000).

All studies presented subjects who had undergone lumbar spinal fusion surgeries. In the first seven studies summarized in Table 17, lumbar fusion surgery was performed on the subjects with post-operative stimulation as part of the treatment regimen. In contrast, the two studies conducted by Simmons supported the use of stimulation as a non-operative approach to achieving bony fusion following failed surgical attempts (Simmons, 1985 and Simmons et al., 2004). Follow-up ranged from 3 months (Simmons et al., 2004) to 5 years (Bose, 2001), with at least 1 year noted in the remaining seven reports. Highlights and details of these studies will be discussed in the text that follows.

Table 17. Overview of Literature Citations for Non-invasive Bone Growth Stimulators for Spinal Fusion

Reference (Author/Year)	Type of Study	Treatment Plan	Control Group	Site	Length of Follow-up	Country of Origin
Bose, 2001	Retrospective	PLF ¹ and PEMF ²	Subject as Own	Lumbar	Mean of 16 months Range 6 months – 5 years	United States
DiSilvestre and Savini, 1992	Prospective	PLF and PEMF	Historical	L4-L5, L5-S1, Post-laminectomy Instability	4 months	Italy
Goodwin et al., 1999	Randomized, Double-blind, Prospective	PLF, ALIF ³ , or PLIF ⁴ and Capacitive Coupling	Concurrent	Primary Lumbar Fusions	2 years	United States
Jenis et al., 2000	Prospective	PLF and PEMF or DC	Concurrent	Lumbar	1 year	United States
Linovitz et al., 2002	Randomized, Double-blind, Prospective	PLF with Combined Magnetic Fields or Sham	Concurrent	Primary Non-instrumented PLF (L3 – S1)	12 months	United States
Marks, 2000	Retrospective	PLF and PEMF	Concurrent	Lumbar Fusion	Mean of 15.6 months	United States
Mooney, 1990	Randomized, Double-blind, Prospective	ALIF or PLIF and PEMF	Concurrent	Lumbar Interbody Fusions	At least 12 months	United States
Simmons, 1985	Prospective	PEMF	Subject as Own	PLIF	12 months	United States
Simmons et al., 2004	Prospective	PEMF	Subject as Own	Posterolateral, PLIF, ALIF	Mean of 8.3 months Range 3-21 months	United States

¹ PLF – Posterolateral lumbar fusion
² PEMF – Pulsed electromagnetic fields
³ ALIF – Anterior lumbar interbody fusion
⁴ PLIF – Posterior lumbar interbody fusion

b) Description of the Study Populations

Table 18 provides the total number of subjects and fusions included in this section of literature reviewed. All subjects received concurrent surgical fusion procedures in the lumbar area, with or without instrumentation, or underwent these surgical procedures within at least the 9-18 month period prior to receiving stimulation. In all but three studies it is reported that subjects had at least one previous surgery before stimulation was included in the treatment regimen. Percentages of subjects having previous treatments ranged from 14.8%-100% (Marks, 2000; Simmons, 1985; and, Simmons, 2004). Over 59% of the subjects in Bose's population had previous procedures performed (e.g., laminectomies, discectomies, fusions, or decompression surgical procedures), and all had bone grafts and instrumentation. Nine subjects (14.8%) in the group studied by Marks (2000) had undergone previous fusions in which all subjects received bone grafts and 11 of the total 61 received instrumentation. Eight subjects (25.8%) treated by DiSilvestre and Savini (1992) had laminectomies prior to fusion surgery. Goodwin and coworkers report that 37.6% of the active group had previous treatment compared to 51% of the sham group (Goodwin et al., 1999). In two studies, the entire study population consisted of subjects where traditional fusion surgeries had failed (Simmons, 1985 and Simmons et al., 2004). Three studies did not report the incidence of previous surgical treatment.

Fusions had been performed using bone grafts with or without instrumentation fixation. Five of the study groups are compared to control groups who received surgery but not the post-operative stimulation regimen (DiSilvestre and Savini, 1992; Goodwin et al.; 1999; Jenis et al., 2000; Marks, 2000; and, Mooney, 1990).

Table 18. Description of the Study Population in the Literature Citations for Non-invasive Bone Growth Stimulators for Spinal Fusion

Reference	Number of Subjects Enrolled	Number of Fusions Evaluated	Type of Fusion	Percentage of Subjects with Previous Treatment and Mean Number of Treatments ¹	Number of Subjects with Concomitant Surgery	Number of Subjects with Stimulation	Number of Subjects with Sham or No Stimulation
Bose, 2001	52	48	PLF ² (with instrumentation)	59.6% (31/52)	Bone Grafts Instrumentation: 48	48	NA ³
DiSilvestre and Savini, 1992	Total: 53 Active: 31 Control: 22	Total: 53 Active: 31 Control: 22	Posterolateral Lumbosacral	25.8% (8/31)	Bone Grafts Instrumentation: 31	31	22
Goodwin et al., 1999	337	Total: 179 Active: 85 Sham: 94	PLF, ALIF ⁴ , PLIF ⁵	Active: 37.6% (32/85) Sham: 51.0% (48/94)	Bone Grafts Instrumentation: 179	85	94
Jenis et al., 2000	Total: 61 PEMF ⁶ : 22 DC ⁷ : 17 Sham: 22	Total: 61 PEMF: 22 DC: 17 Sham: 22	PLF (with instrumentation)	NR ⁸	Bone Grafts Instrumentation: 61	Total: 39 PEMF: 22 DC: 17	22
Linovitz et al., 2002	243	Total: 201 Active: 104 Sham: 97	PLF (without instrumentation)	NR	Bone Grafts: 201	NR	NR

¹ Percentages are calculated based upon the numbers provided in the parentheses, which were obtained from the references. Any noted differences between the percentages reported in this table and the references are slight and the result of rounding differences.

² PLF – Posterolateral lumbar fusion

³ NA – Not Applicable

⁴ ALIF – Anterior lumbar interbody fusion

⁵ PLIF – Posterior lumbar interbody fusion

⁶ PEMF – Pulsed electromagnetic field

⁷ DC – Direct current

⁸ NR – Not reported

Table 18. Description of the Study Population in the Literature Citations for Non-invasive Bone Growth Stimulators for Spinal Fusion (Continued)

Reference	Number of Subjects Enrolled	Number of Fusions Evaluated	Type of Fusion	Percentage of Subjects with Previous Treatment and Mean Number of Treatments	Number of Subjects with Concomitant Surgery	Number of Subjects with Stimulation	Number of Subjects with Sham or No Stimulation
Marks, 2000	Total: 61 Active: 42 Sham: 19	Total: 61 Active: 42 Sham: 19	Lumbar Spinal	14.8% (9/61)	Bone Grafts Instrumentation: 61	42	19
Mooney, 1990	Total: 206 Active: 107 Sham: 99	Total: 195 Active: 98 Sham: 97	ALIF, PLIF (with or without fixation)	NR	Bone Grafts Instrumentation: 195	98	97
Simmons, 1985	13	13	Failed PLIF	100% (13/13)	0	13	NA
Simmons et al., 2004	100	100	PLF, ALIF, PLIF	100% (100/100)	0	100	NA

c) Stimulation Variables and Regimen

The types of stimulation used in the reported clinical studies included capacitive coupling, PEMF, and combined magnetic fields. Table 19 identifies the stimulation type, the device manufacturer, the output waveform parameters, as described by the authors, and also describes the treatment regimen. PEMF was employed post-operatively from 2 hours per day (Simmons et al., 2004) and up to 12 hours per day (DiSilvestre and Savini, 1992). Duration of use varied as well. Capacitive coupling was used for 24 hours per day for 9 months or until healed (Goodwin et al., 1999). Combined magnetic fields were prescribed for 30 minutes per day for 9 months (Linovitz et al., 2002). Despite the variation in stimulation types, output waveform parameters, and treatment regimens, therapeutic signals were delivered, as evidenced by the establishment of fusions.

Table 19. Description of Stimulation Output Waveform Parameters and Treatment Regimen for Non-invasive Bone Growth Stimulators for Spinal Fusion

Reference	Stimulation Type	Device Manufacturer	Output Waveform Parameters ¹ (Tissue Effect)	Treatment Regimen	Time of Disability
Bose, 2001	PEMF ²	Orthofix	NR ³	4 hrs/day until healed	NR ⁴
DiSilvestre and Savini, 1992	PEMF	NR	1.3 msec at 75 Hz (3.5 mV in tissues)	10-12 hrs/day from Days 5- 60 post-operatively	NR
Goodwin et al., 1999	Capacitive Coupling	Bioelectron	60 kHz, 5 V peak to peak	24 hrs/ day until healed or for 9 months if healing delayed	NR
Jenis et al., 2000	PEMF or Direct Current (DC)	Orthofix	PEMF: NR DC: EBI SpF-2T Implantable	PEMF: At least 2 hrs/day for 135 days DC: Implantable	NR
Linovitz et al., 2002	Combined Magnetic Fields	OrthoLogic	NR ⁵	0.5 hr/day for 9 months	NR
Marks, 2000	PEMF	Orthofix	NR	At least 4 hrs/day from Day 2 post-operatively	NR
Mooney, 1990	PEMF	Orthofix	NR	8 hrs/day	NR
Simmons, 1985	PEMF	EBI, L.P.	250 μsec, pulses repeat for 50 msec and the burst of pulses occur at a rate of 2 per second	8-10 hrs/day for 12 months	Mean 40 months Range 18-101 months
Simmons et al., 2004	PEMF	Orthofix	160 mG signal, 5.85 G pulses, 26 msec pulse duration	At least 2 hrs/day for 90 days	Mean 18.7 months Range 9 months – 12.5 years

¹ As described by the authors cited in the reference

² PEMF – Pulsed electromagnetic field

³ Orthofix reports and output waveform parameter of 260 μsec 20 G pulses repeated at 15 Hz.

⁴ NR –Not reported

⁵ OrthoLogic reports an output waveform parameter of 76.6 Hz sinusoidal 40μT (400 mG) peak to peak AC magnetic field superimposed on 20 μT DC magnetic field.

d) Effectiveness Assessments

The key measurements for determining the effectiveness of Non-invasive Bone Growth Stimulators in studies of lumbar spinal fusion surgeries are radiographic and clinical evidence, as described in Table 20. Serial radiographs were taken to assess bony fusion, which is defined in the following ways: no radiolucency, two-point bridging, bilateral mature uninterrupted bony masses, and percent graft assimilation. Bone mineral density was also evaluated in one study (Jenis et al., 2000). Graded responses were defined in another study in the following manner: Grade 1 equated to obvious pseudarthrosis with clefts within the fusion mass and discontinuity between the transverse processes; Grade 2 equated to possible pseudarthrosis with lucencies within the fusion mass; and, Grade 3 equated to solid arthrodesis with trabecular bridging bone (Linovitz et al., 2002).

In six of the studies, the radiographic assessment was combined with a clinical assessment to provide the overall success of the treatment regimen. The clinical definition of union is based upon evaluation of the subject's level of pain, physical activity or work level, and use of medication with the rating of 'excellent', 'good', 'fair', and 'poor'. These ratings are described as follows: 'Excellent' - return to full pre-operative activities or work, no analgesics, and absence of significant pain; 'Good' - return to most pre-operative activities or work, minimal analgesics, and minimal pain; 'Fair' - inability to perform some pre-operative activities or work, moderate analgesics, and moderate pain; and, 'Poor' - inability to perform any pre-operative activities or work, heavy analgesic use, and significant pain. In some studies, these evaluations are combined for an overall assessment of fusion.

Effectiveness is demonstrated with similar success rates to those reported for nonunion fractures. Significant differences are noted when stimulation groups are compared to control groups. 'Excellent' or 'good' clinical outcomes are also related to the inclusion of stimulation in the treatment regimen. Statistically significant differences favoring stimulation are noted in all but one case.

Table 20. Effectiveness Parameters Reported in the Clinical Studies of the Non-invasive Bone Growth Stimulators for Use as an Adjunct to Lumbar Spinal Fusion Surgery

Reference	Radiological Definition of Fusion	Clinical Definition of Success	Radiological Success ¹ (%)	Clinical Success ¹ (%)	Overall Success (Radiographic and Clinical) ¹ (%)
Bose, 2001	Two-point bridging, no radiolucency, intact hardware	Pain, physical activity level, occupational status ²	98% (47/48)	Excellent: 4.2% (2/48) Good: 79.2% (38/48) Fair: 16.7% (8/48) Poor: 0.0% (0/48) Returned to Work: 59% (23/39) Returned to Physical Activity at Equal or Higher Levels: 89% (43/48) Improvement in Pain: 71% (32/45) No Improvement in Pain: 27% (12/45) Worsened Pain: 2% (1/45)	Radiographic Fusion: 97.9% (47/48) Excellent or Good: 83.3% (40/48)
DiSilvestre and Savini, 1992	A0 - A4 ³	Pain assessment	A3: 61.3% (19/31) A4: 35.5% (11/31) A2: 3.2% (1/31)	Pain Regressed: 96.8% (30/31)	PEMF ⁴ : 64.5% (20/31) at 2 months 96.8% (30/31) at 4 months Historical Control: 36.4% (8/22)

¹ Percentages are calculated based upon the numbers provided in parentheses, which were obtained from the references. Any noted differences between the percentages reported in this table and the reference are slight and the result of rounding differences.

² Clinical Assessment: 'Excellent': return to full pre-operative activities/work, no analgesics, absence of significant pain
 'Good': return to most pre-operative activities /work, minimal analgesics, minimal pain.
 'Fair': inability to perform some pre-operative activities/work, moderate analgesics, moderate pain.
 'Poor': inability to perform any pre-operative activities/ work, heavy analgesics, significant pain

³ A0 bilateral non-union; A1 unilateral non-union; A2 insufficient fusion on one side; A3 continuous fusion without hypertrophy; A4 fusion with hypertrophy of fusion mass

⁴ PEMF – pulsed electromagnetic fields

Table 20. Effectiveness Parameters Reported in the Clinical Studies of the Non-invasive Bone Growth Stimulators for Use as an Adjunct to Lumbar Spinal Fusion Surgery (Continued)

Reference	Radiological Definition of Fusion	Clinical Definition of Success	Radiological Success (%)	Clinical Success (%)	Overall Success (Radiographic and Clinical) (%)
Goodwin et al., 1999	Mature-appearing, uninterrupted bony masses bilaterally at fusion levels	Pain, physical activity level, occupational status	Solid Active: 90.6% (77/85) Sham: 81.9% (77/94) NSD ⁵	Excellent or Good: Active: 88.2% (75/85) Sham: 75.5% (71/94) SD ⁶	Active: 84.7% (72/85) Sham: 64.9% (61/94) SD
Jenis et al., 2000 ⁷	Fusion and bone mass density Grade 3 ⁸	Pain, physical activity level, occupational status	Grade 3: Sham: 81.0% PEMF: 65% DC: 61.0% Bone Mass Density: Sham: 106% PEMF: 125.2% DC: 126.4% NSD	Sham: Excellent: 43.0% Good: 43.0% Fair: 14.0% PEMF: Excellent: 35.0% Good: 50.0% Fair: 10.0% Poor: 5.0% DC: Excellent: 32.0% Good: 37.0% Fair: 31.0%	Grade 3: Sham: 81.0% PEMF: 65.0% DC: 61.0% NSD Trends in increasing density with stimulation. Fusion mass bone density 20% greater at 1 year in stimulation groups.

⁵ NSD – No statistically significant difference

⁶ SD – Statistically significant difference

⁷ This article reported percentages only; it did not report the actual number of subjects in each outcome category.

⁸ Grade 1 – obvious pseudarthrosis with clefts within the fusion mass and discontinuity between the transverse processes

Grade 2 – possible pseudarthrosis with lucencies within the fusion mass

Grade 3 – solid arthrodesis with trabecular bridging bone

Table 20. Effectiveness Parameters Reported in the Clinical Studies of the Non-invasive Bone Growth Stimulators for Use as an Adjunct to Lumbar Spinal Fusion Surgery (Continued)

Reference	Radiological Definition of Fusion	Clinical Definition of Success	Radiological Success (%)	Clinical Success (%)	Overall Success (Radiographic and Clinical) (%)
Linovitz et al., 2002	Fusion Grade 2 or 3 ⁹	NR ¹⁰	Active: 64.4% (67/104) Sham: 43.3% (42/97) SD	NR	Active: 64.4% (67/104) Sham: 43.3% (42/97) SD
Marks, 2000	Serial radiographs Incorporation of graft, no radiolucency, no motion	Pain, physical activity level, occupational status	Active: 97.6% (41/42) Sham: 52.6% (10/19) SD	Active: Excellent: 16.7% (7/42) Good: 57.1% (24/42) Fair: 21.4% (9/42) Poor: 4.8% (2/42) Sham: Excellent: 0% (0/19) Good: 57.9% (11/19) Fair: 26.3% (5/19) Poor: 15.9% (3/19)	Active: 97.6% (41/42) Sham: 52.6% (10/19) SD 75% Agreement between Clinical and Radiological Assessments
Mooney, 1990	Serial Radiographs 50% or more graft assimilation	Pain, physical activity level, occupational status	Active: 92.2% (90/98) Sham: 68.0% ¹¹ (66/97) SD	Active: Excellent: 51.0% (50/98) Good: 35.76% (35/98) Fair: 8.2% (8/98) Poor: 5.0% (5/98) Sham: Excellent: 36.1% (35/97) Good: 50.5% (49/97) Fair: 13.4% (13/97)	Active: 91.8% (90/98) Sham: 68.0% ¹¹ (66/97) SD

⁹ Grades 0 – 3 (0 and 1 no fusion; 2 and 3 successful fusion)

¹⁰ NR – Not reported

¹¹ The article references success rates of both 65% and 67.9%. The success rate of 67.9% was more frequently referenced within the article, and, for this reason was used for calculating rates within this table.

Table 20. Effectiveness Parameters Reported in the Clinical Studies of the Non-invasive Bone Growth Stimulators for Use as an Adjunct to Lumbar Spinal Fusion Surgery (Continued)

Reference	Radiological Definition of Fusion	Clinical Definition of Success	Radiological Success (%)	Clinical Success (%)	Overall Success (Radiographic and Clinical) (%)
Simmons, 1985	Serial Radiographs	NR	Significant Increase in Bony Formation: 85% (11/13)	NR	Solid Fusion: 77% (10/13)
Simmons et al., 2004	Serial Radiographs 50% or more graft assimilation	Pain, physical activity level, occupational status	67% (67/100)	Excellent or Good: 42% (42/100)	67% (67/100)

As observed with the use Non-invasive Bone Growth Stimulators for the treatment of nonunions, successful lumbar fusion rates can vary, ranging from 65.0% (Jenis et al., 2000) to 97.9% (Bose, 2001). Simmons treated 100 subjects who had undergone posterolateral lumbar fusion, anterior lumbar interbody fusion (ALIF) or posterior lumbar interbody fusion (PLIF). This population had radiographically documented pseudarthrosis and clinical symptoms indicative of no progression towards healing for at least 3 or more months. PEMF was used as a non-operative salvage attempt to obtain spinal fusion. Success was achieved in 67 subjects and 42 of these had 'excellent' or 'good' clinical outcomes. This rate is comparable to rates observed with revision surgery, but without the inherent risks and costs of additional surgery.

In a randomized prospective trial, PEMF treatment was compared to Direct Current (DC) and non-stimulated therapy (Jenis et al., 2000) in a population at high risk for developing pseudarthrosis. The control group had a higher rate of Grade 3 fusion (81.0%) than both PEMF (65.0%) and DC (61.0%). The PEMF and DC groups, however, showed higher mass bone density at 12 months, each nearly 20% more than the bone mass density of controls. Although not significant, there is a trend of increasing bone density with the use of Non-Invasive Bone Growth Stimulators. One limitation of the study was the small number of subjects in each group, limiting the statistical analyses. It is also noted that the rate of fusion observed in this particular control group is higher than typically mentioned in the literature.

Combined magnetic fields were compared to a sham control (Linovitz et al., 2002), with a statistically significant improvement in the rate of fusion noted in the stimulated group compared to the sham control (64.4% versus 43.3%).

Additional studies of the effects of stimulation as an adjunct to lumbar spinal fusion surgeries show higher rates of fusion, and both clinical and radiographic successes were demonstrated (Bose, 2001). Forty-eight subjects were treated with PEMF following posterolateral lumbar fusion and 47 exhibited successful fusion (97.9%). Forty of these subjects were rated clinically as 'excellent' or 'good,' with 89% returning to physical activity at equal or higher levels and 59% returning to work. Another study population of similar size underwent the same procedures and was compared to historical controls (DiSilvestre and Savini, 1992). At

4 months, 30 of the 31 PEMF-treated subjects (96.8%) achieved fusion with pain also regressing, compared to the 36.4% level in historical controls. Solid fusion was demonstrated in 77% of a group of PLIF subjects at 12 months (Simmons, 1985). Significant differences compared to controls were also observed in two other PEMF studies (Marks, 2000 and Mooney, 1990). In a retrospective review of lumbar spinal procedures, Marks reported 97.6% fusion compared to placebo (52.6%), which is a significant difference. Combined clinical assessments of 'excellent' and 'good' were 73.8% for the PEMF group and 57.9% for the placebo. Mooney also demonstrated this in a prospective randomized study. The PEMF group achieved 92.2% fusion and clinical outcomes of 50.8% and 35.6% were noted in the categories of 'excellent' and 'good,' respectively. It was reported that the placebo group had 67.9% fusion with 36.1% 'excellent' and 50% 'good' clinical outcomes.

Capacitive coupling as an adjunct to lumbar spinal fusion has also been reported (Goodwin et al., 1999). In a randomized, double-blind study, solid fusion was demonstrated radiographically in 90.6% of the stimulated group compared to 81.9% of the placebo group. Clinical evaluations of 'excellent' or 'good' were present in 88.2% of the active group versus 75.5% of the placebo group. In an overall assessment of solid fusion, this resulted in 84.7% for the active group and 64.9% of the controls is a statistically significant difference.

e) Conclusions

Overall, these studies demonstrate that adjunctive treatment with the Non-invasive Bone Growth Stimulator significantly increases the probability for successful lumbar spinal fusion. These devices providing stimulation via either capacitive coupling, PEMF, or combined magnetic fields demonstrated these benefits. Overall, when compared to control groups; the devices increase the rate of successful fusion in treated subjects by a difference of approximately 20%. Statistically significant success rates were associated with the use of Non-invasive Bone Growth Stimulators.

The primary endpoint used in the majority of these well-controlled, randomized clinical studies incorporated a radiographic assessment of fusion. The studies relied upon a radiographic evaluation by a qualified, independent and blinded panel, or expert, to evaluate fusion using predetermined success criteria. The use of independent reviewers to assess the post-operative radiographic

success of fusions in both active and control groups helps to unequivocally prove the overall benefit of the devices to promote bone formation in subjects undergoing lumbar spinal fusion surgery. The Non-invasive Bone Growth Stimulator promoted fusion in subjects with and without grafts, and with and without instrumentation. It also increased the rate of successful fusion in subjects undergoing different surgical techniques, as well as with subjects with one or more levels fused.

With the exception of one output waveform parameter reported in the literature, all of the devices studied were the FDA-approved devices being sought for reclassification. The application of electrical stimulation via capacitive coupling, PEMF, and combined magnetic fields all demonstrate therapeutic effect with regards to increasing the success rate of lumbar spinal fusion.

C. Detailed Description of Risks with Supporting Data

This section analyzes the risks, failure modes, and regulatory controls for the proposed devices for reclassification to provide a reasonable assurance of safety and effectiveness. The petitioner conducted an extensive literature search, including a review of the FDA databases for Medical Device Reports, to demonstrate that the risks associated with these devices do not pose an unreasonable risk of illness or injury. Further, the failure modes for these devices are well understood based upon their design and testing, providing the opportunity to develop General and Special Controls. With the provision of these General and Special Controls, the petitioner concludes that there should be no delay in the reclassification of non-invasive bone growth stimulator.

Based upon the literature review, the risks associated with the Non-invasive Bone Growth Stimulator have been grouped into the following categories:

- electrical shock,
- burn,
- skin irritation and/or allergic reaction, and
- inconsistent or ineffective treatment.

As evidenced by this review, the risks associated with the Non-invasive Bone Growth Stimulator do not pose an unreasonable risk of illness or injury. The adverse events identified, such as electrical shock, burn or skin irritation/allergic reaction, are typically transient, rarely meet the definition of serious injury as defined by 21 CFR § 803.3(bb), and can be addressed by either terminating or modifying device usage. The last risk of inconsistent or ineffective treatment can be mitigated by device design considerations, such as output selection and ensuring the device alerts the user to inappropriate output waveform parameters.

Each risk is summarized, including a discussion of its occurrence and severity.

1. Electrical Shock

A patient or health care professional could be shocked from the use and operation of the device. The potential reasons for this event are explained below in Table 21. The petitioner conducted a search of the FDA Medical Device Reports databases (MDR and MAUDE databases) in efforts to obtain information about the risk of electrical shock, including its frequency and severity. **Attachment 7** provides a summary of this search. In the FDA safety databases, this event was reported in 2 patients over the last 20 years. Details pertaining to this event are available for review in **Attachment 7**.

No cases of electrical shock are reported in the published literature.

The risk of shock is rarely reported. This reflects the fact that the output is so low for many of the devices that any shock experienced by the patient or health care professional is unlikely to cause a serious injury. Further, the application of well recognized electrical safety testing standards minimizes the risk as well. The petitioner concludes that the probability of a patient being shocked is very low, and can be controlled for these devices through the use of General and Special Controls, which will be explained in Section VI.D.

Table 21: Potential Causes for the Risk of Electrical Shock

Risk	Cause
Electrical Shock	Alternating Current (AC) line voltage exposure during charging of device
	Circuitry malfunction
	Connection or disconnection of electrodes or coils, or control unit while receiving treatment
	Control circuit failure
	Damaged channel jacks
	Defective electrodes or coils, delivering inappropriate output
	Faulty lead wires
	Inappropriate output
	Poor connection between electrodes or coils and lead wires
	Poor solder on circuit board
	Repositioning of the electrodes or coils during treatment

2. Burn

A patient or health care professional could be burned from the use and operation of the device. The potential reasons for this event are explained below in Table 22. The petitioner conducted a search of the Medical Device Reports databases in efforts to obtain information about the risk of burn, including its frequency and severity. Sixteen reports were filed for this event over the last 20 years. Details pertaining to these events are available for review in **Attachment 7**. The majority of the reported burns (7 out of 16) were associated with the use and simultaneous charging of the device while sleeping. The charger became disconnected and burned the patient. Subsequently, the labeling for this particular product was changed to warn the patient against concurrently using and charging the device. The control unit, however, may be worn while sleeping and charged while not in use.

No cases of burn are reported in the published literature.

The risk of burn, including serious burn, is rarely reported. This reflects the fact that the output is so low that if a burn were to occur, it is unlikely to cause a serious injury. The petitioner concludes that the probability of a patient or health care professional experiencing a serious burn is very low, and can be controlled for these devices through the use of General and Special Controls, which will be explained in Section VI.D.

Table 22: Potential Causes for the Risk of Burn

Risk	Cause
Burn	Alternating Current (AC) line voltage exposure during charging of device
	Connection or disconnection of the electrodes or coils, or control unit while receiving treatment
	Defective electrodes or coils, delivering inappropriate output
	Incorrect electrode or coil size or alteration of the electrodes or coils to a hazardous size/shape
	Inappropriate output
	Use of an alternate current source for treatment
	Use of the control unit and battery charger while sleeping

3. Skin Irritation and/or Allergic Reaction

A patient could experience skin irritation and/or allergic reaction associated with the use and operation of the Non-invasive Bone Growth Stimulator. The potential reasons for this event are explained below in Table 23. The petitioner conducted a search of the Medical Device Reports databases, in efforts to obtain information about the risk of skin irritation and/or allergic reaction, including its frequency and severity. One report was filed for this event over the last 20 years. Details pertaining to these events are available for review in **Attachment 7**.

Only 5 of the published articles reviewed in support of this petition mentioned subjects experiencing events of skin irritation and/or allergic reactions (Brighton and Pollack, 1985; Goodwin et al., 1999; Linovitz et al., 2002; Mooney, 1990; and, Scott et al., 1994). Of these five published articles, three clinical studies involved greater than or equal to 50 subjects and were analyzed for rates of occurrence.¹

Goodwin et al. (1999) reported 2.6% of subjects (9/337) experienced skin irritation from the surface electrodes. Linovitz et al. (2002) noted this event in 2.6% of subjects (6/243). Mooney reported 1.9% (2/107) of active subjects experienced “a minor skin rash.” This rate considered only those subjects receiving active treatment; it did not consider those subjects exposed to the device materials from sham treatment. If all subjects with device exposure are included (similar as to how the results are reported for Goodwin et al. and Linovitz et al.), the rate of skin irritation and/or allergic reaction is 1% (2/206). The overall rate of occurrence for the risk of skin irritation and/or allergic reaction reported in the literature ranged from 1.0-2.6%.

The petitioner concludes that the probability of a patient experiencing skin irritation and/or allergic reaction is low. Further, this risk rarely meets the definition of a serious injury. This risk can be controlled for these devices through the use of General and Special Controls, which will be explained in Section VI.D.

Table 23: Potential Causes for Risk of Skin Irritation and/or Allergic Reaction

Risk	Cause
Skin Irritation and/or Allergic Reaction	Non-biocompatible device materials
	Non-biocompatible electrode gel (capacitive coupling only)

¹ The other 2 articles include 43 subjects and reported a total occurrence of 3 events of skin irritation and/or allergic reaction.

4. Inconsistent or Ineffective Treatment

The final risk associated with the device is the possibility of the patient receiving inconsistent or ineffective treatment, due to a number of reasons that are listed in Table 24.

Table 24: Potential Causes for Risk of Inconsistent or Ineffective Treatment

Risk	Cause
Inconsistent or Ineffective Treatment	Battery deterioration
	Control circuit failure
	Defective electrode or coils
	Device damage from dropping or bumping
	Device short circuits
	Driver circuit failure
	Electromagnetic interference (EMI) or radio frequency interference (RFI)
	Failure to follow prescribed use
	Hardware failure
	Improper position of electrodes or coils
	Inappropriate output (e.g., such as intermittent signal from control unit to electrodes or coils)
	Incorrect battery or battery charger used with device
	Ineffective output
	Low battery voltage
	Poor interface between electrodes or coils and patient
Switch failure	

The petitioner conducted a search of the Medical Device Reports databases, in efforts to obtain information about the frequency of reports that were filed due to a lack of or a diminished effect in treatment. Fourteen reports were filed over the last 20 years. The reports concern device malfunctions and/or lack of bone growth. Details pertaining to these events are available for review in **Attachment 7**.

While the published literature focuses on reporting successful rates of nonunion or fusion with the Non-invasive Bone Growth Stimulator, there are reports of inconsistent or ineffective treatment. The reasons attributed for this inconsistent or ineffective treatment varied, but were generally related to a subject's non-compliance with the treatment protocol or subjects who did not return to the clinic for appropriate follow-up.

The published articles submitted with this petition were reviewed for information on inconsistent or ineffective treatment. Seventeen articles addressed this issue in some manner (Adam et al., 1992; Bassett et al., 1977; Bassett, 1981; Basset et al., 1982; Bose et al., 2001; Colson et al., 1988; Delima and Tanna, 1989; Frykman et al., 1986; Garland et al., 1991; Goodwin et al., 1999; Heckman et al., 1981; Linovitz et al., 2002; Mooney, 1990; O'Connor, 1985; Scott et al., 1994; Seder et al., 1982; and, Sharrard et al., 1982). Many of the articles do not distinguish between the lack of overall compliance with protocol, including stimulation, non-weight bearing practices and physical therapy, and inconsistent use of the actual stimulator. This review focuses on the later – inconsistent or ineffective stimulation.

In studies of nonunions, Heckman et al. (1981) reported that 14.4% (25/174) either “failed to return for follow-up evaluation, could not comply with the use of the device for a minimum of 3 months for psychological or economic reasons, refused to use the device as instructed, or had mechanical problems with the device which frustrated continued use.” The specific percentages attributable to each of the aforementioned reasons were not provided. O'Connor (1985) reported an inconsistent or ineffective treatment rate of 3.7% (2/54), stating, “Two were withdrawn for non-compliance with the treatment protocol”. Inconsistent or ineffective treatment due to a subject not returning for further follow-up was reported in 1.9% of subjects (1/52) in the Sharrard et al. (1982) study.

In studies of lumbar spinal fusions, Mooney defined inconsistent use of the device as less than 4 hours (1990). In this study, 34 active subjects and 44 placebo subjects used the device inconsistently (less than 4 hours per day), and 4 additional subjects were reported as lost to follow-up, resulting in a rate of inconsistent or ineffective treatment of 39.8% (82/206). For the Goodwin et al. (1999) study, 63 subjects withdrew or

were dropped from the study by their surgeons: “27 for non-compliance (failure to wear the device or return for follow-up visits), 9 for adverse reactions (all skin irritations), 1 for wound infection, 6 for protocol violations by the surgeon, 6 for relocation, and 14 for voluntary reasons,” resulting in a rate of 15.7% (53/337). In the double-blind study conducted by Linovitz et al. (2002), a rate of 20.8% (26/243) for inconsistent or ineffective treatment was determined. Sixteen subjects (8 active, 8 placebo) “voluntarily withdrew from the study before the 9-month visit,” and “10 patients (5 active, 5 placebo) were withdrawn by their physician(s) from the study before the 9-month visit.” The literature does not report any ineffective waveforms from clinical studies.

Inconsistent treatment may have the potential to cause a serious injury to the patient. Nonetheless, the best means to mitigate this risk is through proper professional and patient labeling. The regulatory requirement of a PMA does not provide for assurance of proper patient compliance. Although ineffective waveforms are not reported in the clinical literature, a device could indeed have an ineffective output waveform. A device producing an ineffective waveform, even if properly used by the patient, could result in a serious injury. The proposed guidance document in **Attachment I** addresses this risk by recommending animal and/or clinical tests to show that a new output waveform, other than those established as effective in the literature, is effective. The application of the Quality System Regulation (21 CFR § 820), particularly device verification and validation testing, reduces the risk of a device with a new output waveform being ineffective.

5. Other Information on Device Safety

In an effort to further demonstrate that the Non-invasive Bone Growth Stimulator does not pose an unreasonable risk of illness or injury, the petitioner compared the output waveform parameters of certain Non-invasive Bone Growth Stimulators to those parameters used for Class II muscle stimulators. The details of this comparison are highlighted below in Table 25. This comparison is not meant to establish a direct correlation between the Non-invasive Bone Growth Stimulator and the aforementioned Class II devices, but it shows that the outputs of the Class III devices are similar to the currently classified Class II devices. It should also be noted that the outputs of the Non-invasive Bone Growth Stimulators are much lower than those used with the comparable 510(k) devices.

Table 25: Comparison of Technological Characteristics for Class II Devices and Class III Non-invasive Bone Growth Stimulators (Being Sought for Reclassification)

Technology	Product Example(s)	Class	Waveform	Tissue Electrical Field
Muscle Stimulation	RS-2mi Family (RS Medical product)	Class II	0-57.5 V, 0-115 mA, 7.04 msec-long bursts of 415 μ sec (max) repeated at 142 pps	5.68 mA/cm ²
Interferential Current Stimulation	RS-2mi Family (RS Medical product)	Class II	0-50 V peak, 0-100 mA peak, 5000 Hz (carrier), 5000-5200 Hz (interference)	5 V/m
Capacitive Coupling	Bionicare	Class II	60 kHz, 4.6-7.6 V peak to peak	8 mV/cm to 360 mV/cm
	OrthoPak SpinalPak	Class III	60 kHz, 10 μ A (rms), 6 V peak to peak	0.1 to 20 mV/cm 300 μ A/cm ²
Pulsed Electromagnetic Fields	Physio-Stim Lite Spinal Stim Lite	Class III	4.5msec-long bursts of twenty 220 μ sec 20-G pulses repeated at 15 Hz	1.5 mV/cm 10 μ A/cm ²
	EBI Bone Healing System	Class III	2.5-msec-long bursts of 250 to 400 μ sec 20-G pulses repeated at 5 to 20 Hz	4 mV/cm peak to peak
Combined Magnetic Fields	OrthoLogic 1000 SpinaLogic	Class III	76.6 Hz sinusoidal 40- μ T (400 mG) peak-to-peak AC magnetic field superimposed on 20- μ T DC magnetic field	Magnetic field effect

A review of the literature and FDA safety databases demonstrates the risks associated with the Non-invasive Bone Growth Stimulator are reasonable. These risks can be grouped into four main categories: 1) electrical shock, 2) burn, 3) allergic reaction and/or skin irritation, and 4) inconsistent or ineffective treatment. These risks do not rise to the level of risk to maintain this product as Class III based upon risk alone, as evidenced by the fact that the risks only rarely meet the definition of a serious injury. The risks associated with the Non-invasive Bone Growth Stimulator are similar in nature, frequency and seriousness to many other Class I and Class II medical devices, demonstrating the ability to provide a reasonable assurance of safety and effectiveness through the use of General and Special Controls. Through the implementation of General and Special Controls, the petitioner will demonstrate that the use and operation of the devices can provide safe and effective delivery of the intended output to the patient.

D. Off-setting Special Controls to Minimize Risk

Tables 26-31 specify those General and Special Controls, recommended by the petitioner, to mitigate the risks of the Non-invasive Bone Growth Stimulator. The risks mentioned in the preceding section can be associated with multiple failure modes. Further, the same failure mode may be associated with multiple risks. For this reason, the tables are organized by listing the particular failure mode, followed by the corresponding risk(s) to the patient, the method for minimizing the risk(s) to the patient, and the specific General and Special Controls to provide a reasonable assurance of device safety and effectiveness. The tables are also organized by device components, such as circuitry and electrodes.

Tables 26-31 propose Special Controls commonly applied to medical devices and incorporate well-recognized guidelines, safety standards and performance standards. This includes the development of a guidance document specific for this type of device. The guidance document, a draft of which is provided in **Attachment 1**, specifies those technological characteristics, such as output waveform parameters, which are known to induce osteogenesis and facilitate healing. Section I of this petition describes in detail those technological characteristics known to be effective. The guidance document will allow for the introduction of new technological features, such as new outputs, if supported by appropriate testing, which may include preclinical and clinical testing.

Table 26: A Summary of the Cause of Circuitry Failures, their Risks, Risk Mitigation Strategies and Controls

Failure	Risk	Risk Mitigation	General and Special Controls
Control circuit failure	Shock	Device should generate an output with specifications for a pre-determined performance period.	Design Control (21 CFR §820.30) <ul style="list-style-type: none"> - Design Input - Design Output - Verification Testing - Validation Testing CDRH Software Testing Guidance Document IEC 60601-1 and 60601-1-2 FDA Guidance Document for Non-invasive BGS Labeling (21 CFR § 801) <ul style="list-style-type: none"> - Professional - Patient
	Inconsistent or Ineffective Treatment	If output falls outside of its specifications, visual and audible signals will be activated, and the device will shut down. The labeling should instruct the user to contact the service department if these signals are activated.	
Driver circuit failure	Inconsistent or Ineffective Treatment	Device will generate an output with specifications for a pre-determined performance period.	Design Control (21 CFR §820.30) <ul style="list-style-type: none"> - Design Input - Design Output - Verification Testing - Validation Testing CDRH Software Testing Guidance Document IEC 60601-1 and 60601-1-2 Guidelines for Non-invasive BGS Labeling (21 CFR § 801) <ul style="list-style-type: none"> - Professional - Patient
		If output falls outside of its specifications, visual and audible signals will be activated, and the device will shut down. The labeling should instruct the user to contact the service department if these signals are activated.	
Circuitry malfunction	Shock	The device will automatically shut down when no output is detected.	Design Control (21CFR820.30) <ul style="list-style-type: none"> - Design Input - Design Output - Verification - Validation IEC 60601-1 and 60601-1-2 Labeling <ul style="list-style-type: none"> - Professional - Patient
		Electronics will be encased in water-resistant housing. The labeling will warn users about use of device near liquids. Users will be Instructed on proper replacement procedures for damaged components and/or devices.	

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Table 26: A Summary of the Cause of Circuitry Failures, their Risks, Risk Mitigation Strategies and Controls (Continued)

Failure	Risk	Risk Mitigation	General and Special Controls
Inappropriate output (e.g., intermittent signal from the control unit to the electrodes or coils)	Shock	Device will generate an output with specifications for a pre-determined performance period.	Design Control (21 CFR §820.30) <ul style="list-style-type: none"> - Design Input - Design Output - Verification Testing - Validation Testing CDRH Software Testing Guidance Document FDA Guidance Document for Non-invasive BGS Labeling (21 CFR § 801) <ul style="list-style-type: none"> - Professional - Patient
	Burn	If output falls outside of its specifications, visual and audible signals will be activated, and the device will shut down.	
	Inconsistent or ineffective treatment	The labeling should instruct the user to contact the service department if these signals are activated.	
Device Short Circuit	Inconsistent or ineffective treatment	Device will generate an output with specifications for a pre-determined performance period.	Design Control (21 CFR §820.30) <ul style="list-style-type: none"> - Design Input - Design Output - Verification Testing - Validation Testing CDRH Software Testing Guidance Document IEC 60601-1 and 60601-1-2 Labeling (21 CFR § 801) <ul style="list-style-type: none"> - Professional - Patient
		If output falls outside of its specifications, visual and audible signals will be activated, and the device will shut down.	
		The labeling should instruct the user to contact the service department if these signals are activated.	
Poor solder on circuit board	Shock	Device will generate an output with specifications for a pre-determined performance period.	Design Control (21 CFR §820.30) <ul style="list-style-type: none"> - Design Input - Design Output - Verification Testing - Validation Testing CDRH Software Testing Guidance Document IEC 60601-1 and 60601-1-2 FDA Guidance Document for Non-invasive BGS Labeling (21 CFR § 801) <ul style="list-style-type: none"> - Professional - Patient
		If output falls outside of its specifications, visual and audible signals will be activated, and the device will shut down. The labeling should instruct the user to contact the service department if these signals are activated.	

Table 27: A Summary of the Cause of Failures with Electrodes, Coils, Lead Wires and Cables, their Risks, Risk Mitigation Strategies and Controls

Failure	Risk	Risk Mitigation	General and Special Controls
Connection or disconnection of electrodes or coils or control unit while receiving treatment	Shock	Labeling will warn the user to only connect or disconnect the electrodes or coils when the device is turned off.	Labeling (21 CFR § 801) - Professional - Patient
	Burn		
Defective electrodes or coils	Burn	The device should be designed to meet recognized safety standards.	Design Control (21 CFR §820.30) - Design Input - Design Output - Verification Testing - Validation Testing IEC 60601-1 and 60601-1-2 Performance Standard for Electrodes (21 CFR § 898) Labeling (21 CFR § 801) - Professional - Patient
	Electrical Shock	Labeling will instruct user to discard and replace damaged parts.	
	Inconsistent or ineffective treatment		
Faulty lead wires	Shock	The device should be designed to meet recognized safety standards.	Design Control (21 CFR §820.30) - Design Input - Design Output - Verification Testing - Validation Testing IEC 60601-1 and 60601-1-2 Performance Standard for Electrodes (21 CFR § 898)
Improper position of the electrodes or coils	Inconsistent or ineffective treatment	The labeling will instruct the user on how to select and position the electrodes or coils.	Labeling (21 CFR § 801) - Professional - Patient
Incorrect electrode or coil size or alteration of the electrodes or coils to a hazardous size/shape	Burn	The labeling will instruct the user on how to select the compatible electrodes or coils, and not to alter them.	Labeling (21 CFR § 801) - Professional - Patient

Table 27: A Summary of the Cause of Failures with Electrodes, Coils, Lead Wires and Cables, their Risks, Risk Mitigation Strategies and Controls (Continued)

Failure	Risk	Risk Mitigation	General and Special Controls
Poor connection between electrode or coils and lead wires	Shock	Labeling will emphasize the need to fully insert lead wires into device.	Design Control (21 CFR §820.30) <ul style="list-style-type: none"> - Design Input - Design Output - Verification Testing - Validation Testing IEC 60601-1 and 60601-1-2 Performance Standard for Electrodes (21 CFR § 898) Labeling (21 CFR § 801) <ul style="list-style-type: none"> - Professional - Patient
		The device should use insulated, flexible lead wires with an adjustable harness to place electrodes or coils, and should be designed to meet recognized safety standards.	
Poor interface between electrodes or coils and patient	Inconsistent or ineffective treatment	If output falls outside of its specifications, visual and audible signals will be activated, and the device will shut down.	Design Control (21 CFR §820.30) <ul style="list-style-type: none"> - Design Input - Design Output - Verification Testing - Validation Testing Labeling (21 CFR § 801) <ul style="list-style-type: none"> - Professional - Patient
		The labeling should instruct the user to contact the service department if these signals are activated.	
		Labeling will instruct user to use electrode gel to improve interface (capacitive coupling only).	
Repositioning the electrodes or coils during treatment	Shock	Labeling will warn the user to only reposition the electrodes or coils when the device is turned off.	Labeling (21 CFR § 801) <ul style="list-style-type: none"> - Professional - Patient

Table 28: A Summary of the Cause of Failures with the Power Supply or Charging, their Risks, Risk Mitigation Strategies and Controls

Failure	Risk	Risk Mitigation	General and Special Controls
Alternating Current (AC) line voltage exposure during charging of device	Shock	If feasible, design the device to operate on batteries only, and not AC line.	Design Control (21 CFR § 820.30) <ul style="list-style-type: none"> - Design Input - Design Output - Verification Testing - Validation Testing IEC 60601-1 and 60601-1-2 Labeling (21 CFR § 801) <ul style="list-style-type: none"> - Professional - Patient
	Burn	If AC line is necessary for power, the device should use an isolated line current and should not operate during the charging cycle (PEMF devices only). Labeling should instruct users on proper battery replacement or charging procedures (e.g., not to charge the battery while operating the device).	
Battery Deterioration	Inconsistent or ineffective treatment	Device should be designed to alert user to batteries, which do not provide sufficient power source to generate the output.	Design Control (21 CFR § 820.30) <ul style="list-style-type: none"> - Design Input - Design Output - Verification Testing - Validation Testing Labeling (21 CFR § 801) <ul style="list-style-type: none"> - Professional - Patient
		The labeling should instruct users about operation of the device and its alarms.	
Incorrect Battery or Battery Charger Used with Device	Inconsistent or ineffective treatment	Device should be designed to be compatible with only its battery charger, if feasible.	Design Control (21 CFR § 820.30) <ul style="list-style-type: none"> - Design Input - Design Output - Verification Testing - Validation Testing Labeling (21 CFR § 801) <ul style="list-style-type: none"> - Professional - Patient
		The labeling should instruct users about proper battery size and use of the dedicated battery charger.	
Low Battery Voltage	Inconsistent or ineffective treatment	Device should be designed to alert user to batteries, which do not provide sufficient power source to generate the output.	Design Control (21 CFR § 820.30) <ul style="list-style-type: none"> - Design Input - Design Output - Verification Testing - Validation Testing Labeling (21 CFR § 801) <ul style="list-style-type: none"> - Professional - Patient
		The labeling should instruct users about operation of the device and its alarms.	

Table 28: A Summary of the Cause of Failures with the Power Supply or Charging, their Risks, Risk Mitigation Strategies and Controls (Continued)

Failure	Risk	Risk Mitigation	General and Special Controls
Use of an alternate current source	Shock	Device should be designed to be compatible with only the appropriate current source.	Design Control (21 CFR §820.30) <ul style="list-style-type: none"> - Design Input - Design Output - Verification Testing - Validation Testing
	Burn	The labeling should instruct the users about the importance of using only the specified current source.	IEC 60601-1 and 60601-1-2 Performance Standard for Electrodes (21 CFR § 898) Labeling (21 CFR § 801) <ul style="list-style-type: none"> - Professional - Patient

Table 29: A Summary of the Cause of Failures for Hardware Defects, their Risks, Risk Mitigation Strategies and Controls

Failure	Risk	Risk Mitigation	General and Special Controls
Damaged Channel Jack	Shock	Device should be designed with appropriate specifications to minimize damage.	Design Control (21 CFR §820.30) <ul style="list-style-type: none"> - Design Input - Design Output - Verification Testing - Validation Testing IEC 60601-1 and 60601-1-2 Labeling (21 CFR § 801) <ul style="list-style-type: none"> - Professional - Patient
		The labeling should instruct users to examine the device for defects, and to return a device with apparent physical defects.	
Device damaged from dropping or bumping	Inconsistent or ineffective treatment	If the device fails to produce the specified output, visual and audible signals will be activated, and the device will shut down.	Design Control (21 CFR §820.30) <ul style="list-style-type: none"> - Design Input - Design Output - Verification Testing - Validation Testing Labeling (21 CFR § 801) <ul style="list-style-type: none"> - Professional - Patient
		The labeling should instruct the user to contact the service department if these signals are activated.	
Electromagnetic interference or radiofrequency interference	Inconsistent or ineffective treatment	Device should be designed to minimized interference.	Design Control (21 CFR §820.30) <ul style="list-style-type: none"> - Design Input - Design Output - Verification Testing - Validation Testing IEC 60601-1 and 60601-1-2
Hardware failure	Inconsistent or ineffective treatment	If the device fails to produce the specified output, visual and audible signals will be activated, and the device will shut down.	Design Control (21 CFR §820.30) <ul style="list-style-type: none"> - Design Input - Design Output - Verification Testing - Validation Testing Labeling (21 CFR § 801) <ul style="list-style-type: none"> - Professional - Patient
		The labeling should instruct the user to contact the service department if these signals are activated.	

Table 29: A Summary of the Cause of Failures for Hardware Defects, their Risks, Risk Mitigation Strategies and Controls (Continued)

Failure	Risk	Risk Mitigation	General and Special Controls
Ineffective output	Inconsistent or ineffective treatment	The output produced by the device should either be known to induce osteogenesis or demonstrated to induce osteogenesis through testing.	Design Control (21 CFR §820.30) <ul style="list-style-type: none"> - Design Input - Design Output - Verification Testing - Validation Testing FDA Guidance Document for Non-Invasive BGS
Switch failure	Inconsistent or ineffective treatment	If the device fails to produce the specified output, visual and audible signals will be activated, and the device will shut down.	Design Control (21 CFR §820.30) <ul style="list-style-type: none"> - Design Input - Design Output - Verification Testing - Validation Testing
		The labeling should instruct the user to contact the service department if these signals are activated.	Labeling (21 CFR § 801) <ul style="list-style-type: none"> - Professional - Patient

Table 30: A Summary of the Patient-Contacting Material Failures, their Risks, Risk Mitigation Strategies and Controls

Failure	Risk	Risk Mitigation	General and Special Controls
Non-biocompatible device materials	Skin irritation and/or allergic reaction	The device should be made from materials known to be biocompatible for skin contact.	ISO 10993 Labeling (21 CFR § 801) - Professional - Patient
		The labeling should instruct the user to discontinue use in the event of irritation and/or allergic reaction and to contact the health care professional.	
Non-biocompatible electrode gel	Skin irritation and/or allergic reaction	The electrode gel should be made from materials known to be biocompatible for skin contact.	ISO 10993 Labeling (21 CFR § 801) - Professional - Patient
		The labeling should instruct the user to discontinue use in the event of irritation and/or allergic reaction and to contact the health care professional.	

Table 31: A Summary of the Failures Associated with the Conditions of Use of the Device, their Risks, Risk Mitigation Strategies and Controls

Failure	Risk	Risk Mitigation	General and Special Controls
Failure to follow prescribed use	Inconsistent or ineffective treatment	The device should be designed with a means to monitor patient compliance and delivery of treatment.	Design Control (21 CFR §820.30) - Design Input - Design Output - Verification Testing - Validation Testing Labeling (21 CFR § 801) - Professional - Patient
		The labeling should emphasize the importance of adhering to the prescribed treatment regimen for optimal results.	
Use of the control unit and battery charger while sleeping	Burn	The labeling should instruct the user not to use the control unit and battery charger while sleeping. The labeling should explain that the device should be charged while not in use.	Labeling (21 CFR § 801) - Professional - Patient

VII. Safety and Effectiveness of the Devices to Be Reclassified

This section of the petition is not specifically required by the Agency regulation. Nevertheless 21 CFR § 860.130(g) states:

“A regulation under this section changing the classification of a device from class III to class II may provide that such classification will not take effect until the effective date of a special control for the device established under section 514 of the act.”

The petitioner’s understanding is that this regulatory prerogative was established to ensure that the specific devices within a type to be reclassified do not present unacceptable risks because the Class II controls would not yet have been applied. This problem could apply, for example, to the reclassification of a pre-Amendments Class III type of device for which premarket approval had not been applied, but was proposed for reclassification to Class II. FDA reserved the right to stay the reclassification action until the specific devices moving from Class III to Class II were made to be safe and effective because of the application of the Special Controls.

In this instance, the petitioner has focused on describing the controls that would be applicable to a new device (e.g., QSR provisions, certain testing requirements within a guidance document, and 510(k) review by FDA). These controls would be immediately applicable to new devices of this type. The specific existing devices that would be immediately affected by this petition, however, would not be subject to some of these controls since the devices already exist. Thus, the petitioner recognizes that the Agency must have some assurance that the specific devices to be reclassified are as safe and effective as the new devices which would be developed under the full range of Special Controls that will be applicable to them. This is the purpose of this section of the petition.

The petitioner recognizes that this discussion is somewhat academic. All but one of the devices under consideration have undergone premarket approval and have been found to be safe and effective by the Agency. The petitioner’s device has not undergone premarket approval, but is a device that is the same as the Bioelectron device both in terms of technological features and intended use. Thus, all these devices are known to be safe and effective.

At the same time, the petitioner recognizes that, as a legal matter, information contained in a premarket approval application (PMA) cannot be used to support the safety or effectiveness of a device except by the person who submitted the application [FDCA, Section 520 (h).] Therefore, the information presented below is taken from the public domain. While this information is not as detailed as what would be required for a PMA, the information is consistent with the Agency’s definition of valid scientific evidence, as defined in 21 CFR § 860.7, and is sufficient to justify the immediate reclassification of

existing devices within this type. The information provides compelling evidence that these specific devices are as safe and effective as they would have been if all the proposed General and Special Controls had been applied to them.

The information is presented on a device-by-device basis. The section pertaining to the petitioner's device references the section on the Bioelectron device, given that the petitioner's device has the same technological characteristics and intended use as that device. This section also includes a comparison of the petitioner's device to the Bioelectron device. This, as explained above, is intended to obviate any need for a 510(k) for the petitioner's device subsequent to the reclassification action.

To supplement the comprehensive literature review presented in Section VI, the petitioner completed a review of literature available for each of the commercially available devices. For each Non-invasive Bone Growth Stimulator detailed in this section, those relevant articles that were discussed in Section VI of this petition are highlighted, followed by a listing and brief discussion of the unique articles identified from the Summaries of Safety and Effectiveness (SSEs), device labeling at the time of product approval, and/or other sources, as the articles were not previously detailed. **Attachment 8** includes a complete bibliography and copies of those articles. This publicly available information supports the safety and effectiveness of these devices and justifies the reclassification of the devices within this type.

A. Bioelectron - OrthoPak Bone Growth Stimulator

The following three articles were identified during the comprehensive literature search discussed in Section VI of this petition. The authors acknowledged using a device manufactured by Bioelectron.

Benazzo, F.; Mosconi, M.; Beccarisi, G., and Galli, U. Use of capacitive coupled electric fields in stress fractures in athletes. *Clin Orthop.* 1995 Jan; 310: 145-149.

Brighton, C. T. and Pollack, S. R. Treatment of recalcitrant non-union with a capacitively coupled electrical field. A preliminary report. *J Bone Joint Surg Am.* 1985 Apr; 67 (4): 577-585.

Scott, G. and King, J. B. A prospective, double-blind trial of electrical capacitive coupling in the treatment of non-union of long bones. *J Bone Joint Surg Am.* 1994 Jun; 76 (6): 820-826.

These articles presented information on the use of this device for the treatment of nonunions and reported an overall rate of effectiveness between 60.0% and 88.0%. Of the 63 subjects that were treated in these studies, three related adverse events were reported (skin irritation and/or allergic reaction to the electrodes).

In addition to the literatures search, the petitioner reviewed publicly available information, such as the PMA SSE, product labeling at the time of approval, and other sources, to identify any further references about the safety and effectiveness of the OrthoPak Bone Growth Stimulator. This resulted in the identification of the following articles:

Boyd, H.B.; Lipinski, S.W.; Wiley, J.H. Observations on non-union of the shafts of the long bones, with a statistical analysis of 842 patients. *J Bone Joint Surg Am.* 1961 Mar; 43A (2): 159-168.

Brighton, C.T., Black, J.; Friedenber, Z.B.; Esterhai, J.L. A multicenter study of the treatment of non-union with constant direct current. *J Bone Joint Surg Am.* 1981 Jan; 63A (1): 2-13.

Muller, M.E.; Thomas, R.J. Treatment of non-union in fractures of long bones. *Clin Orthop.* 1979 Jan-Feb; 138: 141-153.

These three articles focus on the treatment of nonunions using techniques other than the Non-invasive Bone Growth Stimulator, explaining why these articles were not identified during the comprehensive literature search. These articles do not pertain directly to the safety and effectiveness of the device; rather they provide background for the nature and treatment of nonunion fractures. A summary of each article follows. **Attachment 8** provides copies of each article.

Boyd et al. (1961) studied 842 subjects retrospectively in a comparison of various bone graft techniques. A 94.0% (794/842) success rate is observed in this study, despite the differences in fractures and the use of various bone graft techniques. These factors are assessed, as well as an analysis of the failures and the indications for amputation.

Brighton et al. (1981) reported on the use of direct current (DC) in the treatment of acquired nonunions in two study populations. The rate of union using the implanted DC electrodes is compared to historical control subjects having bone graft surgery. The rate of union achieved with DC stimulation in the first population is 83.7% (149/178). The second population showed a rate of 78.8% (149/189). Although there appears to be some difference, there was not a significant difference between the DC-treated and control groups. The safety and effectiveness of the implanted DC device is supported, and it is shown that a similar rate of union can be achieved without bone graft surgery. Electrical stimulation can elicit a comparable rate of union.

The effects of rigid stabilization, employing medullary nails and/or compression plates as well as with external or internal fixation, were reported in a series of 113 subjects (Muller and Thomas, 1979). The characteristics of this population demonstrate the long-term disability observed in these cases. Multiple invasive

surgical interventions were required to achieve union. Although not specifically mentioned in this article, the use of the Non-invasive Bone Growth Stimulator provides an option for treatment in these cases.

B. Bioelectron - SpinalPak Fusion Stimulator

The following article was identified during the comprehensive literature search, discussed in Section VI of this petition. The authors acknowledged using a device manufactured by Bioelectron.

Goodwin, C. B.; Brighton, C. T.; Guyer, R. D.; Johnson, J. R.; Light, K. I., and Yuan, H. A. A double-blind study of capacitively coupled electrical stimulation as an adjunct to lumbar spinal fusions. *Spine*. 1999 Jul 1; 24 (13): 1349-1356, discussion 1357.

The article presented information on the use of this device as an adjunct treatment for lumbar spinal fusions, and reported an overall rate of effectiveness of 84.7%. Of the 337 subjects that were enrolled in this study, a total of nine, related adverse events were reported (skin irritation and/or allergic reaction to the electrodes).

No other unique articles were identified in the PMA SSE and/or the product labeling at the time of approval for this product.

C. EBI, L.P. - EBI Bone Healing System

The following sixteen articles were identified during the comprehensive literature search, discussed in Section VI of this petition. The authors acknowledged using a device manufactured by EBI, L.P.

Adams, B. D.; Frykman, G. K., and Taleisnik, J. Treatment of scaphoid nonunion with casting and pulsed electromagnetic fields: a study continuation. *J Hand Surg [Am]*. 1992 Sep; 17 (5): 910-914.

Bassett, C. A.; Mitchell, S. N., and Gaston, S. R. Pulsing electromagnetic field treatment in ununited fractures and failed arthrodeses. *JAMA*. 1982 Feb 5; 247 (5): 623-628.

Bassett, C. A.; Mitchell, S. N., and Schink, M. M. Treatment of therapeutically resistant non-unions with bone grafts and pulsing electromagnetic fields. *J Bone Joint Surg Am*. 1982 Oct; 64 (8): 1214-1220.

Bassett, C. A.; Pilla, A. A., and Pawluk, R. J. A non-operative salvage of surgically-resistant pseudarthroses and non-unions by pulsing

electromagnetic fields. A preliminary report. *Clin Orthop*. 1977 May; 124: 128-143.

Bassett, C. A.; Mitchell, S. N.; Norton, L., and Pilla, A. Repair of non-unions by pulsing electromagnetic fields. *Acta Orthop Belg*. 1978 Sep-1978 Oct 31; 44 (5): 706-724.

Bassett, C.A. Treatment of ununited tibial diaphyseal fractures with pulsing electromagnetic fields. *J Bone Joint Surg Am*. 1981 Apr; 63 (4): 511-523.

Caullay, J. M. and Mann, T. S. Pulsing electromagnetic fields in the treatment of non-union of fractures. *J R Coll Surg Edinb*. 1982 Mar; 27 (2): 102-107.

Frykman, G. K.; Taleisnik, J.; Peters, G.; Kaufman, R.; Helal, B.; Wood, V. E., and Unsell, R. S. Treatment of nonunited scaphoid fractures by pulsed electromagnetic field and cast. *J Hand Surg [Am]*. 1986 May; 11 (3): 344-349.

Heckman, J. D.; Ingram, A. J.; Loyd, R. D.; Luck, J. V. Jr, and Mayer, P. W. Nonunion treatment with pulsed electromagnetic fields. *Clin Orthop*. 1981 Nov-1981 Dec 31; 161: 58-66.

Hinsenkamp, M.; Ryaby, J., and Burny, F. Treatment of non-union by pulsing electromagnetic field: European multicenter study of 308 cases. *Reconstr Surg Traumatol*. 1985; 19: 147-151.

Marcer, M.; Musatti, G., and Bassett, C. A. Results of pulsed electromagnetic fields (PEMFs) in ununited fractures after external skeletal fixation. *Clin Orthop*. 1984 Nov; 190: 260-265.

Meskens, M. W.; Stuyck, J. A., and Mulier, J. C. Treatment of delayed union and nonunion of the tibia by pulsed electromagnetic fields. A retrospective follow-up. *Bull Hosp Jt Dis Orthop Inst*. 1988 Fall; 48 (2): 170-175.

O'Connor, B. T. Treatment of surgically resistant non-unions with pulsed electromagnetic fields. *Reconstr Surg Traumatol*. 1985; 19: 123-132.

Sedel, L.; Christel, P.; Duriez, J.; Duriez, R.; Evrard, J.; Ficat, C.; Cauchoix, J., and Witvoet, J. Results of non unions treatment by pulsed electromagnetic field stimulation. *Acta Orthop Scand Suppl*. 1982; 196: 81-91.

Sharrard, W. J.; Sutcliffe, M. L.; Robson, M. J., and Maceachern, A. G. The treatment of fibrous non-union of fractures by pulsing electromagnetic stimulation. *J Bone Joint Surg Br.* 1982; 64 (2): 189-193.

Simmons, J. W. Treatment of failed posterior lumbar interbody fusion (PLIF) of the spine with pulsing electromagnetic fields. *Clin Orthop.* 1985 Mar; 193: 127-132.

These articles presented safety and effectiveness information on the use of this device for the treatment of nonunions and as an adjunct treatment for lumbar spinal fusions, and reported overall rates of effectiveness ranging from 64.4% - 100%. Of the 2,380 subjects that were treated in these studies, no adverse events were reported that were related to the operation and use of the device.

The following articles were obtained from the PMA SSE and/or the product labeling at the time of approval for the EBI device.

Bassett, C.A.L.; Pawluk, R.J. Acceleration of fracture repair by electromagnetic fields. A surgically noninvasive method. *N.Y. Acad. Sci.* 1974; 238: 242-262.

Bassett, C.A.L. Augmentation of bone repair by inductively coupled electromagnetic fields. *Science.* 1974 May; 575-577.

These two articles describe preclinical studies, explaining why they were not identified during the comprehensive literature search. They provide support for the potential effectiveness of PEMF in stimulating bone growth. A summary of each article follows. **Attachment 8** provides copies of each article.

Following the demonstration that increased osteogenesis stimulated using electrical currents was the result of increased DNA and collagen synthesis, animal studies (rabbits) were conducted (Bassett and Pawluck, 1974). The repair of canine osteotomies using PEMF was also reported (Bassett, 1974). An increase in the organization and repair process is demonstrated 28 days following fracture. These reports provided early support for the potential effectiveness of these devices.

D. Orthofix, Inc. - Physio-Stim Lite

The following article was identified during the comprehensive literature search, discussed in Section VI of this petition. The authors acknowledged using a device manufactured by Orthofix, Inc.

Garland, D.E.; Moses, B.; Salyer, W. Long-term follow-up of fracture nonunions treated with PEMFs. *Cont Orthop.* 1991 Mar; 22 (3): 295-302.

The article presented information on the use of this device for the treatment of nonunions. An overall effectiveness rate of 92.0% was reported. Of the 181 subjects that were enrolled in this study, no adverse events related to the operation and use of the device were reported.

In addition to the comprehensive literature search, the following article was obtained from the PMA SSE and/or the product labeling at the time of approval for the Physio-Stim Lite device.

Beckenbaugh, R.D. Noninvasive pulsed electromagnetic stimulation in the treatment of scaphoid nonunion. *J Bone Joint Surg Am.* 1984; 8(1); 19.

This particular reference is an abstract and not a complete article from a peer-reviewed journal, explaining why this article was not identified in the literature search. A summary of the abstract follows. **Attachment 8** provides a copy of the article. In the abstract, the treatment of 21 subjects with established nonunion of the scaphoid with PEMF is described. In non-displaced fractures, the healing rate was 90.0%, with an overall healing rate of 60.0%. The author concluded that PEMF should be offered as a treatment of choice in non-displaced scaphoid fractures.

E. Orthofix, Inc. – Spinal-Stim Lite

The following five articles were identified during the comprehensive literature search, discussed in Section VI of this petition. The authors acknowledged using a device manufactured by Orthofix, Inc.

Bose, B. Outcomes after posterolateral lumbar fusion with instrumentation in patients treated with adjunctive pulsed electromagnetic field stimulation. *Adv Ther.* 2001 Jan-2001 Feb 28; 18 (1): 12-20.

Jenis, L. G.; An, H. S.; Stein, R., and Young, B. Prospective comparison of the effect of direct current electrical stimulation and pulsed electromagnetic fields on instrumented posterolateral lumbar arthrodesis. *J Spinal Disord.* 2000 Aug; 13 (4): 290-296.

Marks, R. A. Spine fusion for discogenic low back pain: outcomes in patients treated with or without pulsed electromagnetic field stimulation. *Adv Ther.* 2000 Mar-2000 Apr 30; 17 (2): 57-67.

Mooney, V. A randomized double-blind prospective study of the efficacy of pulsed electromagnetic fields for interbody lumbar fusions. *Spine.* 1990 Jul; 15 (7): 708-712.

Simmons, J. W. Jr; Mooney, V., and Thacker, I. Pseudarthrosis after lumbar spine fusion: nonoperative salvage with pulsed electromagnetic fields. Am J Orthop. 2004 Jan; 33 (1): 27-30.

These articles presented information on the use of this Non-invasive Bone Growth Stimulator as an adjunct treatment for lumbar spinal fusions, reporting overall rates of effectiveness ranging from 65.0% - 97.9%. Of the 480 subjects that were enrolled in these studies, no related adverse events were reported.

No other unique articles were identified in the PMA SSE and/or product labeling at the time of approval for this product.

F. OrthoLogic – OrthoLogic 1000

No articles were identified during the comprehensive literature search, acknowledging use of a device manufactured by OrthoLogic for the treatment of nonunions. For this reason, the petitioner conducted an online search of publicly available information, ultimately locating and obtaining a copy of a white paper (Source: <http://regentek.djortho.com/research>). The white paper describes the results from a clinical study investigating device safety and effectiveness. The petitioner searched the PubMed database using the names of the 17 investigators listed in the white paper who participated in the clinical study. None of the names entered into PubMed database generated a peer-reviewed journal pertaining to the application of combined magnetic fields for the treatment of nonunions, explaining why no articles regarding this study were found in the literature search. Details of the study conducted on the OrthoLogic device follows. (Treatment parameters associated with the use of the device are located in Table 2 of this petition.)

A total of 112 subjects were enrolled in this nonunion clinical study across 17 centers between 1989 and 1991, with a total of 116 fractures treated (4 subjects had 2 distinct nonunion sites that were treated concurrently).

Eleven different bones represented the 116 fractures, with the breakdown of these fracture locations as follows:

- Tibia: 52
- Femur: 19
- Scaphoid: 17
- Humerus: 9
- Ulna: 7
- Fibula: 6
- Other: 6 (Malleolus: 2; Radius: 1; Metacarpal: 1; Capitate: 1; Metatarsal: 1)

The mean for prior surgical procedures was 2.5, ranging from 0 to 11. The percentage of subjects that had one or more prior surgical procedures was 81.9% (95/116), and 18.1% (21/116) had no prior procedures. In addition to this information, it should be noted that many of these subjects were destined for additional surgical interventions, possible amputations or continued disability and pain.

The clinical study used the following definition for radiographic and clinical success. "A nonunion was determined to be healed if three or more cortices were bridging the fracture gap based on radiographic assessment by an independent review panel, no motion was seen clinically at the fracture site, and no pain was associated with the fracture. Pain was assessed at rest, with the application of stress, and upon weight-bearing (if applicable) at the nonunion site."

Thirty-two of the 112 subjects did not complete the study for the following reasons: 16 voluntarily withdrew; 5 were non-compliant; 8 withdrew due to study protocol violations; 1 was hospitalized for a pre-existing medical condition; 1 was incarcerated; and 1 geographically relocated and was unable to continue the study.

The average healing time for the fractures treated was 6 months. Forty-eight (51 fractures) of the 80 remaining subjects (84 fractures) with established nonunions and who completed the study were healed, and 32 subjects (33 fractures) did not heal, corresponding to rates of 60% and 40%, respectively. The overall success rate for all fracture types was 60.7% (49/80), 75.6% (60/80) for fractures of the tibia, and 73.6% (59/80) for all fractures less than 2 years post-injury. Of the 48 subjects (51 fractures) who completed the treatment and healed, 100% of the fractures were still healed 3 months post-treatment. When compared to the morbidity and mortality associated with surgical intervention, no significant morbidity occurred.

The following articles were obtained from the PMA SSE and/or the product labeling at the time of approval for the device.

Boyd, H.B.; Lipinski, S.W.; Wiley, J.H. Observations on non-union of the shafts of the long bones, with a statistical analysis of 842 patients. *J Bone Joint Surg Am.* 1961 Mar; 43A (2): 159-168.

DeHaas, W.G.; Beaupré, A.; Cameron, H., English, E. The Canadian experience with pulsed electromagnetic fields in the treatment of ununited tibial fractures. *Clin Orthop.* 1986 July; 208: 55-58.

Heppenstall, R.B. *Fracture Treatment and Healing.* W.B. Saunders Co. 1-1069.

ZumBrunnen, J.D., Brindley, H.H. Nonunion of the shafts of the long bones. JAMA. 1968 Feb, 203 (9): 121-124.

Three of these articles focus on the treatment of nonunions using techniques other than the Non-invasive Bone Growth Stimulator, explaining why the articles were not identified during the comprehensive literature search. Summaries of the articles follow. **Attachment 8** provides copies of each article.

The study reported by Boyd et al. (1961) was previously described in the section detailing the unique articles for the OrthoPak device, and pertains to the comparison of bone graft techniques. The information provided by Heppenstall contains information about fractures of the specific regions of the body, their anatomy, and surgical methods for healing (i.e. fixation and bone grafting). Alternative methods for operating are also discussed, but information on bone growth stimulators was not discussed. ZumBrunnen et al. (1968) presents an analysis of long bone nonunions and surgical treatment options and considerations.

One article describes the treatment of nonunions with the device. Experience with PEMF in the treatment of 54 Canadian patients is presented by DeHaas et al. (1985). A clinical survey of patients with ununited tibial fractures was conducted to evaluate the effect of pulsed magnetic fields (PMF). The time from injury to the initiation of PMF treatment ranged from 6 months to 13 years. Of the 56 patients, 38 had undergone one or more surgical procedures (67.9%). Eighty-seven percent achieved union (47/54). This article did not appear in the comprehensive literature search due to the authors describing the device as using “pulsed magnetic fields.” These devices are commonly referred to as using “electromagnetic fields” and those terms were used in the literature search methodology.

G. OrthoLogic - SpinaLogic

The following article was identified during the comprehensive literature search, discussed in Section VI of this petition. The authors acknowledged using a device manufactured by OrthoLogic.

Linovitz, R. J.; Pathria, M.; Bernhardt, M.; Green, D.; Law, M. D.; McGuire, R. A.; Montesano, P. X.; Rehtine, G.; Salib, R. M.; Ryaby, J. T.; Faden, J. S.; Ponder, R.; Muenz, L. R.; Magee, F. P., and Garfin, S. A. Combined magnetic fields accelerate and increase spine fusion: a double-blind, randomized, placebo controlled study. Spine. 2002 Jul 1; 27 (13): 1383-1389; discussion 1389.

The article presented information on the use of this Non-invasive Bone Growth Stimulator as an adjunct treatment for lumbar spinal fusions with combined

magnetic fields. An overall effectiveness rate of 64.4% was reported. Of the 243 subjects that were enrolled in this study, six related adverse events were reported (skin irritation and/or allergic reaction to the electrodes).

No other unique articles were identified in the PMA SSE and/or product labeling at the time of approval for this product.

H. RS Medical Device

The petitioner is requesting that its new device be reclassified from Class III to Class II as a result of this petition. This section of the petition provides a description of the petitioner's new device and compares it to another commercially available device, the Bioelectron Non-invasive Bone Growth Stimulator to obviate any need for a 510(k) for the petitioner's new device subsequent to the reclassification action. It also compares the testing of this new device to the proposed Special Controls present in the draft guidance document for this generic type of device. The petitioner has not yet developed a trade name for its new device, but simply refers to it as the RS Medical Non-invasive Bone Growth Stimulator.

The RS Medical Non-invasive Bone Growth Stimulator is intended for use for 1) the treatment of established nonunion fractures acquired secondary to trauma (excluding vertebrae and flat bone), and 2) as an adjunct to the treatment of lumbar spinal fusion surgery for one or two levels. The device provides electrical stimulation to promote osteogenesis to facilitate the healing of fractures and lumbar spinal fusions; the device relies upon capacitive coupling technology. The small electrical component of the device delivers stimulation to the treatment site through the application of externally applied electrodes. The RS Medical Non-invasive Bone Growth Stimulator uses the identical output waveform as the Bioelectron Non-invasive Bone Growth Stimulator – a sinusoidal waveform with an amplitude of 3.0 to 6.3 Volts peak to peak and a frequency of 60 kHz.

The RS Medical Non-invasive Bone Growth Stimulator is a compact, battery operated device similar to the Bioelectron Non-invasive Bone Growth Stimulator. The RS Medical Non-invasive Bone Growth Stimulator monitors its output and provides a visual and audible warning if the output falls outside its range or if the battery voltage is low. It uses a 9-Volt alkaline battery as its power source. This is essentially the same as the Bioelectron device. Accessories for the RS Medical Non-invasive Bone Growth Stimulator include additional electrodes, cables and connectors, carrying case, belts and a physician test meter.

The RS Medical Non-invasive Bone Growth Stimulator will meet the General and Special Controls identified in the draft guidance document. The electrodes will either be made from materials with an established biocompatibility performance for skin contact or will be evaluated in accordance with ISO 10993, Biological

Evaluation of Medical Devices Part 1 – Evaluation and Testing. The RS Medical Non-invasive Bone Growth Stimulator will meet the following standards and performance standards: IEC 60601-1, IEC 60601-1-2 and 21 CFR Part 898. The device will undergo software verification and validation testing as well.

I. General Review References

General references on stimulation and bone growth are also provided as overview articles in **Attachment 8**. The early work and development related to the generation of electrical potentials by bone in response mechanical stress (Bassett and Becker, 1962) and developing a non-invasive method for inducing these potentials to stimulate osteogenesis are discussed (Bassett, 1975). The history and development of PEMF, as well as the proposed mechanisms of action, are presented in detail in a chapter by Bassett (1978).

Finally, various physical modalities used to manage nonunions are reviewed (Nelson et al., 2003). This article reviews the stimulation of bone healing, implantable direct current, PEMF, capacitive coupling, combined magnetic fields, and ultrasound. The basic science, clinical data, and current indications for each modality are discussed. Although they have different mechanisms for stimulating osteogenesis and bone healing, an increase in intracellular calcium is elicited by all of those signals.

VIII. Representative Unfavorable Information

Unfavorable information has been cited in Section VI and identified as risks of the device.

IX. Summary of the New Information

All the information presented in this petition is being analyzed for the first time from a new perspective of supporting the reclassification efforts of a generic type of device, rather than demonstrating the safety or effectiveness of a specific device. Thus, all the data and analysis within this petition are new.

X. Copies of Source Documentation

This petition provides the following source documentation:

1. **Attachment 1:** Proposed FDA Guidance Document Entitled “Class II Special Controls Guidance Document: Contents of Premarket Notifications [510(k)s] for Non-invasive Bone Growth Stimulators”
2. **Attachment 2:** Supplemental Data Sheet for the Non-invasive Bone Growth Stimulator

3. **Attachment 3:** Classification Questionnaire for the Non-invasive Bone Growth Stimulator
4. **Attachment 4:** Literature Search Strategy and Results
5. **Attachment 5:** Bibliography of the Benefits of the Non-invasive Bone Growth Stimulator for Nonunions and Delayed Unions
6. **Attachment 6:** Bibliography for the Benefits of the Non-invasive Bone Growth Stimulator as an Adjunct for Spinal Fusion
7. **Attachment 7:** Safety Information on the Non-invasive Bone Growth Stimulator from the Medical Device Reports Databases
8. **Attachment 8:** Bibliography of the Additional Citations Regarding the Commercially Available Non-invasive Bone Growth Stimulators

XI. Financial Certification

The petitioner did not sponsor any of the clinical studies cited in this petition, thus the petitioner has not entered into any financial arrangement with the clinical investigators for the conduct of these studies. The petitioner certifies that all the clinical investigators identified in the published articles do not have a proprietary interest in petitioner's non-invasive bone growth stimulator (the product) or a significant equity interest in the petitioner's company, which is privately owned.