FDA Executive Summary

Prepared for the September 8-9, 2020 Meeting of the Orthopaedic and Rehabilitation Devices Panel

Reclassification of Non-Invasive Bone Growth Stimulators

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1. Introduction

As required by section 513(e) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), the Food and Drug Administration (FDA) is convening the Orthopaedic and Rehabilitation Devices Panel (the Panel) to discuss and make recommendations regarding the regulatory classification of non-invasive bone growth stimulators, currently a postamendments class III device, which FDA has grouped under product codes LOF and LPQ. The scope of this Panel meeting excludes invasive bone growth stimulators, currently designated under product code LOE.

FDA is holding this Panel meeting to obtain input on the risks and benefits of non-invasive bone growth stimulators. The Panel will also be asked to discuss and make recommendations to FDA whether such devices should remain classified as Class III (subject to Premarket Approval) or reclassified to Class II (subject to General and Special Controls), or Class I (subject only to general controls). FDA is proposing to reclassify non-invasive bone growth stimulators into Class II (Special Controls). FDA is also identifying the proposed special controls that the Agency believes will provide a reasonable assurance of safety and effectiveness of the device and mitigate the risks to health. If the Panel believes that Class II is appropriate for non-invasive bone growth stimulators, the Panel will also be asked to discuss whether the proposed special controls are adequate to provide a reasonable assurance of safety and effectiveness and to mitigate the risks to health.

1.1. Background on the Classification Process

FDA regulates medical devices and categorizes them into one of three classes (I, II, or III), as shown in the flowchart in Figure 1.

1.1.1. Class I

Class I devices are subject to the least regulatory controls. They usually present minimal potential for harm to the user and are often simpler in design than Class II or Class III devices. Class I devices are subject only to general controls, which include, but are not limited to, establishment registration and listing; prohibitions against adulteration and misbranding; records and reports; and good manufacturing practices (GMPs). Examples of Class I devices include elastic bandages and examination gloves and hand-held manual surgical instruments. Most Class I devices are exempt from premarket review requirements and can be marketed without a premarket submission.

1.1.2. Class II

Class II devices are those devices for which general controls alone are insufficient to provide reasonable assurance of safety and effectiveness, and for which there is sufficient information to establish special controls to provide such assurance. Examples of special controls are performance standards, postmarket surveillance, patient registries, and special labeling requirements. Special controls may also include specific types of performance testing (e.g., biocompatibility, sterility, electromagnetic compatibility, pre-clinical testing), which FDA may outline in the regulation. Hence, in addition to complying with general controls, Class II devices are also subject to special controls. Most Class II devices must obtain marketing clearance through premarket notification [510(k)] submissions. Examples of Class II devices include intravascular administration sets (e.g., syringes), medical lasers, endoscopes, stereotactic navigation systems, and radiofrequency ablation systems.

1.1.3. Class III

Class III is the most stringent regulatory category for devices. Class III devices are typically high risk

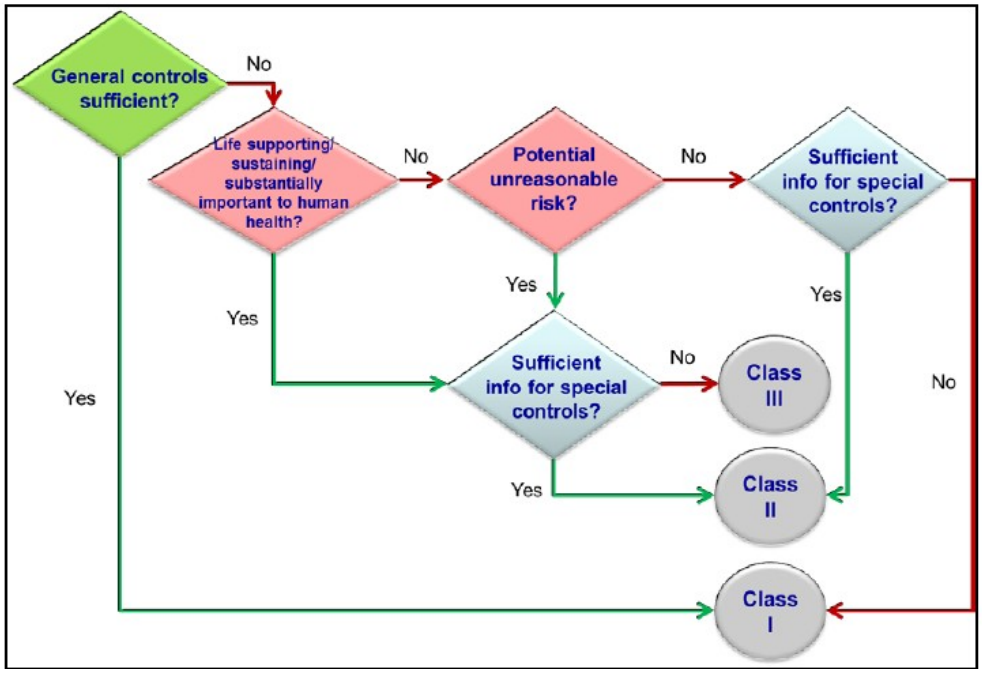
devices and include devices for which insufficient information exists to provide reasonable assurance of safety and effectiveness solely through general or special controls. All devices that are not substantially equivalent to any existing devices in Class I or II are automatically classified in Class III. Examples of Class III devices include breast implants, dermal fillers, and endodontic dry heat sterilizers. Class III devices typically require marketing approval through a premarket approval (PMA) application.

In accordance with section 513 of the Food, Drug, and Cosmetic Act (FD&C Act), a device should be classified in Class III if:

- insufficient information exists to determine that general controls and special controls are sufficient to provide reasonable assurance of its safety and effectiveness, and

- the device 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 if the device presents a potential unreasonable risk of illness or injury.

Figure 1: Classification Flowchart



2. Device Description and Current Classification

Non-invasive bone growth stimulators, currently designated under product code LOF and LPQ, are typically composed of a waveform generator and transducer (e.g., coils, electrodes, and/or ultrasound transducers). Patient-contacting surfaces include the transducers, lead wires, and the device outer casing.

Non-invasive bone growth stimulators utilize an electrical component to produce an output electrical, magnetic, or ultrasonic waveform that is delivered to a treatment site via a non-invasively applied transducer (e.g., electromagnetic coil or ultrasound transducer) or electrodes. The device also incorporates an 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.

The induced electrical and/or magnetic fields are generated using one of the following modalities:

- Capacitive Coupling (CC), in which a pair of electrodes are placed on the skin such that a current can be driven across that target site,
- Pulsed Electromagnetic Fields (PEMF), in which a modulated electromagnetic field is generated near the treatment site though an external coil,
- Combined Magnetic Fields (CMF), in which a coil generates a combination of a static and pulsed magnetic field near the treatment site, and
- Low Intensity Pulsed Ultrasound (LIPUS), in which pulsed ultrasonic signals are generated using ultrasonic transducers.

The specific mechanism of action of these devices varies depending on the technology. The underlying theory behind the mechanism of the PEMF, CC, and CMF devices is that the electronic field causes voltage-gated Ca2+ channels in the cell walls of osteocytes to open, changing intercellular and cytosolic Ca2+ levels [1]. This triggers signaling molecules to promote osteoblastic differentiation and formation, and thus upregulating bone formation activity [2]. For LIPUS signals, the ultrasound wave is a mechanical signal that may directly stimulate cellular mechanotransducers resulting in the a signaling cascade resulting the same increase in intracellular Ca2+ levels and upregulation of osteoblastic activity [3].

Currently, non-invasive bone growth stimulators are grouped under two product codes

- LOF – Stimulator, Bone Growth, Non-Invasive
- LPQ – Stimulator, Ultrasound And Muscle, For Use Other Than Applying Therapeutic Deep Heat

The CC, PEMF, and CMF devices were all approved under the LOF product code, and the LIPUS device was originally approved under the LPQ product code. The non-invasive nature of the device obviates the need for sterile components; however, patient-contacting surfaces should be capable of being cleaned as needed and biocompatibility must be ensured.

3. Indications for Use

The Indications for Use (IFU) statement describes the disease or condition the device will diagnose, treat, prevent, cure or mitigate, including a description of the patient population for which the device is intended. Generally, a non-implantable bone growth stimulator is a device that is intended to promote osteogenesis as adjunct to primary treatments for fracture fixation or spinal fusion. The indications for use statements approved through PMA submissions depends on the specific device characteristics, but have included:

- treatment of an established non-union secondary to trauma of the appendicular system,

- treatment of congenital pseudarthrosis,
- treatment of failed fusions of the appendicular system,
- early treatment of certain fresh fractures, and
- as an adjunct to lumbar or cervical spinal fusion.

The specific examples presented above are not necessarily representative of all the approved indications but are provided to illustrate the relatively narrow range of statements. FDA recognizes that science and clinical practice have evolved over time, and indications for use that have been approved historically may not represent current clinical practice.

In addition, non-invasive bone growth stimulators are currently prescription use only devices under 21 CFR 801.109.

4. Regulatory History

In accordance with section 513(f)(1) of the FD&C Act, non-invasive bone growth stimulator devices were automatically classified into class III because they were not introduced or delivered for introduction into interstate commerce for commercial distribution before May 28, 1976, and have not been found substantially equivalent to a device placed in commercial distribution after May 28, 1976, which was subsequently classified or reclassified into class II or class I. Therefore, the device is subject to premarket approval (PMA) requirements under section 515 of the FD&C Act (21 U.S.C. 360e).

Accordingly, on November 6, 1979, FDA approved a PMA for the Bio Osteogen System 204 (P790002). Since that time, five additional original PMAs have been approved of this device type (P850007, P850022, P900009, P910066, and P030034) (Table 1).

Table 1: Non-Invasive Bone Growth Stimulators (LOF, LPQ) Approved Through PMA

Product	Present Application Holder	Application Number	Treatment Modality	Approval Date
EBI Bone Healing System	Zimmer Biomet	P790002	Pulsed Electromagnetic Field	November 6, 1979
Physio-Stim™ I & II SpinalStim	Orthofix, Inc.	P850007	Pulsed Electromagnetic Field	February 21, 1986
OrthoPak SpinalPak	Zimmer Biomet	P850022	Capacitive Coupling	February 18, 1986
Exogen Ultrasound BGS	Bioventus, LLC	P900009	Ultrasound	October 5, 1994
OL1000 BGS SpinaLogic	DJO, LLC	P910066	Combined Magnetic Field	March 4, 1994
Cervical Stim	Orthofix, Inc.	P030034	Pulsed Electromagnetic Field	December 23, 2004

On February 9, 2005, FDA received a reclassification petition submitted by RS Medical Corporation requesting that FDA reclassify certain non-invasive bone growth stimulator from class III to class II [4]. FDA requested additional information and the petitioner amended the petition on November 30, 2005. In accordance with the FD&C Act and regulations, FDA referred the petition, as amended, to the Orthopaedic and Rehabilitation Devices Panel ("the 2006 Panel") for its recommendations on the requested reclassification.

On June 2, 2006, the 2006 Panel deliberated on the information in RS Medical's petition; the presentations made by RS Medical, FDA, and members of the public; and their own experience with non-invasive bone growth stimulators [5]. The Panel discussed the information provided in the petition, the risks to health associated with non-invasive bone growth stimulators, whether non-invasive bone growth stimulators should be reclassified or remain in class III, and possible special controls for these devices if reclassified into class II. The 2006 Panel identified the following risks to health associated with the non-invasive bone growth stimulator: electric shock; burn; skin irritation and/or allergic reaction; inconsistent or ineffective treatment; adverse interaction with electrical implants; adverse interactions with internal/external fixation devices; and biological risks. The 2006 Panel did not specifically address risks associated with ultrasound-based devices, as these were outside the scope of the RS Medical petition; however, as discussed below, based on our review of information since the Panel meeting, the risks identified with ultrasound-based devices, along with their reported benefits, are comparable to those of non-invasive bone growth stimulators incorporating other modalities.

The majority of the 2006 Panel recommended that non-invasive bone growth stimulators should be retained in class III because there was insufficient information in the petition by RS Medical to establish that special controls in conjunction with general controls would provide a reasonable assurance of the safety and effectiveness of the device. Specifically, the Panel recommended that the proposed special controls by RS Medical were sufficient to control for the risk of electric shock, burn, skin irritation, and/or allergic reaction; adverse interaction with electrical implants; adverse interactions with internal/external fixation devices; and biological risks. However, the Panel believed that there was insufficient evidence presented by RS Medical to control for the risk of inconsistent or ineffective treatment because there is a lack of knowledge about how waveform characteristics (e.g., pulse duration, amplitude, power, frequency), including potential modifications to the device, affect the clinical response to treatment. The Panel requested additional clinical data and/or special controls, which were not adequately devised by the petitioner, to control for the risk of inconsistent or ineffective treatment.

FDA concurred with the 2006 Panel's recommendation, and similarly believed that RS Medical's petition was inadequate in that FDA had concerns about the petitioner's proposed special controls to control the risk of inconsistent or ineffective treatment. In the *Federal Register* of January 17, 2007 (72 FR 1951), FDA published a Notice of Panel Recommendations ("the 2007 Notice").

In a letter dated April 2, 2007, RS Medical requested that its petition be withdrawn [6]. On July 10, 2007, FDA granted RS Medical's request for withdrawal of the petition and did not take any further action on the petition [7]. FDA has not received any subsequent petition requesting reclassification of these devices.

In response to the 2007 Notice, FDA received several comments, many of which supported the Panel's recommendation to retain these products in class III. The reasons cited in these comments were primarily related to concerns that the specific parameters, which govern clinical success for these devices, are generally not well-understood and, subsequently, it was unclear how special controls could be developed to provide a reasonable assurance of effectiveness of these devices. As such, non-invasive bone growth stimulators remained classified in class III because they were not introduced or delivered for introduction into interstate commerce for commercial distribution before May 28, 1976, and have not been found substantially equivalent to a device placed in commercial distribution after May 28, 1976, which was subsequently classified or reclassified into class II or class I.

Subsequently, as part of the Center for Devices and Radiological Health's 2014-2015 strategic priority, "Strike the Right Balance Between Premarket and Postmarket Data Collection," a retrospective review of all PMA product codes with active PMAs approved prior to 2010 was conducted to determine whether, based on our current understanding of the technology, certain devices could be reclassified (down-classified). On April 29, 2015, FDA published a document in the *Federal Register* identifying certain product codes as potential candidates for reclassification (80 FR 23798), including non-invasive bone growth stimulators under LOF and LPQ product codes for reclassification from class III to class II [8]. One comment was received in response to this proposal for reclassification of LOF and LPQ – this comment did not support FDA's intention to reclassify these devices citing the concerns discussed during the 2006 Panel. Note, invasive bone growth stimulators, designated under product code LOE, are outside the scope of this proposed reclassification. As noted in the 2006 Panel, these devices have added risk compared to non-invasive bone growth stimulators, and therefore would require a separate classification discussion. Furthermore, invasive bone growth stimulators were also considered as part of the aforementioned PMA retrospective review and FDA determined that these devices should remain class III [9]. Therefore, FDA intends to continue to regulate invasive bone growth stimulators as a class III device, subject to PMA requirements.

While RS Medical's petition inadequately addressed all of the risks associated with non-invasive bone growth stimulators for reclassification, FDA, on its own initiative, is proposing to reclassify these devices from class III to class II, and believes that sufficient information exists to establish special controls that, together with general controls, can provide a reasonable assurance of safety and effectiveness for this device type. Additionally, RS Medical in its petition excluded use of these devices as an adjunct to cervical fusion surgery in patients at high risk for non-fusion, as well as for use in congenital pseudarthrosis. Based upon the review of the evidence and FDA's ability to establish special controls, FDA believes the indications that have been approved for currently-marketed non-invasive bone growth stimulator devices should be included in this proposed reclassification.

5. Overview of Proposed Reclassification

In accordance with section 513(f)(3) of the FD&C Act and 21 CFR part 860, subpart C, FDA is proposing to reclassify non-invasive bone growth stimulator devices under product codes LOF and LPQ from class III to class II. This includes devices that generate electrical or magnetic fields using CC, PEMF, and CMF, and LIPUS signals.

FDA believes that there is sufficient information available by way of FDA's accumulated experience with these devices from review of premarket submissions, peer-reviewed literature, medical device reports (MDRs), recalls, and an understanding of the risks associated with these devices to establish special controls that effectively mitigate the risks to health. FDA is proposing to create a classification regulation for non-invasive bone growth stimulators, which would include devices designated under product codes LOF and LPQ. This regulation would identify a non-invasive bone growth stimulator as a prescription device. As such, the prescription device must satisfy prescription labeling requirements (see § 801.109 (21 CFR 801.109), Prescription devices).

Section 510(m) of the FD&C Act provides that FDA may exempt a class II device from the premarket notification requirements under section 510(k) of the FD&C Act if FDA determines that premarket notification is not necessary to provide reasonable assurance of the safety and effectiveness of the device. For non-invasive bone growth stimulators, FDA has determined that premarket notification is necessary to provide reasonable assurance of the safety and effectiveness. Therefore, the Agency does not propose to exempt these devices from 510(k) requirements. Persons who intend to market this type of device would need to submit to FDA a 510(k) and receive clearance prior to marketing the device.

Invasive bone growth stimulators, designated under product code LOE, are outside the scope of this proposed reclassification. As noted in the 2006 Panel, these devices have added risks compared to non-invasive bone growth stimulators, and therefore would require a separate classification discussion. Furthermore, invasive bone growth stimulators were also considered as a part of the aforementioned PMA retrospective review and FDA determined that these devices should remain as class III. [9] FDA will continue to regulate implantable bone growth stimulators as a class III device, subject to PMA requirements.

The Panel will be asked to discuss whether special controls can provide reasonable assurance of safety and effectiveness of non-invasive bone growth stimulator devices.

6. Summary of Data to Support Reclassification

The available evidence demonstrates that there are probable health benefits derived from the use of these devices, and that the nature and incidence of risks are well known so that special controls can be established to adequately mitigate the risks to health. FDA is proposing a single device class for non-invasive bone growth stimulators considering that FDA did not identify any unique risks associated with the different modalities. FDA has considered and analyzed the following: data in PMA applications P030034, P850022/S009, and P910066/S011 available to FDA under section 520(h)(4) of the FD&C Act; information presented at the June 2, 2006 Panel Meeting concerning RS Medical's petition to down-classify certain non-invasive bone growth stimulators [4] and the 2007 Notice; peer-reviewed articles that discussed the use of, as well as the probable benefits and risks of, these devices; reported adverse events (AEs) identified through a search of FDA's internal Medical Device Reporting (MDR) system; and a review of recalls associated with these device types identified through a search of FDA's Medical Device Recall database.

6.1. Data Available from Approved PMA Devices

In accordance with the "six-year rule" described in section 520(h)(4) of the FD&C Act, FDA considered data contained in three original PMAs or supplements, P030034, P850022/S009, and P910066/S011, approved for non-invasive bone growth stimulators. [10] These PMAs/PMA supplements include three different device modalities: a PEMF device (P030034), a CC device (P850022/S009), and a CMF device (P910066/S011). In review of the reported clinical data in the Summary of Safety and Effectiveness Data documents (SSEDs), the studies conducted in support of these devices include a total study size of 831 enrolled subjects. The adverse event profiles for the devices in each study were similar to those of the control groups, with a similar distribution of event types. With regards to benefit, the clinical data reported in the SSEDs demonstrate an improved rate of bone fusion compared to placebo controls, with an 83.6% vs. 68.6% fusion rate at 6 months in P030034 (cervical spine), an 85% vs. 75% clinical success shown in P850022/S009 (lumbar spine), and a 67% vs. 43% fusion rate at 9 months in P910066/S011 (lumbar spine).

P030034 included a clinical study of a PEMF based device for adjunct treatment to cervical spine fusion surgery. [11] A controlled, randomized clinical study was performed on 323 adults at high risk for non-fusion. All subjects underwent anterior cervical discectomy and fusion using the same technique and implant system. Subjects were randomly assigned to the control group (n = 160) and the treatment group (n = 163), and were followed for 12 months. A total of 67 AEs were reported in the control group and 90 AEs were reported in the treatment group. The most common AEs were an increase in neck pain (n = 10 in the control group, n = 16 in treatment group), shoulder/arm pain (n = 10, 16), re-injury to cervical spine (n = 10, 9), adjacent level pathology (n = 3, 8), surgical complications (n = 2, 7), and lumbar pathology (n

= 8, 5). No significant difference was reported between the two groups, and the conclusion of the investigation was that the adverse events reported were not related to the use of the device.

P850022/S009 was a panel-track supplement for the CC-based SpinalPak device. [12] This was the identical device approved in P850022 as the OrthoPak, with a new indication for use (lumbar spinal fusion). The clinical study described in the SSED is a randomized double blinded study of 369 subjects (177 treatment, 172 placebo control) for 12 months. Safety reporting in the SSED states that nine subjects withdrew from the study due to skin irritation (four in active group, five in placebo group). Three subjects withdrew due to adverse events: one placebo subject had a non-device related infection, one placebo subject had back spasms, and one active subject was "not progressing." Eight additional subjects reported adverse events (four in placebo group and four in active group) but completed the study.

P910066/S001 was a panel-track supplement for the CMF-based SpinaLogic device, which utilizes the same technology as the previously approved OrthoLogic device, with a new indication (lumbar spinal fusion). [13] The clinical study included was a randomized double-blinded study. The 253 subjects were followed for 9 months to assess fusion rates. In the SSED, no adverse reactions or medical complications related to the use of the device were reported.

6.2. Literature Review on Non-Invasive Bone Growth Stimulators

6.2.1. Historic Literature

A literature review was performed to evaluate both the historical context of non-invasive bone growth stimulator devices, including studies up to the date of the 2006 Panel, as well as any new clinical information published since the 2006 Panel. Literature published at the time of the 2006 Panel included a 1953 seminal paper by Yasuda on the use of electrical signals to stimulate bone formation in rabbits exposed to direct current (DC) stimulation [14]. In the following decades, other researchers expanded on this finding in animal and clinical models. In a canine study, a DC current was shown to cause complete ossification of the femoral medullary canal [15]. The first clinical case report demonstrated that electrical stimulation could treat a non-union fracture [16]. An early publication regarding the effects of DC stimulation on spinal fusion was published by Dwyer [17]. Another early clinical study published by Becker showed successful fracture fusion with a success rate of 77% [18].

In the 1990's and early 2000's, several literature articles were found assessing the effects of non-invasive bone growth stimulators on various anatomic locations. These studies generally included various therapeutic modalities (magnitude, frequency, duration, etc.) and demonstrated varying results regarding the effectiveness of these treatments. In two studies of PEMF devices, Basset [19] found a 72% fusion rate in patients with congenital pseudarthrosis of the tibia, and in a study of non-unions of the scaphoid, Adams [20] reported a fusion rate of 69%, as a follow up to an earlier study that found a fusion rate of 80%. When looking at the rate of compliance of PEMF devices as a factor in effectiveness, Garland [21] found that fusion rates ranged from 35.7% to 80% depending on how often the devices were used. In studies of CC devices, fusion rates in long bones varied from 60% [22], 68.8% [23], and 72.7% [24], to no difference between treatment and a placebo-treated group in a study by Fourie [25]. While there was a large range of observed efficacies, there was no reporting of treatment-related adverse events. These reports of variability of effectiveness and low adverse event profiles were consistent with the conclusions of the 2006 Panel.

6.2.2. Methods for Systematic Literature Search

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6.2.3. Overview of the Published Literature Since the 2006 Panel

Phillips [26] looked at registry data of 2370 subjects who were treated with DJO OL1000, a CMF device, in various fracture sites and reported an average healing rate of 75.1% (ranging from 57.2% in the humerus to 89.7% in the finger phalanx). DeVries [27] also evaluated the OL1000 device in a retrospective analysis of 144 subjects, finding a fusion rate of 57.1% in tibiotalocalcaneal fusions of the ankle.

With respect to LIPUS, Zura [28] [29] published two papers evaluating subjects in the Exogen (Bioventus) Post Market Registry. One of the studies assessed how various patient risk factors affected healing rate in 4,190 subjects. The study demonstrated an overall healing rate of 95.7%, and in another single arm study of 767 subjects, showed a healing rate varying from 81.8% to 87.9% depending on fracture site. Nolte [30] evaluated the Exogen registry in conjunction with a medical claims database to examine metatarsal fractures, and reported a healing rate of 97.4% overall, while Elvey [31] evaluated 26 cases with the use of Exogen in hand and wrist non-unions, and found a fusion rate of 54 to 58%. In two smaller studies of the Exogen device, Majeed [32] and Mizra [33] both evaluated foot and ankle fractures and found a 78.7% and 67% fusion rate in a 47 and 18 patient study, respectively. Biglari [34] also performed an observational study using the Exogen device, and found a much lower fusion rate of 32.8% in 60 subjects having existing non-unions of various long bones.

For PEMF devices, a retrospective study by Coric [35] on the effects of the CervicalStim (Orthofix) device on 593 subjects showed a 73.2% fusion rate in the cervical spine at 6 months. In a single arm prospective study by Assiotis [36], a 77.3% fusion rate in the tibia was demonstrated with use of the Physiostim (Orthofix). Murray [37] performed a 1,382-subject retrospective study of the use of the EBI device (Zimmer Biomet) for non-unions of the scaphoid, tibia, and fibula; while an assessment of healing rates was not performed, the data show reduction in time to healing between 35% and 40% when the device was used as prescribed.

In addition, two randomized control studies on PEMF devices were identified that were conducted by Foley [38] and by Streit [39]. Foley evaluated 323 subjects using the Orthofix CervicalStim device in cervical fusion and found an 83.6% fusion rate in the treatment group compared to a 68.6% fusion rate in the control group, with no difference in pain scores or adverse events between groups. Streit performed a small, 8-subject clinical study using the EBI device to treat non-unions of the fifth metatarsal and found the time to fusion was reduced on average from 14.7 weeks to 8.9 weeks with the use of the device.

6.2.4. Literature Summary

In summary, FDA's literature review resulted in findings that are consistent with available clinical data from PMA submissions. These studies suggest that there are probable benefits to the use of these devices; however, differences in methodology, including differences in devices used, treatment waveform and frequency, patient populations, as well as anatomic location, could have had significant effects on reported device effectiveness, which ranged from 32.8% to 97.4%. Regarding safety, the findings from these studies demonstrate that the devices are relatively safe as the adverse event profile associated with these devices using various modalities was similar to controls. Overall the studies involved 10,566 subjects (including control subjects), with only a single report of a serious adverse event [34]; however, a direct link to the use of the device could not be established for this event.

6.3. Medical Device Reports (MDRs)

6.3.1. Overview of the MDR System

The MDR system provides FDA with information on medical device performance from patients, health care professionals, consumers and mandatory reporters (manufacturers, importers and device user facilities). The FDA receives MDRs of suspected device-associated deaths, serious injuries, and certain malfunctions. The FDA uses MDRs to monitor device performance, detect potential device-related safety issues, and contribute to benefit-risk assessments of approved/cleared products. MDRs can be used effectively to:

- Establish a qualitative snapshot of adverse events for a specific device or device type
- Detect actual or potential device problems used in a "real world" setting/environment

Although MDRs are a valuable source of information, this passive surveillance system has limitations, including the submission of incomplete, inaccurate, untimely, unverified, duplicated or biased data. In addition, the incidence or prevalence of an event cannot be determined from this reporting system alone due to potential under-reporting of events and lack of information about the frequency of device use. Finally, the existence of an adverse event report does not definitely establish a causal link between the device and the reported event. Because of these limitations, MDRs comprise only one of the FDA's tools for assessing device performance. As such, MDR numbers and data should be taken in the context of the other available scientific information.

6.3.2. MDR Data

A search of the MDR database was conducted for both non-invasive bone growth stimulators under product code LOF (Stimulator, Bone Growth, Non-Invasive) and ultrasonic stimulators under product code LPQ (Stimulator, Ultrasound And Muscle, For Use Other Than Applying Therapeutic Deep Heat) to obtain a comprehensive picture of the safety profile for these devices. The database was searched for all individual MDR reports received through October 31, 2019 using the product codes LOF and LPQ.

The results yielded a total of 270 reports. Of the 270 reports received, there were 187 events of skin reaction/issue, 59 events of pain, and 21 events of device functional issue. A sampling of the adverse events found that a majority of injury events were related to skin reaction due to irritation from the electrode adhesive or ultrasound gel used. For cases where follow up was described, patients recovered when treatment was discontinued.

For reports in which a device problem code is used, 47% do not have a specific problem identified (e.g. "No Information" or "No Known Device Problem." For identified events, the most commonly reported

device problems for these adverse event reports were patient-device incompatibility (16%), device operates differently than expected (3%), reaction (3%), biocompatibility (2%), design/structure problem (2%), and device issue (2%).

In the 270 reports, 451 patient problem codes were used; a single report may include several patient problem events or several patients. The most commonly reported patient problems were pain (12% of events), rash (6%), skin irritation (6%), burns (4%), and swelling (3%).

In addition, 11 reports of “mass/tumor” were identified; however, the nature of the relationship between the mass/tumor to the device was unrelated or unclear. Based upon FDA assessment of other systematic reviews of these devices [40] [41] [42] [43] [44], no other such reports have been identified.

Among 5 death reports, all were for product code LOF. One report is from 1993, three are from 2004, and one from 2015. One patient died in her sleep from heart failure, two were patients with pacemakers who died due to heart failure, one patient died from cancer, and one had no cause of death reported. There is no indication in any of the reports that the deaths were related to use of the device.

6.4. Recall History

6.4.1. Overview of the Recall Database

The Medical Device Recall database contains Medical Device Recalls classified since November 2002. Since January 2017, it may also include correction or removal actions initiated by a firm prior to review by the FDA. The status is updated if the FDA identifies a violation and classifies the action as a recall and again when the recall is terminated. FDA recall classification may occur after the firm recalling the medical device product conducts and communicates with its customers about the recall. Therefore, the recall information posting date ("create date") identified on the database indicates the date FDA classified the recall; it does not necessarily mean that the recall is new.

6.4.2. Recall Results: LOF

No recalls were found when searching the database for product code LOF.

6.4.3. Recall Results: LPQ

Two class 2 recalls were reported for product code LPQ, one for the Exogen Express Bone Healing System and one for the Exogen 4000+ Ultrasound Bone Healing System (two different trade names for the device approved under P900009). Both were posted on August 4, 2009 and initiated by the manufacturer because of “problems with [the] transducer [which] may result in a reduced ultrasound output” [45] [46]. These recalls were terminated on November 18, 2010.

6.5. Clinical Conclusions

The results of the data available from SSEDs for legally marketed BGS devices, systemic literature review, MDR analysis, and recall history show that the most common adverse events were skin irritation and pain at the treatment site, as well as swelling and infections. Device functional issues consisted primarily of the device not activating or the transducers malfunctioning. Clinical data in literature did not identify any adverse events or device malfunctions with the exception of a single report of an abscess that was not demonstrated to be device related. Non-invasive bone growth stimulator devices are used as

an adjunct treatment in patients primarily with established non-unions or as an adjunct to spinal fusion, and many of the adverse events reported here are common for the condition the device is being used to treat (pain, swelling, infection). The most comment event that is clearly linked to the use of the device is skin irritation, due to reaction to the electrode adhesive or ultrasound gel, which was typically resolved by cessation of treatment or movement of the treatment location.

In conclusion, based on clinical evidence available in SSEDs, literature, MDR analysis, and recall history reporting, the overall rate of device malfunction and adverse events is low. The same data show variability in clinical effectiveness of the devices, which varied based on inclusion criteria, anatomic location, patient population, and treatment compliance, among many other factors. Based upon the totality of the evidence, FDA believes the risks of the device can be mitigated through a combination of general and special controls. Due to the variability identified in clinical effectiveness, as well as the unknown factors of how changes in signal characteristics (e.g. waveform shape and power) may affect effectiveness, clinical performance testing is being recommended as a special control.

7. Risks to Health

Based on available information for non-invasive bone growth stimulators, including the 2005 reclassification petition request from RS Medical Corp, data in PMA applications P030034, P850022/S009, and P910066/S011 available to FDA under section 520(h)(4) of the FD&C Act, published literature, and postmarket experience associated with use of these devices, along with the input from the 2006 Panel, FDA identifies the following risks to health associated with non-invasive bone growth stimulators:

a. *Failure or delay of osteogenesis* – A patient could receive ineffective treatment, contributing to failure or delay of osteogenesis that may lead to clinical symptoms (e.g., pain) and the need for surgical interventions. Ineffective treatment could be a result of various circumstances (e.g., inadequate therapeutic signal output or device malfunction or misuse).
b. *Burn* – A patient or health care professional could be burned from the use and operation of the device. This could be a result of various circumstances including device malfunction (e.g., electrical fault) or misuse of the device (e.g., use while sleeping).
c. *Electrical Shock* – A patient or health care professional could be shocked from the use and operation of the device. This could be a result of various circumstances including device malfunction (e.g., electrical fault) or misuse of the device (e.g., use of AC current source during treatment).
d. *Electromagnetic Interference (EMI)* – A patient with electrically-powered implants (such as cardiac pacemakers, cardiac defibrillators, and neurostimulators) could experience an adverse interaction with the implanted electrical device via EMI or Radiofrequency Interference.
e. *Adverse Tissue Reaction* – A patient could experience skin irritation and/or allergic reaction associated with the use and operation of the device via the use of non-biocompatible device materials.
f. *Adverse Interaction with Internal/External Fixation Devices* – The signal output could be impacted by certain metallic internal or external fixation devices leading to inadequate treatment signals, device malfunction, or tissue damage.
g. *Adverse Biologic Effects* – A patient may experience adverse biologic effects resulting from prolonged exposure to the treatment signal via biologic interaction with the treatment signal at a cellular level. Excessive energy transmission could cause tissue damage or aberrant tissue behavior if signal output parameters exceed established safety thresholds.

The risks to health identified above are consistent with those identified in the 2005 reclassification petition, as amended. The 2006 Panel agreed with these identified risks; however, in some cases the risk or accompanying description was reworded for clarity (e.g., "inconsistent treatment or ineffective treatment" is described in terms of risk to health, which may entail "failure or delay in osteogenesis"). Also, the risk of adverse biologic effects previously specified risks of carcinogenicity, genotoxicity, mutagenicity, and teratological effects. The petitioner noted in the amended petition that "…the evidence points to lack of genotoxic, carcinogenic, and teratologic potential of the subject waveforms," which is corroborated by the lack of such reports identified in the literature. While FDA similarly has found a lack of such reports, it considers this risk more generally as potential deleterious effects at the tissue or cellular level due to signal output parameters that exceed established safety thresholds.

The panel will be asked to discuss the risks to health that FDA has identified and whether these risks are appropriate, or whether there are additional risks to health that should be considered for non-invasive bone growth stimulators.

8. Mitigation of Risks to Health/Proposed Special Controls

FDA believes that special controls, in addition to general controls, can be established to mitigate the risks to health identified in Section 7 above, and provide reasonable assurance of the safety and effectiveness of non-invasive bone growth stimulators.

When evaluating the adequacy of the special controls, it is important to understand that the FDA correlates the ability of each special control identified to mitigate an identified risk to health. Hence, FDA proposes that the special controls/mitigation methods included in Table 2 below would provide reasonable assurance of safety and effectiveness.

Table 2: Risks to Health and Mitigation Measures for Non-Invasive Bone Growth Stimulators

Identified Risk to Health	**Mitigation Method**
Failure or delay of osteogenesis	Clinical performance data Non-clinical performance testing Software verification, validation, and hazard analysis Labeling
Burn	Non-clinical performance testing Electrical safety testing Labeling
Electrical shock	Electrical safety testing Labeling
Electromagnetic interference	Electromagnetic compatibility (EMC) testing Labeling
Adverse tissue reaction	Biocompatibility evaluation Labeling
Adverse interaction with internal/external fixation devices	Labeling
Adverse biological effects	Non-clinical performance testing Software verification, validation, and hazard analysis

The risk of failure or delay of osteogenesis is clinically significant. To mitigate this risk, FDA proposes that manufacturers conduct clinical performance testing to demonstrate that the device yields positive outcomes (e.g., fusion of the non-union) in accordance with its intended use. Further, FDA proposes non-clinical performance testing to demonstrate that the device performs as intended under anticipated

conditions of use to achieve the identified successful clinical performance characteristics. This would include verification and validation of critical performance characteristics, including characterization of the designed outputs of the device as well as the outputs which are delivered to the patient, thermal safety and reliability testing, reliability testing consistent with the expected device use-life, and validation that signal characteristics are within safe physiologic limits. Also, FDA proposes appropriate software verification, validation, and hazard analysis to ensure that any device software performs as intended. Lastly, FDA proposes labeling to provide appropriate instructions (e.g., duration, frequency of use) to the end user.

To mitigate the risk of skin burns, FDA proposes non-clinical performance testing of the device to verify and validate critical performance characteristics, demonstrate thermal safety and reliability, validate that signal characteristics are within safe physiologic limits, and demonstrate reliability of the device consistent with its expected use-life. FDA also proposes electrical safety testing to minimize the risk of thermal burns to the patient, and specific instructions regarding proper usage and specific warnings associated with the risk of burns.

To mitigate electrical shocks, FDA proposes electrical safety testing to minimize the risk of shock to the patient. Furthermore, FDA proposes labeling provisions, including instructions on appropriate usage and maintenance, and specific warnings regarding electrical shock.

To mitigate electromagnetic interference, FDA proposes electromagnetic compatibility and labeling to minimize the risk of adverse interaction with other electronic devices such as implanted electronic devices.

To mitigate the risk of adverse tissue reactions, FDA proposes biocompatibility evaluation to ensure that the materials used in patient-contacting components of the device are safe for skin contact and labeling that includes warnings against use on compromised skin or when there are known sensitivities, as well as instructions on appropriate cleaning of any reusable components.

To mitigate the risk of adverse interaction with internal/external fixation devices, FDA proposes labeling, specifically inclusion of appropriate warnings for patients with implanted internal/external devices.

To mitigate the risk of adverse biologic effects, FDA proposes non-clinical performance testing to verify and validate critical performance characteristics of the device, demonstrate thermal safety and reliability, validate safety of the signal by reference to known biological safety limits, and demonstrate reliability of the device over the expected use-life. Furthermore, FDA proposes software verification, validation, and hazard analysis.

The following special controls are proposed for non-invasive bone growth stimulators:

(1) Clinical performance data must support the intended use of the product.

(2) Non-clinical performance testing must demonstrate that the device performs as intended under anticipated conditions of use. The following must be provided:
  (i) Verification and validation of critical performance characteristics of the device, including characterization of the designed outputs of the device as well as the outputs that are delivered to the patient.
  (ii) Thermal safety and thermal reliability testing.
  (iii) Validation that signal characteristics are within safe physiologic limits.
  (iv) Reliability testing consistent with the expected use-life of the device.

(3) Patient-contacting components of the device must be demonstrated to be biocompatible.

(4) Performance data must demonstrate the electrical safety and electromagnetic compatibility of the device.

(5) Appropriate software verification, validation, and hazard analysis must be performed.

(6) Labeling for the device must include the following:

(i) Warning against use on compromised skin or when there are known sensitivities;

(ii) Appropriate warnings for patients with implanted medical devices;

(iii) A detailed summary of the clinical testing, which includes the clinical outcomes associated with the use of the device, and a summary of adverse events and complications that occurred with the device;

(iv) A clear description of the device;

(v) Instructions on appropriate usage, duration, and frequency of use;

(vi) Instructions for maintenance and safe disposal;

(vii) Instructions for appropriate cleaning of any reusable components;

(viii) Specific warnings regarding user burns, electrical shock, and skin irritation; and

(ix) The risks and benefits associated with use of the device.

The Panel will be asked whether the proposed special controls can adequately mitigate the risks to health for non-invasive bone growth stimulators and provide a reasonable assurance of safety and effectiveness.

9. Summary

FDA's proposal would require that clinical performance of any non-invasive bone growth stimulator device be evaluated in support of the intended use. Rather than prescribe specific study requirements, FDA's proposal would allow for flexibility in study design and the level of clinical evidence needed taking into consideration certain parameters, e.g., the intended use, treatment population, and technological characteristics of the device, including any similarities between the device and legally marketed predicate device(s), as appropriate. The requirement of clinical performance is intended to mitigate the risk of inconsistent or ineffective treatment, as cited by the 2006 Panel and in various comments received in response to the 2007 Notice.

Non-invasive bone growth stimulators are currently classified in Class III. In light of the information available, the Panel will be asked to comment on whether non-invasive bone growth stimulators fulfill the statutory definition associated with a Class III device designation. FDA believes that this device may be more appropriately regulated as:

- Class II, meaning general and special controls are sufficient to provide reasonable assurance of its safety and effectiveness

  as opposed to:

- Class III, meaning

  - insufficient information exists to determine that general and special controls are sufficient to provide reasonable assurance of its safety and effectiveness, and

  - the device is life-supporting or life-sustaining, or for a use which is of substantial importance in preventing impairment of human health, or if the device presents a potential unreasonable risk of illness or injury.

For the purposes of classification (refer to the Regulatory Reference Sheet for additional information), FDA considers the following items, among other relevant factors, as outlined in 21 CFR 860.7(b):

1. The persons for whose use the device is represented or intended;
2. The conditions of use for the device, including conditions of use prescribed, recommended, or suggested in the labeling or advertising of the device, and other intended conditions of use;
3. The probable benefit to health from the use of the device weighed against any probable injury or illness from such use; and
4. The reliability of the device.

Part (g)(1) of this regulation further states that "It is the responsibility of each manufacturer and importer of a device to assure that adequate, valid scientific evidence exists, and to furnish such evidence to the Food and Drug Administration to provide reasonable assurance that the device is safe and effective for its intended uses and conditions of use. The failure of a manufacturer or importer of a device to present to the Food and Drug Administration adequate, valid scientific evidence showing that there is **reasonable assurance of the safety and effectiveness** of the device, if regulated by general controls alone, or by general controls and special controls, may support a determination that the device be classified into class III."

9.1. Indications for Use

A non-invasive bone growth stimulator is for prescription use and is intended to be used externally to promote osteogenesis as an adjunct to primary treatments for fracture fixation or spinal fusion.

9.2. Reasonable Assurance of Safety

According to 21 CFR 860.7(d)(1), "There is reasonable assurance that a device is safe when it can be determined, based upon valid scientific evidence, that the probable benefits to health from use of the device for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use, outweigh any probable risks. The valid scientific evidence used to determine the safety of a device shall adequately demonstrate the absence of unreasonable risk of illness or injury associated with the use of the device for its intended uses and conditions of use."

In plain language, the definition states that a reasonable assurance of safety exists if, when using the device properly:

- The probable benefits to health outweigh the probable risks, and
- There is an absence of unreasonable risk of illness or injury

FDA has identified potential risks to health associated with non-invasive bone growth stimulators, based on the public and non-public information (published literature, MDRs, recalls, and Summary of Safety and Effectiveness Data documents) available to FDA. The risks to health are discussed in Section 7 of this document.

FDA will ask the Panel whether the evidence demonstrates a reasonable assurance of safety for the indications for use described above.

9.3. Reasonable Assurance of Effectiveness

According to 21 CFR 860.7(e)(1), "There is reasonable assurance that a device is effective when it can be determined, based upon valid scientific evidence, that in a significant portion of the target population, the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will provide clinically significant results."

In plain language, the definition states that if using the device properly provides clinically significant results in a significant portion of the target population, there is a reasonable assurance of effectiveness.

FDA will ask the Panel whether there is a reasonable assurance of effectiveness for non-invasive bone growth stimulators for the indications for use described above.

9.4. Special Controls

If the Panel were to recommend a Class II determination, FDA believes that the special controls proposed in Section 8, above, should be included as special controls.

The Panel will be asked whether the proposed special controls can adequately mitigate the risks to health for non-invasive bone growth stimulators and provide a reasonable assurance of safety and effectiveness in light of the available scientific evidence.

9.5. Reclassification

As previously noted, FDA considers a device Class II when general and special controls are sufficient to provide reasonable assurance of its safety and effectiveness.

In order to change the classification of non-invasive bone growth stimulators from Class III to Class II, FDA must have sufficient information to establish special controls that can provide reasonable assurance of the safety and effectiveness that, when using the device properly:

1. The probable benefits to health from using the device will outweigh the probable risks (per the definition of a reasonable assurance of safety, 21 CFR 860.7(d)(1))

2. There is an absence of unreasonable risk of illness or injury (per the definition of a reasonable assurance of safety)

3. The device will provide clinically significant results in a significant portion of the target population (per the definition of a reasonable assurance of effectiveness, 21 CFR 860.7(e)(1))

Special controls include "the promulgation of performance standards, postmarket surveillance, patient registries, development and dissemination of guidance documents (including guidance on the submission of clinical data in premarket notification submissions in accordance with section 510(k) of the FD&C Act), recommendations, and other appropriate actions as the Commissioner deems necessary to provide such assurance."

FDA believes that the available evidence supports a reasonable assurance of safety and effectiveness; the proposed special controls, in addition to general controls, would be sufficient to provide such assurance; and there is not an unreasonable risk of illness or injury for non-invasive bone growth stimulators. Consequently, FDA recommends that non-invasive bone growth stimulators be reclassified to Class II (Special Controls).

Based on the available scientific evidence and proposed special controls, the Panel will be asked whether a Class III or Class II designation is appropriate for non-invasive bone growth stimulators.

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