Attachment VII

Proposed FDA Guidance Document Entitled "Class II Special Controls Guidance Document: Contents of Premarket Notifications [510(k)s] for Non-invasive Bone Growth Stimulators"

NOVEMBER 30, 2005
~~FEBRUARY 2, 2005~~

1.0 Introduction

This guidance document was developed as a special control guidance to support the reclassification of Non-invasive Bone Growth Stimulators into class II. The 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. This guidance will be issued in conjunction with a Federal Register notice announcing reclassification of this device type.

As stated on the coversheet, this guidance supersedes "Guidance Document for Industry and CDRH Staff for the Preparation of Investigational Device Exemptions and Premarket Approval Applications for Bone Growth Stimulator Devices," dated March 18, 1998.

Following the effective date of the final rule classifying the device, any firm submitting a premarket notification 510(k) for a Non-invasive Bone Growth Stimulator will need to address the issues covered in the special control guidance. However, the firm need only show that its device meets the recommendations of the guidance or in some other way provides equivalent assurances of safety and effectiveness.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

2.0 Background

FDA believes that special controls, when combined with the general controls, will be sufficient to provide reasonable assurance of the safety and effectiveness of Non-invasive Bone Growth Stimulators. Thus, a manufacturer who intends to market a device of this generic type should (1) conform to the general controls of the Federal Food, Drug & Cosmetic Act (the Act), including the 510(k) requirements described in 21 CFR 807 Subpart E, (2) address the specific risks to health associated with Non-invasive Bone

Growth Stimulators identified in this guidance and (3) obtain a substantial equivalence determination from FDA prior to marketing the device.

This special control guidance document identifies the classification regulations and product codes for the Non-invasive Bone Growth Stimulators to which it applies (refer to Section 4 – **Scope**). In addition, other sections of this special control guidance document list the risks to health identified by FDA and describe measures that, if followed by manufacturers and combined with the general controls, will generally address the risks associated with these Non-invasive Bone Growth Stimulators and lead to a timely 510(k) review and clearance. This document supplements other agency documents regarding the specific content requirements of a 510(k) submission. You should also refer to 21 CFR 807.87 and other agency documents on this topic, such as the **510(k) Manual - Premarket Notification: 510(k) - Regulatory Requirements for Medical Devices**, http://www.fda.gov/cdrh/manual/510kprt1.html.

Under "**The New 510(k) Paradigm - Alternate Approaches to Demonstrating Substantial Equivalence in Premarket Notifications; Final Guidance**," http://www.fda.gov/cdrh/ode/indicate/html, a manufacturer may submit a traditional 510(k) or has the option of submitting either an Abbreviated 510(k) or a Special 510(k). FDA believes an Abbreviated 510(k) provides the least burdensome means of demonstrating substantial equivalence for a new device, particularly once a Class II Special Controls Guidance Document has been issued. Manufacturers considering modifications to their own cleared devices may lessen the regulatory burden by submitting a Special 510(k).

The Least Burdensome Approach

The issues identified in this guidance document represent those that we believe need to be addressed before your device can be marketed. In developing the guidance, we carefully considered the relevant statutory criteria for Agency decision-making. We also considered the burden that may be incurred in your attempt to comply with the statutory and regulatory criteria in the manner suggested by the guidance and in your attempt to address the issues we have identified. We believe that we have considered the least burdensome approach to resolving the issues presented in the guidance document. If, however, you believe that there is a less burdensome way to address the issues, you should follow the procedures outlined in the "**A Suggested Approach to Resolving Least Burdensome Issues**" document. It is available on our Center web page at: http://www.fda.gov/cdrh/modact/leastburdensome.html.

3.0 The Content and Format of an Abbreviated 510(k) Submission

An Abbreviated 510(k) submission must include the required elements identified in 21 CFR 807.87, including the proposed labeling for the device sufficient to describe the device, its intended use, and the directions for its use. In an Abbreviated 510(k), FDA may consider the contents of a summary report to be appropriate supporting data within

the meaning of 21 CFR 807.87(f) or (g); therefore, we recommend that you include a summary report. The report should describe how this special control guidance document was used during the device development and testing and should briefly describe the methods or tests used and a summary of the test data or description of the acceptance criteria applied to address the risks identified in this guidance document, as well as any additional risks specific to your device. This section suggests information to fulfill some of the requirements of 807.87 as well as some other items that we recommend you include in an Abbreviated 510(k).

Coversheet

The coversheet should prominently identify the submission as an Abbreviated 510(k) and cite the title of this Class II Special Controls Guidance Document.

Proposed Labeling

Proposed labeling should be sufficient to describe the device, its intended use, and the directions for its use. (Refer to Section 14 for specific information that should be included in the labeling for devices of the types covered by this guidance document.)

Summary Report

We recommend that the summary report contain:

Description of Device and Its Intended Use

We recommend that the description include a complete discussion of the performance specifications and, when appropriate, detailed, labeled drawings of the device. (Refer to Section 5 for specific information that we recommend you include in the device description for devices of the types covered by this guidance document.) You should also submit an "indications for use" enclosure.[1]

Description of Device Design Requirements

We recommend that you include a brief description of the device design requirements.

Identification of Risk Analysis Method

We recommend that you identify the Risk Analysis Method(s) used to assess the risk profile, in general, as well as the specific device's design and the results of this analysis. (Refer to Section 6 for the risks to health generally associated with the use of this device that FDA has identified.)

[1] Refer to http://www.fda.gov/cdrh/ode/indicate/html for the recommended format.

Discussion of Device Characteristics

We recommend that you discuss the device characteristics that address the risks identified in this Class II Special Controls Guidance Document, as well as any additional risks identified in your risk analysis.

Description of Performance Aspects

We recommend that you include a brief description of the test method(s) you have used or intend to use to address each performance aspect identified in Section 7 of this Class II Special Controls Guidance document. If you follow a suggested test method, you may cite the method rather than describing it. If you modify a suggested test method, you may cite the method but should provide sufficient information to explain the nature of and reason for the modification. For each test, you may either (1) briefly present the data resulting from the test in clear and concise form, such as a table, **or** (2) describe the acceptance criteria that you will apply to your test results.[2] (See also 21 CFR 820.30, Subpart C - Design Controls for the Quality System Regulation.)

Reliance on Standards

If you choose to rely on a recognized standard for any part of the device design or testing, you may include either a:

- Statement that testing will be conducted and meet specified acceptance criteria before the product is marketed; or
- Declaration of conformity to the standard.[3]

Please note that testing must be completed before submitting a declaration of conformity to a recognized standard. For more information, please refer to 21 USC 514(c)(2)(B) of the Act and the FDA guidance, **Use of Standards in Substantial Equivalence Determinations; Final Guidance for Industry and FDA**, http://www.fda.gov/cdrh/ode/guidance/1131.html.

If it is not clear how you have addressed the risks identified by FDA or through your risk analysis, we may request additional information about aspects of the device's performance characteristics. We may also request additional information if we need it to

[2] If FDA makes a substantial equivalence determination based on acceptance criteria, the subject device should be tested and shown to meet these acceptance criteria before being introduced into interstate commerce. If the finished device does not meet the acceptance criteria, and thus differs from the device described in the cleared 510(k), FDA recommends that submitters apply the same criteria used to assess modifications to legally marketed devices (21 CFR 807.81(a)(3)) to determine whether marketing of the finished device requires clearance of a new 510(k).

[3] See Required Elements for a Declaration of Conformity to a Recognized Standard (SCREENING CHECKLIST FOR ALL PREMARKET NOTIFICATION [510(k)] SUBMISSIONS), http://www.fda.gov/cdrh/ode/reqrecstand.html.

assess the adequacy of your acceptance criteria. (Under 21 CFR 807.87(l), we may request any additional information that is necessary to reach a determination regarding substantial equivalence.)

As an alternative to submitting an Abbreviated 510(k), you can submit a traditional 510(k) that provides all of the information and data required under 21 CFR 807.87 and described in this guidance. A traditional 510(k) should include all of your methods, data, acceptance criteria, and conclusions. Manufacturers considering modifications to their own cleared devices should consider submitting Special 510(k)s.

The general discussion above applies to any device subject to a special controls guidance document. The following is a specific discussion of how you should apply this special controls guidance document to a premarket notification for Non-invasive Bone Growth Stimulators.

4.0 Scope

The scope of this guidance document is currently limited to Non-invasive Bone Growth Stimulators as described in 21 CFR 8XX.XXXX.

§ 8XX.XXXX Non-invasive Bone Growth Stimulator

(a) *Identification.* A Non-invasive Bone Growth Stimulator 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, or 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 (Sspecial Ceontrols). 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~~and.~~
~~(vi)~~vi. Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices~~.~~.

In the companion final rule, FDA is finalizing the names and identification of this device type as described above. ~~This classification regulation is limited to those technologies described in **Table 1**.~~

~~**Table 1** also identifies those accompanying output parameters (waveforms) and tissue effects demonstrated to be safe and effective. Alternative waveforms and/or tissue effects may be demonstrated to be substantially equivalent with appropriate preclinical and/or clinical testing.~~

~~**Table 1: Designated Non-invasive Bone Growth Stimulators**~~

~~**Technology**~~	~~**Waveform**~~	~~**Tissue Electrical Field**~~
~~Capacitive Coupling~~	~~60 kHz, 10μA (rms), 6 V peak to peak~~	~~0.1 to 20 mV/cm~~ ~~300 μA/cm²~~
~~Pulsed Electromagnetic Fields~~	~~4.5-msec-long bursts of 20, 220-μsec 18-G pulses repeated at 15 Hz~~	~~1.5 mV/cm~~ ~~10 μA/cm²~~
	~~790-mG field of a burst of 21, 260-μsec pulses repeated at 15 Hz~~	~~4 mV/cm peak-to-peak~~
~~Combined Magnetic Fields~~	~~76.6 Hz sinusoidal 40-μT (400 mG) peak-to-peak AC magnetic field superimposed on 20-μT DC magnetic field~~	~~Magnetic field effect~~

~~Adapted from Nelson et al., 2003. Use of Physical Forces in Bone Healing. *Journal of the American Academy of Orthopedic Surgeons*, 11: 344-354.~~

5.0 Device Description

Description of Output Waveform Generator

We recommend that you provide a thorough description of the proposed device with the predicate devices. This description should include the following information:

- A written description of the proposed device, including its power source, all accessories, and any new features of the device.
- Identification of the relevant dimensions, weight, and material composition for the proposed device and accessories.
- A description of the user controls, displays, functions, and alarms emphasizing those that facilitate proper device operation and patient compliance when using the device.
- A description of how the proposed device interconnects with its accessories and how to connect electrodes and/or coils to the patient, including the use of any positioning accessories (guides and blocks).
- The specific intended anatomical location and orientation of each unique electrode and/or coil, including the use of any positioning accessories, relative to the treatment site.
- Engineering drawings and/or photographs of the proposed device.
- A detailed table comparing the relevant features and specifications of the proposed and predicate devices. This side-by-side comparison table should be accompanied by a discussion of the similarities and differences between the devices and should be sufficiently detailed to provide a basis for a substantial equivalence determination.

Additional information on the technological characteristics, such as the output waveform for each technology, should be provided as described later in this document.

Description of Accessories

All relevant technological characteristics should be listed and described for each device accessory. -Each device accessory should be compared to the predicate device using a table, including a side-by-side comparison of its design, materials, and technological characteristics. For any accessory that is not currently legally marketed, the following information should be provided (this information is identified below by accessory):

Electrodes

A description of the ~~The~~ type and size of all available and recommended electrodes, including ~~should be specified. Describe the~~ dimensions, surface area, materials, and configuration of the leads and electrodes. This should include a description of the ~~, and clearly indicate the method of~~ attach~~ing~~ment of the leads and electrodes to the patient. This description should be supplemented with pictures and/or engineering diagrams with specifications.

Electrode Conductive Medium (Gel)

If the electrodes are to be used with a conductive medium, provide the chemical composition and specifications of that medium.

Electrode Lead Wires and Patient Cables

A complete ~~D~~description~~e~~ of the wires and cables, including the length(s), construction, materials, and connections, and compliance with the ~~between the stimulator device and the electrodes. The electrode lead wires and patient cables intended for use with a medical device are subject to the~~ mandatory performance standard set forth in 21 CFR Part 898. This description should be supplemented with pictures and/or engineering diagrams with specifications.

Coils and Positioning Accessories

A complete description of the recommended coils, including ~~The~~ type, ~~and~~ size, materials, geometry, configuration, number of turns and windings, and method of ~~of all available and recommended coils should be specified. Describe the dimensions, materials, and configuration of the coils, and clearly indicate the method of~~ attach~~ing~~ment to ~~the coils to~~ the patient, including any positioning accessories (blocks or guides). This description should be supplemented with pictures and/or engineering diagrams with specifications for the coils and positioning accessories.

Batteries

For those devices that are battery-powered, the requirements for the number, the size and chemical type (e.g. alkaline, lithium, Ni-Cad) of batteries should be provided, in addition to the battery's duration of operation relative to the treatment duration.

Battery Charger

If the device can be used with rechargeable batteries, provide a description of the recharging equipment, recharging procedures, and the time required to fully recharge depleted batteries. For those devices that operate on alternating current (AC), identify the method for isolating the line current from the patient, and leakage current results.

Physician Test Meter

The Non-invasive Bone Growth Stimulator may have a Physician Test Meter to monitor the number of days of device use, and to evaluate the device's output waveforms. If you intend to supply such a Physician Test Meter, please provide a complete description of this accessory, including user controls, displays and functions.

6.0 Risks to Health

In the table below, FDA has identified the risks to health generally associated with the use of Non-invasive Bone Growth Stimulators addressed in this document. The measures recommended to mitigate these identified risks are given in this guidance document, as shown in the table below. You should also conduct a risk analysis, prior to submitting your 510(k), to identify any other risks specific to your device. Your 510(k) should describe the risk analysis method. If you elect to use an alternative approach to address a particular risk identified in this guidance document, or have identified risks additional to those in the guidance, you should provide sufficient detail to support the approach you have used to address that risk.

Table ~~2~~1: Identified Risks and Mitigation Measures for the Non-invasive Bone Growth Stimulators

Identified Risk	Recommended Mitigation Measures
Electrical shock	Section 7: Preclinical Analysis and Testing Section 9: Electrical Equipment Safety Section 11: Software Life Cycle and Risk Management Section 14: Labeling
Burn	Section 7: Preclinical Analysis and Testing Section 9: Electrical Equipment Safety Section 11: Software Life Cycle and Risk Management Section 14: Labeling
Skin irritation~~/~~ and/or allergic reaction	Section 8: Biocompatibility Section 14: Labeling
Inconsistent or ineffective treatment	Section 7: Preclinical Analysis and Testing Section 9: Electrical Equipment Safety Section 10: Electromagnetic Compatibility (EMC) Section 11: Software Life Cycle and Risk Management Section 12: Animal Testing Section 13: Clinical Studies Section 14: Labeling
Ineffective treatment due to magnetic fixation device	Section 14: Labeling
Damage to electrical implant function	Section 14: Labeling
Biological Effects of Stimulation	Section 14: Labeling

7.0 Preclinical Analysis and Testing

We recommend that you provide a thorough description and documentation of the technological characteristics of the output waveform of the proposed device and the electrodes or coils to deliver the treatment. In addition, please provide a detailed table comparing the output waveforms and the electrodes or coils of the proposed and predicate device. This side-by-side comparison table should be accompanied by a discussion of the similarities and differences between the ~~output waveforms.~~proposed device and the predicate device, and should be sufficiently detailed to provide a basis for a substantial equivalence determination.

Capacitive Coupling Devices

For a Non-invasive Bone Growth Stimulator that achieves its effects through capacitive coupling, we recommend that you provide the following information.

Provide a complete description of the output waveform, including the following:

- A minimum of four oscilloscope tracings of the output waveform (with appropriate electrode connected) under loads through the range of operation (e.g., ~~of 5~~200-700 Ω~~), 1000Ω, and 2000Ω~~ should be presented as voltage versus time. If the generator is capable of producing more than one waveform type and/or can be used with electrodes of more than one type or size, an oscilloscope tracing of each waveform/electrode combination should be submitted. In addition to quantitatively identifying all salient features of the voltage and time variables, the horizontal and vertical oscilloscope gain settings should be specified. The procedure for making the waveform measurements should be described.
- Maximum output current
- Maximum and RMS output voltage
- Whether the signal is constant current or constant voltage
- Open circuit detection range
- Waveform shape and description ~~(e.g. biphasic or monophasic) and frequency~~
- Waveform frequency
- Spectral analysis to determine the extent and/or existence of a 2nd order harmonic frequency and its strength (such testing may need to be performed in an isolation chamber)

- Current density at the electrode/skin interface (for each waveform / electrode combination~~using the area of the smallest electrode available for use with the device~~)

- Indicate the estimated current density and/or electric field strength at the treatment site.

- Power density at the electrode/skin interface (for each waveform / electrode combination~~using the area of the smallest electrode available for use with the device~~)

- Charge per pulse and charge density at the electrode/skin interface (for each waveform / electrode combination~~using the area of the smallest electrode available for use with the device~~)

- Estimated current density at the treatment target site

- Recommended duration of use per day

- Provide a diagram of the output waveform with all stimulation parameters and temporal characteristics clearly labeled to supplement the oscilloscope tracings. In conjunction with this diagram, provide a table that summarizes the output specifications, with each specification listed as an acceptable range or as a single value ± tolerance.

- Provide an equivalent circuit diagram for the output generator and all electrodes, noting all impedance values.

- Describe the method of attaching the leads and electrodes to the patient. Describe the placement of the anode(s) and cathode(s) relative to each other, relative to the treatment site, and relative to surrounding structures and excitable tissues (e.g., heart, peripheral nerves, spinal nerves, etc.).

- Compare the information described above with the same information for the predicate device.

~~Describe the method of attaching the leads and electrodes to the patient. Identify the anode(s) and cathode(s) (if applicable), and describe the surface area, current density, charge density, and power density for each electrode. Provide an equivalent circuit diagram for the output generator and all electrodes, noting all impedance values. Indicate the estimated current density and/or electric field strength at the treatment site. Describe the placement of the anode(s) and cathode(s) relative to each other, relative to the treatment site, and relative to surrounding structures and excitable tissues (e.g., heart, peripheral nerves, spinal nerves, etc.).~~

~~Compare the output waveform of the proposed device to the predicate device as previously described.~~

PEMF ~~and Combined Magnetic Field~~ Devices

For a Non-invasive Bone Growth Stimulator which achieves its effects through PEMF ~~or combined magnetic fields~~, we recommend that you provide the following information.

Define the treatment target tissue and the specific location of the treatment target area. Identify the anatomical structures that define the target area and describe the location of these structures relative to the magnetic field and relative to each unique coil orientation.

Provide a detailed description of the output waveform and its specifications, including the magnetic field (B) and the time rate of change of the magnetic field (dB/dt).

Provide a detailed description of the magnetic fields and of dB/dt throughout the region over which the device's therapeutic signal is targeted. For each coil and for each coil orientation or configuration, provide the following:

- Provide oscilloscope waveforms of the magnetic fields and of the time rate of change of the dynamic magnetic field (i.e., dB/dt) corresponding to one complete cycle of the output signal. The measurements should be made with the magnetic field probe (e.g., detector coil) located in a region representative of the center of the treatment target area.

- Provide diagrams of the output waveforms with all parameters and temporal characteristics clearly labeled to supplement the oscilloscope tracings. In conjunction with the diagrams, provide a table that summarizes the output specifications, with each specification listed as an acceptable range or as a single value ± tolerance. This should include the following: burst period, number of pulse pairs in a burst, average amplitude of pulse 1, average amplitude of pulse 2, rise time for pulse 1, rise time for pulse 2, duration of pulse 1 and duration of pulse 2.

- Provide a complete mapping (i.e., throughout the entire treatment target area) which characterizes the magnetic field, and dB/dt, averaged over the duration of the primary pulse. Specifically, for each coil and for each coil position, present three-dimensional mapping data which show the measured values at each location. A sufficient number of locations should be used to adequately describe the fields throughout the entire treatment target area. Spatial intervals of no greater than 2 cm are recommended.

- Describe the methodologies used to obtain the waveforms and field maps. Include a complete description of the instrumentation, calibration procedures, and conversion factors used in the acquisition and presentation of data, and specify the physical dimensions, number of turns, winding arrangement and spatial resolution of the detector coil.

- Provide spectral analyses to characterize the frequency content of the signal delivered through each coil. Identify the gain setting and bandwidth for each plot and describe the methods and instrumentation used to obtain the data.

- Describe the type, size, materials, geometry, configuration,~~Describe the~~ number of turns and the winding arrangement of each coil, and provide a description of the electrical characteristics of the transmitting coil including the resistance, inductance and capacitance (where applicable).

- Provide the r~~R~~ecommended hours of use per day.

- Compare the information described above with the same information for the predicate device.

8.0 Biocompatibility

We recommend that you conduct biocompatibility testing for device components with patient contact as described in the FDA-modified **Use of International Standard ISO-10993, Biological Evaluation of Medical Devices Part-1: Evaluation and Testing,** http://www.fda.gov/cdrh/g951.html. You should conduct testing appropriate to the body contact and contact duration for your proposed device. Typically, a Non-invasive Bone Growth Stimulator is categorized as a "Surface-contacting Device" which contacts intact skin surfaces only. Its duration of contact is Permanent Contact (Category C) because its multiple or long-term use exceeds 30 days. For such devices, the recommended testing includes cytotoxicity, sensitization, and irritation or intracutaneous reactivity.

If the materials which contact the patient are used in other medical devices with similar body contact and duration, you may be able provide a justification for not conducting the biocompatibility tests.

9.0 Electrical Equipment Safety

We recommend that you address the electrical safety, e.g., electrical and mechanical safety, of your proposed device, by following one or more of the standards identified next or by equivalent methods:

- International Electrotechnical Commission (IEC) 60601-1 Medical Electrical Equipment – Part 1: General Requirements for Safety

- Underwriters Laboratory (UL) 60601-1 Medical Electrical Equipment, Part 1: General Requirements for Safety

10.0 Electromagnetic Compatibility (EMC)

Electromagnetic compatibility (EMC) encompasses both emissions (interference with other electronic devices) and immunity (interference with device performance created by emissions from other electronic devices). We recommend that you evaluate the EMC of your device as discussed below.

Emissions

EMC testing should demonstrate that the device will not adversely interfere with the performance of other electronic equipment, including emergency radio services, diagnostic devices, and active implantable devices, e.g., pacemakers and defibrillators. Testing should include radio frequency (RF) and electromagnetic and conducted emissions.

Immunity

EMC testing should also demonstrate that the device will perform as expected in the presence of other electrical and electronic devices or other sources of electromagnetic disturbance (EMD) in the intended environment of use (immunity). The device should operate in an acceptable manner (few EMC standards require operation within specifications) during and after exposure to various forms of electromagnetic disturbance. Testing should include radiated RF electromagnetic fields and low-frequency magnetic fields.

11.0 Software Life Cycle and Risk Management

If the device includes a microprocessor component, FDA recommends that you submit documentation that provides evidence of proper software life cycle and risk management for all programs associated with the device, including any firmware (embedded software). FDA guidances, Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices, www.fda.gov/cdrh/ode/57.html and Guidance for Off-the-Shelf Software Used in Medical Devices, www.fda.gov/cdrh/ode/1252.html, contain information about the documentation required. Also, General Principles of Software Validation, www.fda.gov/cdrh/comp/guidance/938.html, contains useful information about software life cycle and risk management.

FDA believes that the software used in the Class II, Non-invasive Bone Growth Stimulator meet the definition given in these guidances for a "minor level of concern." This is because although the software controls treatment delivery, a software error or malfunction in treatment delivery, if were to occur, would not result in a death or serious injury.

12.0 Animal Testing

The degree to which a premarket notification needs to provide animal and/or clinical testing depends upon the differences between the new and predicate devices (e.g. new output waveforms). If the new and predicate devices have the same output waveforms, further animal and clinical testing would not be required. If the output waveform of the proposed device differs from the predicate device, additional animal or clinical testing may be required. Potential options may include reference to previously published scientific literature, animal testing, and theoretical rationales for the selection of the output parameters based on current knowledge. Animal testing should be considered in the absence of an appropriate bench model, scientific literature or other supporting information. We recommend that the animal study evaluate:

- Delivery of the therapeutic output waveform under conditions selected based upon the clinical indication
- Achievement of the desired tissue electrical effects
- Acute reactions following stimulation
- Biomechanical strength testing comparing the healed fracture to the biomechanical properties of the native bone
- Histomorphology and histopathology

We recommend that you perform follow-up evaluations with appropriate frequency to characterize the healing process. We also recommend that you provide an explanation of how the animal model relates to the human condition through any pertinent literature references and/or supporting testing.

13.0 Clinical Studies

In accordance with the Least Burdensome provisions of the FDA Modernization Act of 1997, FDA will rely upon well-designed bench and/or animal testing rather than requiring clinical studies for new devices unless there is a specific justification for asking for clinical information to support a determination of substantial equivalence. While, in general, clinical studies will not be needed for most Non-invasive Bone Growth Stimulators, FDA may recommend that you collect clinical data for a Non-invasive Bone Growth Stimulator with:

- An output waveform dissimilar from previously marketed devices;
- A new technology, i.e., technology different from that used in the legally marketed devices of the same type; or
- Indications for use dissimilar from indications from devices of the same type.

FDA will always consider alternatives to clinical testing when the proposed alternatives are supported by an adequate scientific rationale. The Division of General, Restorative, and Neurological Devices (DGRD) is available to discuss any clinical testing with you before you initiate studies.

If a clinical study is needed to demonstrate substantial equivalence, i.e., conducted prior to obtaining 510(k) clearance of the device, the study must be conducted under the Investigational Device Exemptions regulation (21 CFR 812). FDA has carefully considered the risks associated with this device and concluded that the device's risks are not significant except in one respect. When a clinical investigation is needed in order to establish that new device is substantially equivalent, there is possibility that the device may be ineffective. Thus, FDA has determined that Non-invasive Bone Growth Stimulators which need clinical investigation prior to marketing are significant risk devices as defined in 21 CFR 812.3(m).[4] In addition to the requirement of having an FDA-approved IDE application, sponsors of such trials must comply with the regulations governing institutional review boards (21 CFR Part 56), informed consent (21 CFR Part 50), and financial disclosure (21 CFR Part 54).

After FDA determines that the device is substantially equivalent, clinical studies conducted in accordance with the indications reviewed in the 510(k), including clinical design validation studies conducted in accordance with the quality systems regulation, are exempt from the Investigational Device Exemptions (IDE) requirements. Such studies must be performed in conformance with the regulations governing institutional review boards (21 CFR 56) and informed consent (21 CFR 50).

We recommend that you consider the information below.

Endpoints

We recommend that the study protocol include clearly defined primary and secondary endpoints and specific success/fail criteria for the study. We recommend that you define and report all adverse events.

We recommend that effective endpoints for nonunion fractures include the following:

- Pain and motion at the fracture site
- Presence or absence of the fracture line
- Number of cortices bridged by the callus

[4] Refer to Blue Book Memorandum entitled "SIGNIFICANT RISK AND NONSIGNIFICANT RISK MEDICAL DEVICE STUDIES" at http://www.fda.gov/cdrh/d861.html.

- Presence or absence of trabeculae crossing the fracture
- These parameters may vary depending upon the anatomical location of the nonunion.

We recommend that effectiveness endpoints for use as adjunct to lumbar spinal fusion surgery include the following:

- Radiographic success
- Clinical success
- Overall success combining both radiographic and clinical success

We recommend, when possible, that the evaluation of endpoints be independent and masked.

Patient Population

We recommend that the protocol define the patient population using objective inclusion and exclusion criteria that can be applied in a consistent manner across multiple centers. For the indication for nonunion, the protocol should specify the fracture location and type. It should also specify the definition of nonunion; e.g., the minimum length of time that the fracture site shows no visible progressive signs of healing. For the indication of spinal lumber fusion, the protocol should identify the level of the fusion, the number of fusions, and the surgical techniques, including use of instrumentation.

Treatment and Follow-up

We recommend that the protocol describe the output waveforms used for treatment, define the recommended treatment duration, including hours per day of device use and total duration of use. We also recommend that the protocol document actual product use by patients, such as compliance.

The protocol should specify additional patient care procedures to be employed during the treatment period, such as surgery and/or weight bearing. Such considerations will vary based upon the specific use of the device (nonunions versus spinal fusion) and the anatomical location of the nonunion.

The protocol should specify defined follow-up visits for subjects and the required evaluations at each visit.

Statistical Considerations

The protocol should describe the rationale and description of the statistical analyses to be employed in assessing the effectiveness and safety of the treatment. For statistical purposes, the study hypothesis should frame the research question

in terms of equivalence, non-inferiority, or superiority to the performance of legally marketed devices within the type.

14.0 Labeling

The premarket notification should include labeling in sufficient detail to satisfy the requirements of 21 CFR § 807.87(e). The following suggestions are aimed at assisting you in preparing labeling that satisfies the requirements of 21 CFR Part 801.[5]

Prescription Use

As a prescription device, under 21 CFR § 801.109, the device is exempt from having adequate directions for lay use. Nevertheless, under 21 CFR § 807.87(e), we expect to see clear and concise instructions that delineate the technological features of the specific device and how the device is to be used on patients.

Warnings/Precautions

We recommend that the device labeling include the following:

- A warning which describes that electrical implants, such as pacemakers, cardiodefibrillators and neurostimulators, may be adversely affected by the use of the non-invasive bone growth stimulator
- A warning about the potential risk of using and charging the device at the same time (if applicable)
- A warning/precaution which describes that magnetic fixation devices may interfere with the delivery of an effective treatment for a PEMF-based non-invasive bone growth stimulator
- A warning/precaution which addresses the fact that the long term effects of electrical stimulation or magnetic fields have not been studied extensively in humans
- A warning/precaution which addresses the fact that the safety of the device during pregnancy and nursing has not been studied or established

Instructions for Use

We recommend that the instructions for use include:

[5] Although final labeling is not required for 510(k) clearance, final labeling must comply with the requirements of 21 CFR Part 801 before a medical device is introduced into interstate commerce. In addition, final labeling for prescription medical devices must comply with 21 CFR § 801.109. Labeling recommendations in this guidance document are consistent with the requirements of 21 CFR Part 801.

- Proper ~~A~~application of the device and any considerations needed to personalize the device for particular patients
- An explanation of each control mechanism, indicator and alarms
- Operating instructions for the specific indication, including duration of treatment
- Information about how to properly use the device to reduce potential risks (e.g. shock, burn, irritation, and inconsistent or ineffective treatment)

Patient Brochure

We recommend that you prepare a patient information brochure or fact sheet that includes:

- The reason for use of the device
- Proper use of the device, including alarms and indicators
- Proper care of the device
- Risks and benefits of the device
- Circumstances in which the patient should contact the health care provider

For information on using a question and answer format and other useful techniques, please refer to the Guidance on Medical Device Patient Labeling, http://www.fda.gov/cdrh/ohip/guidance/1128.html.