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Division of Dockets Management  
Food and Drug Administration  
5630 Fishers Lane  
Room 1061 (HFA-305)  
Rockville, MD 20852

**Re: FDA Docket 2005P-0121/CCP 1;  
Comments in Opposition to the Reclassification of External Bone Growth Stimulators**

Dear Sir or Madam:

On behalf of the BGS Reclassification Opposition Group (“BGS Group”), we submit the following comments in opposition to the RS Medical petition, which proposes the reclassification of external bone growth stimulator (“BGS”) devices from Class III to Class II.<sup>1</sup> The BGS Group is comprised of the leaders in this device field—dj Orthopedics, Inc., EBI, L.P., and Orthofix Inc. Collectively, we represent over 50 years of experience with BGS devices and are responsible for 100% of the electrical/electromagnetic external BGS market. By contrast, RS Medical is a newcomer to the field and proposes using its reclassification petition to bypass both PMA and 510(k) review of its first BGS device. As demonstrated by the significant errors in its petition, RS Medical does not understand the fundamentals of BGS technology and device reclassification.

BGS devices are used for potentially debilitating medical conditions, such as serious non-unions and spinal fusions. Throughout the history of these devices, FDA has required rigorous PMA clinical studies and premarket review of manufacturing before marketing. RS Medical has not demonstrated that the safety and effectiveness of new BGS devices can be reasonably assured by its proposed special controls in the absence of these requirements. In fact, the proposed down-classification would potentially expose patients to ineffective or harmful treatments (i.e., subject patients to further surgical interventions), stunt continuing research (i.e., on new indications and device mechanisms of action), and undermine the integrity of BGS technology by permitting the influx of potentially unsafe and ineffective devices. For the reasons set forth below, FDA should deny RS Medical’s petition to down-classify BGS devices.

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<sup>1</sup> William Carroll, Vice President, Research and Development, RS Medical, *Reclassification Petition for the Non-invasive Bone Growth Stimulator under Section 513(e) of the FDCA*, Docket 2005P-0121/CCP 1 (filed Feb. 9, 2005) [“RS Medical Petition”].

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## I. Introduction

### A. Regulatory Framework

The Federal Food, Drug, and Cosmetic Act (“FDCA”) recognizes three classes of medical devices, depending on the extent of regulatory controls necessary to provide a “reasonable assurance” of device safety and effectiveness: Class I (general controls), Class II (special controls), and Class III (premarket approval). BGS devices are currently classified as “postamendments”<sup>2</sup> Class III devices in accordance with FDCA section 513(f). FDA requires BGS study sponsors to obtain an approved IDE before initiating clinical trials and an approved PMA before marketing these devices. As a newcomer to the BGS field, RS Medical submitted its reclassification petition under the “catch-all” FDCA section 513(e), which permits any interested person to petition for device reclassification on the basis of new information.<sup>3</sup>

RS Medical seeks to reclassify from Class III to Class II external BGS devices that use capacitive coupling (“CC”), combined magnetic fields (“CMF”), or pulsed electromagnetic fields (“PEMF”) for the treatment of non-union fractures acquired secondary to trauma<sup>4</sup> or for lumbar spinal fusions.<sup>5</sup> The petition specifically discusses seven marketed devices: Bioelectron’s OrthoPak Bone Growth Stimulator, Bioelectron’s SpinalPak Fusion Stimulator,<sup>6</sup> EBI’s Bone Healing System, Orthofix’s Physio-Stim Lite, Orthofix’s Spinal-Stim Lite, djOrthopedics’ OL 1000, and djOrthopedics’ SpinaLogic.<sup>7</sup> RS Medical attempts to circumvent the 510(k) process altogether for its unapproved BGS device. RS Medical asserts that the brief description of its new device that is included in the reclassification petition “obviate[s] any need for a 510(k) for the petitioner’s device subsequent to the reclassification action.”<sup>8</sup>

FDA has continued to regulate BGS devices under Class III because PMA requirements are necessary to reasonably assure the safety and effectiveness of these devices. In 1998, FDA released a *Draft Guidance Document for Industry and CDRH Staff for the Preparation of Investigational Device Exemptions and Premarket Approval Applications for Bone Growth Stimulator Devices* (“FDA Draft Guidance”).<sup>9</sup> The FDA Draft Guidance addressed both implanted

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<sup>2</sup> Postamendments devices are those devices that were not in commercial distribution prior to May 28, 1976, the enactment date of the Medical Device Amendments.

<sup>3</sup> FDCA § 513(e). This new information may include “a reevaluation of the data before the agency when the device was originally classified, as well as information not presented, not available, or not developed at that time.” *Denial of Request for Change in Classification of Hip Joint Metal/Metal Semi-Constrained, With a Cemented Acetabular Component, Prosthesis and Hip Joint Metal/Metal Semi-Constrained, With an Uncemented Acetabular Component, Prosthesis*, 67 Fed. Reg. 57024, 57025 (Sept. 6, 2002).

<sup>4</sup> RS Medical excludes vertebrae and flat bones, as well as cervical fusion. RS Medical Petition, at 1.

<sup>5</sup> RS Medical limits the lumbar spinal fusion surgery to one or two levels. *Id.*

<sup>6</sup> EBI acquired Bioelectron’s OrthoPak and SpinalPak Fusion Stimulators in September 2000.

<sup>7</sup> RS Medical Petition, at 89-99.

<sup>8</sup> *Id.* at 90.

<sup>9</sup> Draft Guidance Document for Industry and CDRH Staff for the Preparation of Investigational Device Exemptions and Premarket Approval Applications for Bone Growth Stimulator Devices (April 28, 1998) [“FDA Draft Guidance”].

and external BGS devices as well as a variety of indications, i.e., fracture healing, spinal fusion, osteoarthritis, avascular necrosis, osteoporosis, etc.<sup>10</sup> FDA concluded that “[b]ased upon the potential for serious risk associated with chronic exposure to electrical, electromagnetic, and ultrasound energies at the cellular and molecular levels, [FDA] regards all bone growth stimulators as significant risk devices.”<sup>11</sup> FDA noted that the different BGS modalities and intended uses required tailored testing.<sup>12</sup> Furthermore, FDA has emphasized that seemingly minor alterations to BGS devices (e.g., to their waveforms or designs) may adversely impact their safety and effectiveness.

External BGS devices are not Class II devices. Class II designation is appropriate only when “general controls by themselves are insufficient to provide reasonable assurance of the safety and effectiveness of the device, and for which there is sufficient information to establish special controls to provide such assurance.”<sup>13</sup> Thus, to support its reclassification petition, RS Medical must first identify a “generic type of device” for reclassification—a “grouping of devices that do not differ significantly in purpose, design, materials, energy source, function, or any other feature related to safety and effectiveness, and for which similar regulatory controls are sufficient to provide reasonable assurance of safety and effectiveness.”<sup>14</sup> Second, RS Medical must provide sufficient information, e.g., “valid scientific evidence,” to demonstrate that the proposed special controls would reasonably assure BGS safety and effectiveness. “Valid scientific evidence” includes:

Evidence from well-controlled investigations, partially controlled studies, studies and objective trials without matched controls, well-documented case histories conducted by qualified experts, and reports of significant human experience with a marketed device, from which it can fairly and responsibly be concluded by qualified experts that there is reasonable assurance of the safety and effectiveness of a device under its conditions of use.<sup>15</sup>

RS Medical may rely only on publicly available “valid scientific evidence,” not on another sponsor’s trade secret or confidential commercial information,<sup>16</sup> to support reclassification. Furthermore, RS Medical bears the burden of proof throughout the review of its petition. FDA places the burden wholly “on those who support reclassification, regardless of whether those

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<sup>10</sup> *Id.*

<sup>11</sup> *Id.* (emphasis added).

<sup>12</sup> *Id.*

<sup>13</sup> FDCA § 513(a)(1)(B) (emphasis added).

<sup>14</sup> 21 C.F.R. § 860.3(i).

<sup>15</sup> 21 C.F.R. § 860.7(c)(2).

<sup>16</sup> *See* FDCA § 520(c) (information used in any investigation concerning the safety and effectiveness of a device); FDCA § 520(h)(3) (information in the detailed summary of safety and effectiveness of a PMA-approved device).

opposing reclassification can or do submit evidence showing that reclassification is not appropriate.<sup>17</sup> As discussed below, RS Medical’s petition falls far short of this burden.

**B. RS Medical has failed to demonstrate that its proposed special controls would reasonably assure BGS device safety and effectiveness.**

Although we are “not required to provide any evidence that reclassification is inappropriate,”<sup>18</sup> we have conducted a comprehensive review of RS Medical’s petition and the scientific literature on BGS devices. This review establishes the following conclusions:

1. RS Medical’s petition is deficient on its face. First, RS Medical has ignored the regulatory requirement to provide representative data that are unfavorable to its reclassification petition. Second, rather than identifying a single type of device for reclassification, RS Medical’s petition contains three distinct proposals. RS Medical’s apparent confusion about how to define BGS devices simply underscores that these devices are difficult for the inexperienced to define, let alone to manufacture. *See* Section II.
2. RS Medical has failed to identify a generic type of device (e.g., a predicate device) for reclassification. BGS devices encompass a range of distinct technologies, waveform parameters, functionalities, designs, dosimetries, and intended uses that do not constitute a generic type of device. Given the dissimilarities among BGS devices, a similar set of special controls could not reasonably assure the safety and effectiveness of each distinct type of BGS device. Even minor changes to BGS devices may profoundly impact their safety and effectiveness. In addition, the basic characteristics of these devices, i.e., their mechanisms of action and effects at the cellular level, are not fully understood. BGS devices fall squarely within Class III designation because “insufficient information exists to determine that the special controls . . . would provide reasonable assurance of its safety and effectiveness.”<sup>19</sup> *See* Section III.
3. RS Medical has failed to provide valid scientific evidence demonstrating that its proposed special controls would reasonably assure the safety and effectiveness of BGS devices. Although manufacturing tolerances are essential to the safe and effective performance of these devices, RS Medical ignores them entirely. Consistent and controlled manufacturing is particularly important for BGS devices because of their sensitivity to seemingly minor changes in design or waveform parameters. Unlike the 510(k) process, the

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<sup>17</sup> *Reclassification of Daily Wear Spherical Contact Lenses Consisting of Rigid Gas Permeable Plastic Materials; Withdrawal of Proposed Rule* [“Contact Lens Rule”], 48 Fed. Reg. 56778, 56783 (emphasis added). The D.C. Circuit has upheld “FDA’s assignment of the burden of proof to those seeking to change the status quo.” *Contact Lens Mfrs. Ass’n v. FDA*, 766 F.2d 592, 599 (D.C. Cir. 1985).

<sup>18</sup> Contact Lens Rule, 48 Fed. Reg. at 56892 (emphasis added).

<sup>19</sup> FDCA § 513(a)(1)(C).

PMA process provides for FDA's premarket review and inspection of manufacturing. The proposed special controls inadequately address several known risks posed by BGS devices, such as the effect of duration-of-use on the risk for skin irritation and the risk to patients who use electrical or metallic implants. Further, RS Medical relies on studies that suffer from a variety of deficiencies and do not constitute sufficient valid scientific evidence to support down-classification. The current scientific literature on BGS devices clearly indicates that only the rigors of the PMA process—e.g., PMA clinical studies and premarket review of manufacturing—will reasonably assure the safety and efficacy of these devices. *See* Section IV.

**II. FDA must reject RS Medical's petition on its face because the petition fails to include representative data and to identify a device for reclassification.**

**A. RS Medical has failed to include representative unfavorable data known to the petitioner.**

FDA must reject the petition on its face because RS Medical has failed to include representative unfavorable data. FDA regulations require that the reclassification petitioner include "representative data and information known by the petitioner that are unfavorable to the petitioner's position."<sup>20</sup> RS Medical's selective gloss of the literature is highly misleading. Our literature search readily revealed numerous studies that contained data unfavorable to the petition. Data that are commonly known in the BGS field and available in databases such as PubMed certainly constitute the type of publicly available information that should be "known" to RS Medical. *See* Appendix B for a bibliography of our independent literature search and Appendix D for select summaries of these studies.

The relevant literature undermines RS Medical's contention that Class II substantial equivalence determinations are appropriate for BGS devices.

- First, studies show that the basic mechanisms of action of the various BGS devices differ by modality and are not fully understood. For example, Brighton et al. (2001) reported that CC, CMF, and PEMF modalities exhibited different biochemical pathways and produced different responses in bone-forming cells *in vitro*.<sup>21</sup> Aaron et al. (2004) similarly found distinct differences between the mechanisms of action of the modalities.<sup>22</sup> These studies evidence the unique, not generic, nature of these devices and undermine RS Medical's contention that sufficient scientific information exists to demonstrate the adequacy of its proposed special controls.

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<sup>20</sup> 21 C.F.R. § 860.123(a)(7).

<sup>21</sup> C.T. Brighton et al., *Signal Transduction in Electrically Simulated Bone Cells*, J. BONE JOINT SURG. AM. 1514-23 (2001).

<sup>22</sup> R.K. Aaron et al., *Stimulation of Growth Factor Synthesis by Electric and Electromagnetic Fields*, 419 CLIN. ORTHOP. RELATED RES. 30-37 (2004).

- Second, studies show that seemingly minor changes to the BGS devices may profoundly affect their safety and effectiveness. For example, R. J. Fitzsimmons et al. (1992 and 1994) reported that a small deviation in waveform frequency, e.g., as little as 2 Hz, can result in an ineffective signal.<sup>23</sup> Brighton et al. (1985) also found that increases in the signal amplitude are similarly restricted to a narrow window of efficacy.<sup>24</sup> These studies demonstrate that the various BGS modalities and intended uses require specific, not generic, waveform parameters. As discussed *infra* Section III, RS Medical instead provides inaccurate and incomplete waveform parameters for the currently marketed devices in its Table 1. The precision required to produce waveforms of proven safety and effectiveness renders the BGS device unsuitable for comparative determinations of “substantial equivalence.”
- Third, studies report that the preclinical data and comparative descriptions that usually drive 510(k) determinations are insufficient to reasonably assure BGS safety and effectiveness. For example, Fredericks et al. (2000) reported a signal that worked in animal models but failed clinically.<sup>25</sup>

See *infra* Section III, for additional examples of studies containing unfavorable data that RS Medical excluded from its petition.

FDA must enforce the clear regulatory mandate to include unfavorable data in reclassification petitions. Otherwise, the agency will encourage petitioners to selectively report and misrepresent the relevant scientific information.

#### **B. RS Medical has failed to define a BGS device for reclassification.**

FDA must reject RS Medical’s petition on its face because it has failed to identify the device for reclassification. The petition contains the three distinct proposals described below.

(1) RS Medical’s proposed reclassification regulation identifies the reclassification of BGS devices that use CC, PEMF, or CMF, regardless of specific waveform parameters.<sup>26</sup>

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<sup>23</sup> R.J. Fitzsimmons et al., *Low-amplitude, Low-frequency Electrical Field-stimulated Bone Cell Proliferation May in Part be Mediated by Increased IGF-II Release*, 150 J. CELL. PHYSIOL. 84-89 (1992); R.J. Fitzsimmons et al., *Combined Magnetic Fields Increased Net Calcium Flux in Bone Cells*, 55 CALCIF. TISSUE INT. 376-380 (1994).

<sup>24</sup> C.T. Brighton et al., *Fracture Healing in the Rabbit Fibula When Subjected to Various Capacitively Coupled Electrical Fields*, J. ORTHOP. RES. 331-340 (1985).

<sup>25</sup> D.C. Fredericks et al., *Effects of a Pulsed Electromagnetic Fields on Bone Healing in a Rabbit Tibial Osteotomy Model*, 14 J. ORTHOPAEDIC TRAUMA 93-100 (2000).

<sup>26</sup> RS Medical’s proposed classification regulation states: “The stimulation may be delivered through capacitive coupling with electrodes placed directly over the treatment site, through pulsed electromagnetic fields (PEMF) with treatment coils placed into a brace or over a cast at the treatment site, or through combined magnetic fields with treatment coils applied to the site. . . .” RS Medical Petition, at 1-2.

(2) RS Medical's section on "Description of 'Devices Covered by Reclassification Petition'" limits reclassification to currently marketed devices and RS Medical's unapproved device.<sup>27</sup> For its new device, RS Medical is impermissibly attempting to bypass not only PMA requirements, but also those for a 510(k).

(3) RS Medical's proposed guidance document limits reclassification to those devices that use the waveform parameters identified in the petition's Table 1.<sup>28</sup> As we discuss *infra* Section III, however, Table 1 inaccurately and incompletely defines the waveforms for the PMA-approved BGS devices.

These inconsistent proposals do not identify a device for reclassification, but rather reveal RS Medical's misunderstanding of basic BGS device characteristics and functioning. If RS Medical intended to limit reclassification to PMA-approved devices, then it has completely failed.

RS Medical's inconsistent proposals lead to equally contradictory results. If RS Medical intended to limit reclassification to the PMA-approved devices and their specific waveform parameters, then RS Medical has implicitly acknowledged the absence of a generic type of BGS device for reclassification. As discussed *infra* Sections III and IV, RS Medical has failed to recognize that the 510(k) standard of substantial equivalence would render meaningless any limitation of the waveforms to those found in PMA-approved devices. In any case, RS Medical only provides an inaccurate and incomplete description of the waveform parameters used in these devices. Alternatively, if RS Medical did not intend to limit reclassification to PMA-approved waveforms, then RS Medical has proposed the reclassification of BGS devices for which there is no record of safety and effectiveness. Only the specific waveform parameters used in the PMA-approved BGS devices have proven safety and effectiveness. As discussed *infra* Section III, any change to a BGS device's electrical or magnetic output could result in an ineffective and harmful device.

Given the petition's failures to provide representative unfavorable data and to define the device for reclassification, FDA must reject the petition on its face.

**III. RS Medical has failed to identify a generic type of device for which similar regulatory controls would reasonably assure device safety and effectiveness.**

RS Medical inaccurately defines and inappropriately groups dissimilar devices for reclassification. This failure to identify a generic type of BGS device reflects the complexity and diversity of devices that are loosely termed, "bone growth stimulators." Ultimately, the failure to

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<sup>27</sup> RS Medical's petition states: "The petitioner proposes that seven commercially available devices and one new device, manufactured by the petitioner, be reclassified as a result of this petition. . . ." RS Medical Petition, at 7.

<sup>28</sup> RS Medical's petition states: "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. . . ." RS Medical Petition, at 107.

describe a generic type of device—the cornerstone of the device classification system—is fatal to RS Medical’s petition. In upholding FDA’s refusal to down-classify rigid gas permeable [“RGP”] contact lenses, the D.C. Circuit concluded: “Independently sufficient and far more persuasive is the FDA’s determination that all reclassification proposals to date ‘inadequately characterize’ the class of RGP lenses. . . . [T]hus, at least for the present, the premarket approval process is unavoidable.”<sup>29</sup>

A “generic type of device” is a “grouping of devices that do not differ significantly in purpose, design, materials, energy source, function, or any other feature related to safety and effectiveness, and for which similar regulatory controls are sufficient to provide reasonable assurance of safety and effectiveness.”<sup>30</sup> By contrast, the BGS devices in the petition differ significantly in terms of their modalities, mechanisms of action, waveforms, dosimetries, designs, and intended uses. Indeed, these BGS devices would not be considered substantially equivalent to each other under 510(k) review. Although they have overlapping intended uses, they have distinct technological characteristics (e.g., “a significant change in the materials, design, energy, source, or other features of the device”) that raise different questions of safety and effectiveness, which cannot be addressed by the same set of special controls.<sup>31</sup> RS Medical implicitly acknowledges that the devices proposed for reclassification are not substantially equivalent to each other. The petition specifically includes the three different modalities and seven marketed devices because the reclassification of any one of these modalities or devices would not result in the reclassification of the rest.<sup>32</sup>

Substantial equivalence determinations under 510(k) review are completely inappropriate for BGS devices. Purportedly minor alterations to a BGS device may profoundly impact safety and effectiveness. In refusing to down-classify RGP contact lenses to Class II, FDA reasoned that “[t]he safety and effectiveness of contact lenses is a function of the complex interrelationship of material, design, and manufacture that results in a unique set of physical, chemical, mechanical, and optical characteristics.”<sup>33</sup> Here, the safety and effectiveness of BGS devices are similarly “a function of a complex relationship” of manufacturing, technological method, waveform, design, dosimetry, and intended use. As with the RGP contact lenses, even “minor changes . . . can significantly affect the safety and effectiveness” of BGS devices.<sup>34</sup> Down-classification would permit an inexorable regulatory creep in which seemingly similar—but unproven—BGS devices could enter the marketplace, thereby exposing patients to potentially unsafe or ineffective treatments.

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<sup>29</sup> *Contact Lens Mfrs. Ass’n*, 766 F.2d at 600-601 (emphasis added).

<sup>30</sup> 21 C.F.R. § 860.3(i) (emphasis added).

<sup>31</sup> 21 C.F.R. § 807.100(b)(2).

<sup>32</sup> 21 C.F.R. § 860.120(b) (“The reclassification of any device within a generic type of device causes the reclassification of all substantially equivalent devices within that generic type.”).

<sup>33</sup> Contact Lens Rule, 48 Fed. Reg. at 56792.

<sup>34</sup> In the Contact Lens Rule, FDA concluded “that minor changes in lens material formulation or manufacturing process can significantly affect the safety and effectiveness of lenses manufactured from the material.” *Id.* at 56780.

In any case, it is impossible to down-classify the BGS devices based on the specifications provided by RS Medical. In Table 1, RS Medical inaccurately and incompletely describes the characteristics of the proposed predicate devices. RS Medical also ignores crucial considerations such as dosimetry, device design, and manufacturing tolerances. Furthermore, important characteristics of these devices, e.g., their mechanisms of action and effects on the cellular level, differ significantly by modality and are not fully understood. Even assuming that the specifications of the currently marketed BGS devices could be accurately and fully characterized, compelling new devices to meet such exact specifications would completely undermine the requirement to identify a generic type of device for reclassification. *See infra* Section IV for further discussion.

### **A. Technological Differences**

The RS Medical petition proposes the reclassification of BGS devices that use three different types of technologies: (1) CC, (2) CMF, and (3) PEMF.<sup>35</sup> CC devices use surface electrodes placed on the skin with a high-frequency, oscillating electric current passed between them. CMF devices use a low-frequency sinusoidal AC magnetic field overlaid onto a static DC magnetic field. PEMF devices use conducting coils and induce electric current by creating a time-varying (pulsed) electromagnetic field with particular pulse trains, pulse shapes, pulse repetition frequency (prf), and magnetic field strength. Along with differences in signals, the designs of PEMF devices also differ by intended use. For spinal fusion, a PEMF device may use a Helmholtz coil design that surrounds the area and focuses a low-level magnetic field to the spinal fusion site. For long bone non-union, a PEMF device may use a custom-designed transducer unique to the particular anatomy for treatment, i.e., a triangular shape for the proximal humerus and a rectangular shape for the clavicle.

The dissimilarities among the petition's BGS devices present different risks for which a similar set of regulatory controls would not reasonably assure device safety and effectiveness. FDA has recognized that "[t]he similarity in health risks is fundamental to the concept of classification by generic type of device. If devices thought to be within the same generic type present different risks, it is likely that the devices are not really of the same generic type."<sup>36</sup> Hence, the FDA Draft Guidance stated that the different BGS device modalities raised different safety concerns which required testing "to address the safety issues related to the specific modality involved."<sup>37</sup>

#### **1. The mechanisms of action for BGS devices differ by modality and are not fully understood.**

Current research on BGS mechanisms of action reports that CC, CMF, and PEMF modalities affect cellular processes in different ways, e.g., different mechanisms of action. There is little predictive theory, however, on how these various BGS signals positively affect bone growth: the biological and biophysical pathways that explain the effects of these devices are not

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<sup>35</sup> RS Medical arbitrarily excludes ultrasound BGS devices from its petition.

<sup>36</sup> *Final Rule on Medical Device Classification Procedures*, 43 Fed. Reg. 32987, 32992 (July 28, 1978).

<sup>37</sup> FDA Draft Guidance (emphasis added).

fully understood. For example, with PEMF devices it remains unknown whether the treatment area responds positively to the electromagnetic field or to the induced current.<sup>38</sup> Lacking a clear understanding of these pathways, it is impossible to conclude that a new BGS signal is safe and effective without PMA-type clinical trials and FDA premarket review of manufacturing. RS Medical's petition, however, completely ignores this important issue and the relevant literature.

Furthermore, even with the same field parameters, variable responses in different model systems illustrate that there are cell-specific and/or tissue-specific circumstances which mediate the cellular effects. Thus, a device shown to be effective in one clinical application may not be effective in another clinical application. After reviewing studies on CC, CMF, and PEMF, Morone et al. (2002) concluded that "[n]ot all adjunctive ES [electrostimulation] devices . . . are equally effective in promoting fusion."<sup>39</sup>

In a study on the biochemical pathways for CC, CMF, and PEMF, Brighton et al. (2001) highlighted the need for additional inquiry in this area:

[T]he precise mechanism by which the electrical and electromagnetic fields are transduced at these sites is not yet understood in terms of a rigorous model. Also, one should be cautioned that an *in vitro* state, in which isolated bone cells are grown under exacting conditions, is an artificial environment; such conditioned cells may respond only in a limited way by following limited biochemical pathways in response to limited stimulation. The same cells in their natural setting *in vivo* are exposed to a myriad of different upregulating and downregulating signals and thus may respond differently from those in the present study.<sup>40</sup>

In this study, Brighton et al. found that CC, CMF, and PEMF modalities exhibited different biochemical pathways and produced different responses in bone-forming cells *in vitro*.<sup>41</sup> The initial cellular signaling pathways that characterize each treatment modality are different. The study concluded that CC signals appear to activate voltage-gated calcium channels leading to an increase in cytosolic calcium. By contrast, CMF and PEMF signals affected intracellular calcium release. Furthermore, each signal produced cell proliferation at different times and for different durations. When cultures were exposed to CC, CMF, or PEMF signals for 0.5, 2, 6, or 24 hours, the results suggested that these signals affect cellular pathways differently. CC exhibited dosage dependency, with the greatest increase in DNA when exposed to the CC signal for 24 hours as compared to 30 minutes. Conversely, both CMF and PEMF exhibited minimal dosage dependency, with a similar amount of DNA at 24 hours and at 30 minutes.

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<sup>38</sup> M.W. Otter et al., *Effects of electromagnetic fields in experimental fracture repair*, 355S CLIN. ORTHOP. REL. RES. S90-104 (1998).

<sup>39</sup> M.A. Morone et al., *The Use of Electrical Stimulation to Enhance Spinal Fusion*, 13 NEUROSURGERY Focus, Art. 5 (2002). See also N. Kahanovitz, *Electrical Stimulation of Spinal Fusion: A Scientific and Clinical Update*, 2 SPINE 145-50 (2002).

<sup>40</sup> C.T. Brighton et al., *Signal Transduction in Electrically Simulated Bone Cells*, J. BONE JOINT SURG. AM. 1514-23 (2001).

<sup>41</sup> *Id.*

As described below, several other studies have found differing mechanisms of action for the BGS modalities.

- Ryaby (1998) reported IGF-II as the major cellular entity affected.<sup>42</sup> Aaron et al. (1997) reported stimulation of TGF-Beta mRNA.<sup>43</sup> Nagai and Ota (1994) reported upregulation of BMP-2 and -4.<sup>44</sup>
- Aaron et al. (2004) noted distinct differences between treatment modalities.<sup>45</sup> This review paper examined studies in four areas: (1) transmembrane signaling, (2) channel activation, (3) receptor stimulation or blockade, and (4) growth factor stimulation. Aaron et al. concluded that “[t]ransmembrane signaling mechanisms may be unique to cell type and cell cycle position, and the type of biophysical input whether strictly electrical (DC or CC) or electrical and magnetic (IC).”
- For PEMF devices, Bassett (1984) concluded that “it is clear that different pulses affected different biologic processes in different ways. Selection of the proper pulse for a given pathologic entity has begun to be governed by rational processes similar, in certain respects, to those applied to pharmacologic agents.”<sup>46</sup>

While we know that PMA-approved BGS devices are safe and effective, we do not fully comprehend how they work. Class II down-classification is appropriate only when there is sufficient information to establish that the proposed special controls would reasonably assure device safety and effectiveness. A device for which significant questions remain about its key performance parameters is ill-suited to serve as a predicate device for the 510(k) process. Without a well-defined predicate device, evaluating new BGS devices under 510(k) review would undoubtedly present even greater difficulties. Further clinical study in this area is

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<sup>42</sup> J.T. Ryaby et al., *The Role of Insulin-Like Growth Factor in Magnetic Field Regulation of Bone Formation*, 35 BIOELECTROCHEM. BIOENERG. 87-91 (1994). J. T. Ryaby, *Clinical Effects of Electromagnetic and Electric Fields on Fracture Healing*, CLIN. ORTHOP. RELATED RES., SUPP., S205-15 (Oct. 1998).

<sup>43</sup> R.K. Aaron et al., *Bone Induction by Decalcified Bone Matrix and mRNA of TGFb and IGF-1 are Increased by ELF Field Stimulation*, 22 TRANS. ORTHOP. RES. SOC. 548 (1997).

<sup>44</sup> M. Nagai & M. Ota, *Pulsating Electromagnetic Field Stimulates mRNA Expression of Bone Morphogenetic Protein-2 and -4*, 73 J. DENT. RES. 1601-1605 (1994). See also T. Sahinoglu et al., *Pulsed Electromagnetic Fields Induce Osteogenesis and Upregulate Bone Morphogenetic Protein-2 and -4 mRNA in Rat Osteoblasts In Vitro*, 21 TRANS. ORTHOP. RES. SOC. 204 (1996); T. Bodamyali et al., *Pulsed Electromagnetic Fields Simultaneously Induce Osteogenesis and Upregulate Transcription of Bone Morphogenetic Proteins 2 and 4 in Rat Osteoblasts In Vitro*, 18 BIOCHEM. BIOPHYS. RES. COMMUN. 458-61 (1998).

<sup>45</sup> R.K. Aaron et al., *Stimulation of Growth Factor Synthesis by Electric and Electromagnetic Fields*, 419 CLIN. ORTHOP. RELATED RES. 30-37 (2004).

<sup>46</sup> C.A. Bassett, *The Development and Application of Pulsed Electromagnetic Fields (PEMFs) for Ununited Fractures and Arthrodeses*, 15 ORTHOP. CLIN. NORTH AM. 61-87 (Jan. 1984) (emphasis added).

necessary to improve our understanding of currently marketed BGS devices and to reasonably assure the safety and effectiveness of new BGS devices.

**2. BGS modalities present different dosimetry and design considerations that impact device safety and effectiveness.**

RS Medical's petition fails to address dosimetry and coil configurations—two crucial elements in BGS safety and effectiveness.

**(a) Dosimetry**

Dosimetry is fundamental to a BGS device's safety and effectiveness.<sup>47</sup> Dosages vary by device modality and intended use. RS Medical's petition, however, is silent on the dosimetry of the BGS devices proposed for reclassification. Different BGS technologies have been proven to be safe and effective at dosages ranging from 30 minutes/day (i.e., CMF devices) to 24 hours/day (i.e., CC devices). Even within the same modality, different intended uses may require different dosages. Certain PEMF devices for non-unions are indicated for 3 hours per day; other PEMF devices for lumbar spinal fusions are indicated for 2 and 10 hours of use. The PMA-approved BGS devices have undergone detailed preclinical studies to determine the doses at which each device will provide maximum effectiveness with minimal safety issues. Unlike the dosages for PMA-approved devices, the safety and effectiveness of new signals at undefined dosages remain unknown.

**(b) Coil Configuration**

In PEMF devices, different coils are required for different parts of the body and necessitate specific parameters. During the review of the PMA supplement for the Physio-Stim and Spinal-Stim PEMF devices, FDA "requested that you [Orthofix] provide detailed comparisons of the electrical output of the modified and original coil designs and that you relate these changes to the clinical study of the original coils. We also requested that you identify your specific reasoning as to why these changes would not adversely impact the effectiveness of the device."<sup>48</sup> FDA required specific information on the "local field strengths at the boundaries of the coils and the location and maximum of all maximum field strength values outside the treatment area" and a comparison to the devices studied. FDA emphasized that "increases in magnetic strength of the coils may require a demonstration of safety." FDA also required information regarding "maximum flux values (e.g., at the center of the coil)" that could affect "the shape of the magnetic field and respective local field strengths along the entire area of the coil."<sup>49</sup>

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<sup>47</sup> E.g., C.T. Brighton et al., *Signal Transduction in Electrically Simulated Bone Cells*, J. BONE JOINT SURG. AM. 1514-23 (2001).

<sup>48</sup> Letter from FDA to Orthofix (July 28, 2004) (regarding P850007/S27 Physio-Stim Models 3203, 3303, 3313, 3314, and 3315, and Spinal-Stim Model 2212).

<sup>49</sup> Letter from FDA to Orthofix (Nov. 13, 2003) (regarding P850007/S27 Physio Stim Models 3203, 3303, 3313, 3314, and 3315, and Spinal-Stim Model 2212).

In CMF devices, magnetic field output and distribution are extremely sensitive to changes in the coil configuration. Minor changes to coil geometry—e.g., addition of radii, changes in the plane of the coil, number of turns in the coil, or distance between the coil segments or secondary coil in a Helmholtz configuration—all significantly change the field distribution. Such changes in coil configuration are known to affect the magnetic field characteristics of the device, which could also affect efficacy.

It is axiomatic to state that dosimetry and design directly impact a BGS device’s safety and effectiveness. RS Medical’s omission of these basic elements underscores its failure to adequately define a generic type of device for reclassification and the inadequacy of its proposed special controls.<sup>50</sup>

## **B. Waveform Differences**

RS Medical has failed to define the waveform parameters that are necessary for the reproduction of waveforms with proven safety and effectiveness, e.g., the parameters used in PMA-approved BGS devices. These parameters are proprietary to each manufacturer and are not found in the published literature. FDA has required extensive testing for even minor modifications to PMA-approved BGS devices. In fact, FDA has maintained that the alteration of one signal parameter in a BGS device results in a new signal that requires additional clinical study.

### **1. RS Medical inaccurately and incompletely describes waveform parameters for the PMA-approved BGS devices.**

As demonstrated by the petition’s Table 1 excerpted below, RS Medical fails to understand or account for the complexities of BGS technology. Contrary to RS Medical’s assertion, the parameters listed in Table 1 would not generate waveforms that are identical, or even substantially equivalent, to those used in currently marketed devices. Table 1 omits and inaccurately describes parameters that are crucial to establishing the safety and effectiveness of these devices. RS Medical describes Table 1 as a “summary,” yet does not elaborate on the BGS waveforms later in the petition or in the proposed guidance document. Despite its multiple inaccuracies and omissions, Table 1 does successfully highlight the distinct differences between the BGS technologies: the different modalities and intended uses require specific, rather than generic, waveform parameters.

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<sup>50</sup> See *infra* Section IV.

The BGS Group bears no obligation to advise RS Medical on the correct and proprietary parameters for these devices. We have indicated below, however, the inaccurate parameters and those requiring additional information.

**RS Medical Petition's Table 1**  
**With Parenthetical Annotations by the BGS Opposition Group**

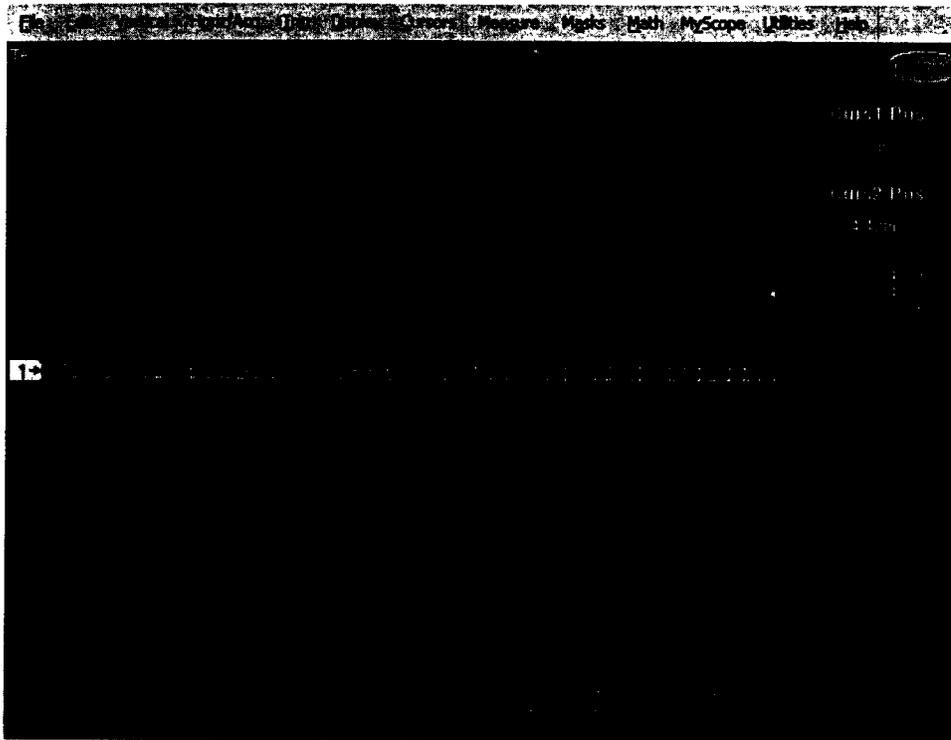
<u>Technology</u>	<u>Waveform</u>	<u>Tissue Electrical Field</u>
<u>Capacitive Coupling</u>  (CC)	60 kHz, 10 $\mu$ A (rms), 6.V peak to peak  <b>(These parameters are inaccurate.)</b>	0.1 to 20 mV/cm  300 $\mu$ A/cm <sup>2</sup>
<u>Pulsed Electromagnetic Fields</u>  (PEMF)	4.5-msec-long bursts of 20, 220- $\mu$ sec 18 G pulses repeated at 15 Hz  <b>(These parameters are incomplete and inaccurate.)</b>	1.5 mV/cm  10 $\mu$ A/cm <sup>2</sup>
	790-mG field of a burst of 21, 260- $\mu$ sec pulses repeated at 15 Hz  <b>(These parameters are incomplete and inaccurate)</b>	4 mV/cm peak to peak
<u>Combined Magnetic Fields</u>  (CMF)	76.6 Hz sinusoidal 40- $\mu$ T (400 mG) peak-to-peak AC magnetic field superimposed on 20- $\mu$ T DC magnetic field  <b>(These parameters are incomplete.)</b>	Magnetic field effect

RS Medical has failed to define a predicate BGS device. Indeed, RS Medical would rely on regulatory creep to reclassify PEMF devices for lumbar spinal fusion: Table 1 does not provide any PEMF parameters for this indication although RS Medical proposes its down-classification. Table 1 also does not account for the fact that CMF devices monitor and dynamically compensate for the ambient magnetic fields in which they operate. This feedback system ensures that the treatment area is consistently exposed to the PMA-approved signal. Without this feedback system, a CMF device based on the parameters in Table 1 would have unknown signal characteristics. The signal could fluctuate in an uncontrolled fashion, depending on the ambient magnetic field in which the device was operating.

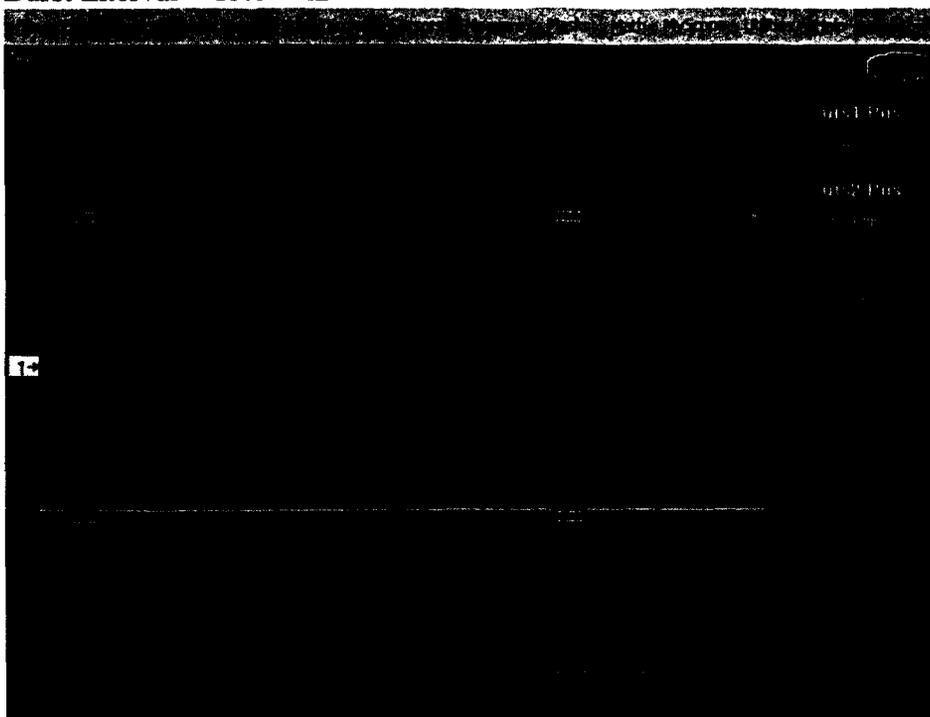
Based on the parameters in RS Medical's Table 1, a manufacturer could produce a variety of waveforms of unknown safety and effectiveness, thereby exposing patients to potentially ineffective or harmful devices and increasing the probability that a patient will require subsequent surgery. Using the PEMF parameters provided in RS Medical's Table 1, we were able to generate a number of different waveforms, as presented below and in Appendix C.

**Waveform 1: A Pulsed Square Wave Operating at the PEMF Parameters in Table 1**  
**(4.5-msec-long bursts of 20, 220- $\mu$ sec 18 G pulses repeated at 15 Hz)**

Number of Pulses = 20; Burst Width = 4.42 msec



Burst Interval = 15.02 Hz

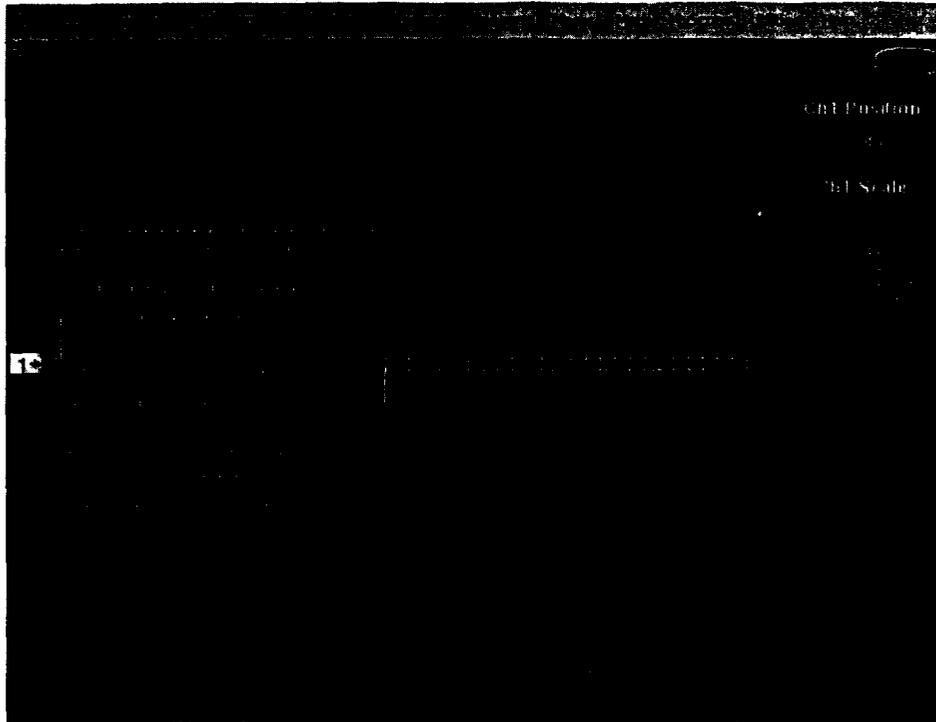


Pulse Width = 220  $\mu$ sec

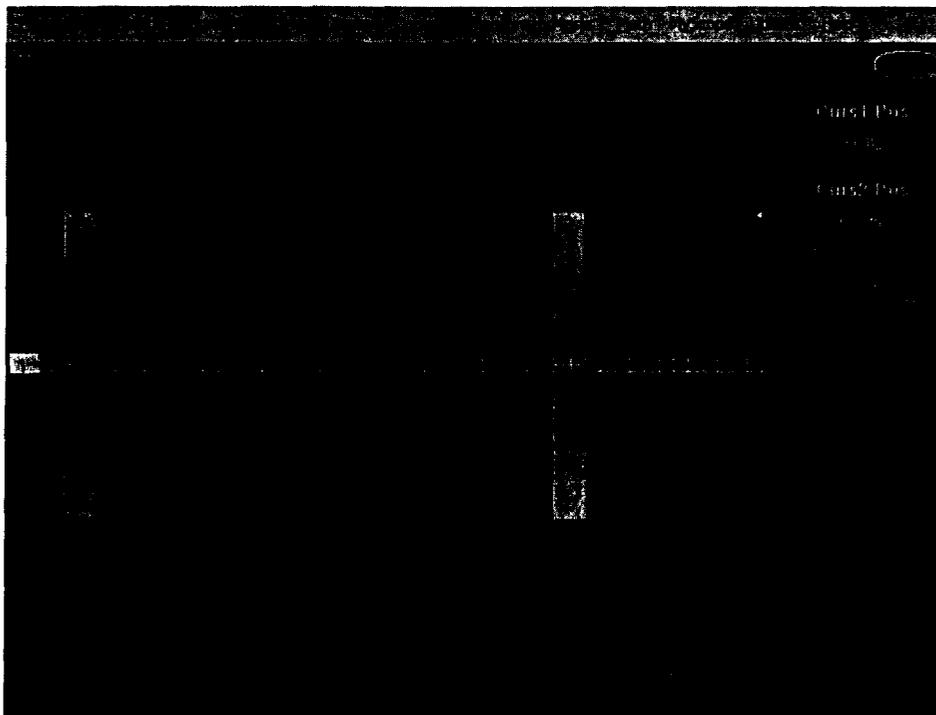


**Waveform 2: A Pulsed Sine Wave Operating at the PEMF Parameters in Table 1**  
**(4.5-msec-long bursts of 20, 220- $\mu$ sec 18 G pulses repeated at 15 Hz)**

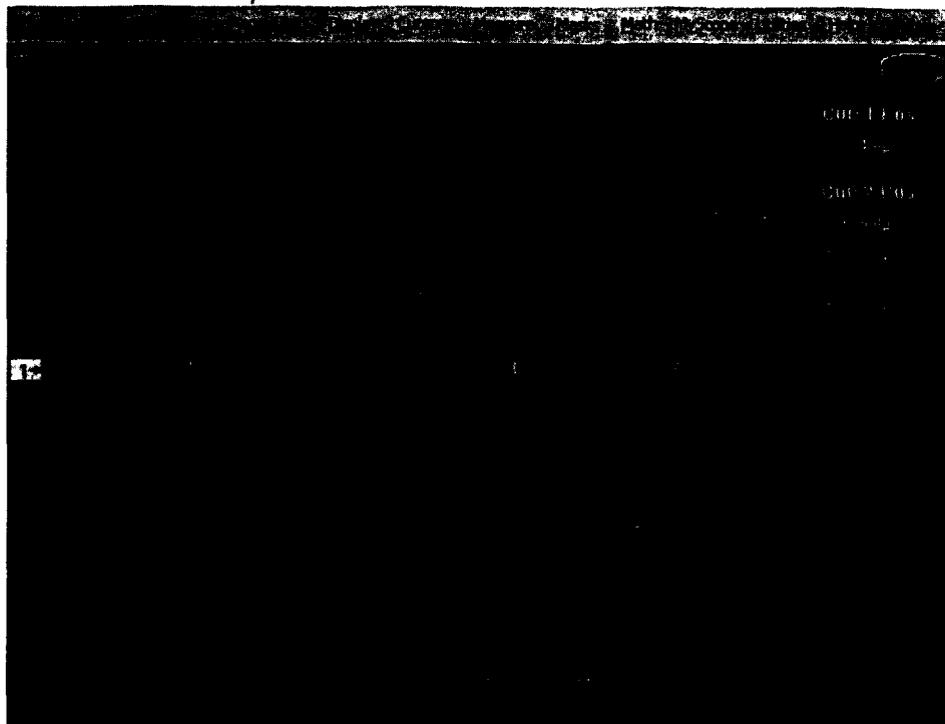
Number of Pulses = 20; Burst Width = 4.409 msec



Burst Interval = 15.02 Hz



Pulse Width = 222  $\mu$ sec



Contrary to RS Medical's assertion that Table 1 provides parameters for marketed devices, none of the above graphs depict a waveform with proven safety and effectiveness, yet devices with these waveforms would be marketable under the proposed down-classification. *See Appendix C* for additional graphs of potentially unsafe and ineffective waveforms that could be produced based on RS Medical's PEMF parameters.

## 2. Minor alterations to waveforms may adversely affect device safety and effectiveness.

FDA has long recognized that changes to BGS waveforms may adversely impact device safety and effectiveness. During the 1998 panel discussion on the FDA Draft Guidance, the panelists specifically noted the need for additional clinical evidence to accompany any changes to a device's signal.

Ms. [Erin] Keith: If I might, our major concern was more with design changes that changed the sort of electrical outputs of the devices and whether or not you thought that we should see animal or clinical data when that happened. . . .

Dr. [Richard] Coutts: It is my understanding that the manufacturers use specific signals and claim that the effect is related to that signal so that any change in the signal would in my mind fairly require that there be a new set of evidence that that is effective for what they want to claim.

Ms. Keith: Would there be under any circumstance where you would want to see clinical data for that or do you think that in most circumstances animal data would be sufficient? . . .

Dr. [Barbara] Boyan: Does anybody want to make a comment about that?

Dr. [Yadin] David: The two issues of safety and efficacy will require that there will be clinical data to support that as well.<sup>51</sup>

In approving the PMA for EBI's Bi-Osteogen System 204, FDA cautioned that "any change in the electrical or material characteristics must be approved by FDA prior to instituting the change in marketed devices" because the PMA application "did not contain sufficient information to allow an assessment of the effects of electrical stimulation induced by parameter ranges other than those chosen for conducting your clinical study."<sup>52</sup> In a later correspondence, FDA reiterated that EBI was "required to notify FDA of any significant modification of the originally approved device that may affect the safety and effectiveness of this device," including modifications to the "coil design" or "signal amplitude."<sup>53</sup>

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<sup>51</sup> Orthopedics and Rehabilitation Devices Advisory Panel Meeting, (April 28, 1998) (emphasis added). The Panel members were: Barbara D. Boyan, Ph.D., Cato T. Laurencin, M.D./Ph.D., Harry B. Skinner, M.D./Ph.D., Leela Rangaswamy, M.D., Albert A. Aboulaflia, M.D., Edward Y. Cheng, M.D., Richard D. Coutts, M.D., Yadin David, Ph.D., Jeremy L. Gilbert, Ph.D., Joseph E. Hale, Ph.D., Stephen Li, Ph.D., Kinley Larmtz, Ph.D., Michael Urban, M.D., Raymond Silkaitis, Ph.D. (industry representative), and Donald Altman, D.D.S. (consumer representative).

<sup>52</sup> Letter from David M. Link, Director, FDA Bureau of Medical Devices, to John P. Ryaby, President, Electro-Biology, Inc. (Nov. 6, 1979) (regarding P790002, Bi-Osteogen System 204) (emphasis added).

<sup>53</sup> Letter from Robert G. Britain, Associate Director for Device Evaluation, Office of Medical Devices, to Kenneth A. Klivington, Vice President, Research & Development, Electro-Biology, Inc. (Oct. 3, 1983).

Numerous studies demonstrate that even minor alterations to BGS waveforms can adversely affect device safety and effectiveness. For CC signals, Brighton et al. (1992) found that field strength plays a dominant role in determining bone cell proliferation.<sup>54</sup> The importance of pulse configuration and duty cycle depended on the application of the proper field strength to the cell. This conclusion concurred with his 1989 study finding that “*in vitro* growth plate chondrocytes exposed to [a certain signal] . . . showed no change when the same . . . signal consisted of a [different] duty cycle.”<sup>55</sup>

We review below several of these waveform studies for PEMF and CMF modalities. RS Medical’s petition neither addressed these studies nor the general issue of waveform changes that adversely impact BGS safety and effectiveness.

#### (a) PEMF Signal

- Midura et al. (2005) performed a side-by-side comparison of two distinct PEMF waveform treatments on the healing response after the same type of bone trauma.<sup>56</sup> This study tested the hypothesis that PEMF treatments augment and accelerate the healing of bone trauma. It utilized micro-computed tomography imaging of live rats that had received bilateral 0.2 mm fibular osteotomies (~0.5% acute bone loss) as a means to assess the *in vivo* rate dynamics of hard callus formation and overall callus volume. Starting 5 days post-surgery, osteotomized right hind limbs were exposed 3 hours/day to the Physio-Stim PEMF, 7 days/week for up to 5 weeks of treatment. The contralateral hind limbs served as sham-treated, within-animal internal controls. Although both PEMF and sham-treatment groups exhibited similar onset of hard callus at ~9 days after surgery, a 2-fold faster rate of hard callus formation was observed thereafter in PEMF-treated limbs, yielding a 2-fold increase in callus volume by 13-20 days after surgery. The quantity of the new woven bone tissue within the osteotomy sites was significantly better in PEMF-treated versus sham-treated fibulae, as assessed via hard tissue histology. The apparent modulus of each callus was assessed via a cantilever bend test and indicated a 2-fold increase in callus stiffness in the PEMF-treated over sham-treated fibulae. PEMF-treated fibulae exhibited an apparent modulus at the end of 5 weeks that was ~80% that of un-operated fibulae.

Overall, these data indicate that the Physio-Stim PEMF treatment improved osteotomy repair. These beneficial effects on bone healing were not observed when a

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<sup>54</sup> C.T. Brighton et al., *In vitro Bone-Cell Response to a Capacitively Coupled Electric Field: the Role of Field Strength, Pulse Pattern, and Duty Cycle*, CLIN. ORTHOP. RELATED RES. 255-62 (Dec. 1992).

<sup>55</sup> C.T. Brighton et al., *Proliferative and Synthetic Response of Bovine Growth Plate Chondrocytes to Various Capacitively Coupled Electrical Fields*, 7 J. ORTHOP. RES. 759-65 (1989). See also C.T. Brighton et al., *In vitro Growth of Bovine Articular Cartilage Chondrocytes in Various Capacitively Coupled Electrical Fields*, 2 J. ORTHOP. RES. 15-22 (1984) (noting that the cellular responses depended on “appropriate electrical signal[s]”).

<sup>56</sup> R.J. Midura et al., *Pulsed Electromagnetic Field Treatments Enhance the Healing of Fibular Osteotomies*, accepted for publication by J. ORTHOP. RES. (date pending).

different PEMF waveform, the Osteo-Stim, was used. This latter observation demonstrates the “specificity in the relationship between waveform characteristics and biological outcomes.” Midura also found that “PEMF-induced effects on normalized callus volume are dependent on select spectral waveform characteristics, and are not generic effects of all electromagnetic energy.” Therefore, the “spectral characteristics and energy output of PEMF treatments are additional factors that need to be considered and accounted for when assessing whether PEMF treatments are efficacious.”

- T. Patterson (2005) recently concluded that two different PEMF waveforms produced different outcomes with respect to TGF-Beta production.<sup>57</sup> The study hypothesized that these outcomes resulted from different signaling pathways triggered by different PEMF waveforms. The physical-chemical interactions between biological tissues and pulsed electromagnetic fields are essentially unknown, although it is likely that the internal interaction occurs outside the cell and is then propagated and amplified through conventional or novel signal transduction pathways. The study found that the mTOR pathway is activated within minutes of PEMF exposure. Three different components of this pathway—mTOR itself, p70 S6 kinase (its immediate downstream target), and the ribosomal protein S6 (the p70 S6 kinase target)—all exhibited increased levels of activating phosphorylations following PEMF exposure. The PEMF-dependant phosphorylation of p70 S6 kinase and S6 was abolished by rapamycin, further supporting that PEMF exposure affects the mTOR signaling pathway. The highly selective PI-3 kinase inhibitor LY294002 blocks the PEMF-dependent activation of the mTOR pathways, suggesting that PEMF exposure activates mTOR through the conventional, rather than a novel, pathway. Thus, by following the effect of PEMF exposure upstream in this pathway, future work might succeed in identifying the putative “PEMF receptor” that initially interacts with the PEMF energy. Finally, the rapidity with which the mTOR pathways are activated by PEMF exposure suggests that it is an early event in the cellular response to PEMF.
- M. Zborowski et al. studied how different PEMF waveforms cause different amounts of energy absorption in target tissues.<sup>58</sup> The study examined the PEMF power attenuation in tissues representative of clinical applications (blood and cortical bone) to determine the amount of power available for PEMF-purported biological effects. The experimental system consisted of a pair of nearly-circular, parallel, and coaxial coils separated by a distance of one coil diameter. The power attenuation was measured using a small search coil connected to a digital oscilloscope. The coils were powered by a voltage switch operating at two different frequencies (3.8 kHz and 63 kHz), producing bursts of pulses (numbering 21 and 1619), and triggered at two different frequencies (1.5 Hz and 15 Hz, respectively). The tissue samples were

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<sup>57</sup> T. Patterson, *Exposure of Mouse Pre-Osteoblast Cells to Pulsed Electromagnetic Fields Rapidly Activates the mTOR Signaling Pathway*, abstract presented at the 2005 European Calcified Tissue Society—International Bone and Mineral Society (Switzerland).

<sup>58</sup> M. Zborowski et al., *Attenuation of Pulsed Electromagnetic Field (PEMF) in Blood and Cortical Bone Determined Experimentally and from the Theory of Ohmic Losses* (publication pending).

placed inside the coils so as to expose them to either the transverse electric field (at the center of coils) or the transverse magnetic field (at the coil wire). The cylindrical coil geometry yielded closed-form expressions for power attenuation due to ohmic losses based on bulk tissue magnetic permeability and electrical conductivity. The measured weak power attenuation at these PEMF frequencies was well-explained by the theory for the 3.8 kHz, but less so for the 63 kHz frequency PEMF.

These results provide important insights regarding settled biological effects of weak PEMF, and the difference in the propagation of the transverse magnetic and transverse electric fields that are used in the PEMF treatments. In particular, the results indicate the expected higher distortion in tissues for the transverse magnetic field as compared to the transverse electric field. This may have a direct bearing on the PEMF coil design, demonstrating a better control over the waveform parameters using a solenoid field design rather than a single coil design.

- Y. Sakai's study underscored the "substantial between-waveform differences in the time-amplitude domain . . . which are reflected in the distribution of power in the frequency-amplitude domain."<sup>59</sup> The between-waveform differences in total spectral power are also large. The study found that "the extent of the decrease in the amount of alpha1(I) collagen in the conditioned medium of exposed cells displayed sensitivity to the signals used and the coil orientation used to deliver the signal, a finding not previously reported in the literature. . . . [T]he sensitivity to the waveforms used was attributable to the between-waveform differences in the pulse period." Furthermore, only Osteo-Stim, not Physio-Stim, showed "sensitivity to coil orientation."

### (b) CMF Signal

The PMA-approved CMF devices utilize a specific and complex signal based on theoretical calculations of ion resonance. The resonance theory predicts that certain, specific combinations of static and dynamic magnetic fields can positively affect ion transport across cell membranes as well as ion-dependent cell signaling. This theory has been confirmed experimentally.<sup>60</sup>

The fact that this specific CMF signal has been proven safe and effective does not suggest that new CMF signals will be safe and effective. In fact, the available data support the contrary conclusion: minor variations in frequency, DC amplitude, and AC amplitude in CMF devices can profoundly impact effectiveness. Studies show that CMF devices are effective within sharp resonance frequencies, and that minor changes in the frequencies dramatically reduce efficacy. RS Medical, however, failed to discuss any of the studies below.

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<sup>59</sup> Y. Sakai, *Reduction of Soluble Type 1 Collagen in the Extracellular Matrix After Exposure of Mouse Preosteoblasts to Pulsed Electromagnetic Fields Can Be Attributed to Specific Waveform Characteristics*, J. OF ORTHOPAEDIC RESEARCH (publication pending).

<sup>60</sup> M.C. Deibert et al., *Ion Resonance Electromagnetic Field Stimulation of Fracture Healing in Rabbits with a Fibular Ostectomy*, 12 J. ORTHOP. RES. 878-85 (1994).

- The effectiveness of the CMF signal is highly sensitive to minor changes in frequency. Fitzsimmons et al. (1993) performed an IGF-II assay of TE-85 osteosarcoma cells, exposed to 72.6, 74.6, 76.6, 78.6, and 80.6 Hz CMF signals.<sup>61</sup> The results were striking. The 76.6 Hz CMF signal resulted in the largest increase in IGF-II production, an approximate 10-fold increase over the control. For the 74.6 and 78.6 Hz signals, IGF-II production dropped by nearly 50%.
- Smith et al. (1987) examined the effects of variations in CMF signals on calcium ion transport in a marine diatom model.<sup>62</sup> This study found that an ineffective or less effective CMF signal could result from: (1) even harmonics rather than odd harmonics, i.e., odd multiples of 15 Hz; (2) a CMF signal without either an AC or a DC component; (3) improper alignment of the AC and DC fields; or (4) a signal with a peak-to-peak amplitude above and below 20.9  $\mu$ T.
- Smith et al. (1991) found that certain combinations of signal parameters could be ineffective or inhibitory in an *in vitro* chick embryo femur development model.<sup>63</sup> The authors used 8-day-old chick femoral rudiments exposed to four different CMF signals. Three signals were 16 Hz, 20  $\mu$ T peak-to-peak AC signals, having a DC component of 20.9  $\mu$ T, 12.7  $\mu$ T, or 40.9  $\mu$ T. The fourth signal was a 80 Hz, 20  $\mu$ T AC, 20.9  $\mu$ T DC signal. Femoral rudiment development was quantified by measures of length (L), mid-shaft diameter (D), diaphyseal collar length (l), diaphyseal collar thickness (t), and their ratios, L/D and l/t. When exposed to the CMF signals for 30 minutes/day over 7 days, all signals—except the 40.9  $\mu$ T DC, 16 Hz signal—increased L, D, l, t and reduced the L/D and l/t ratios, indicating increases in rudiment robustness. The 40.9  $\mu$ T DC, 16 Hz signal actually inhibited femoral development relative to the contralateral controls, (e.g., decreasing L, l, and t, while having no effect on D). For example, this signal decreased diaphyseal collar length by 38% and collar thickness by 67%.
- Deibert et al. (1994) similarly concluded that minor variations in CMF signals could adversely affect efficacy.<sup>64</sup> The study involved fibular osteotomies on rabbits which were then exposed to sham, or to two variations of a CMF signal, for 0.5, 3, or 24 hours per day for 28 days. The CMF signal differed only in the magnitude of the DC component, 20.9  $\mu$ T versus 12.7  $\mu$ T. For the 30 minute treatment groups, the study found that the 20.9  $\mu$ T signal resulted in a significant increase in fibular stiffness compared to the control (175%,  $p < 0.05$ ). The 12.7  $\mu$ T group had a smaller, non-significant increase in stiffness (55%,  $p > 0.05$ ).

<sup>61</sup> R.J. Fitzsimmons et al., *EMF-Stimulated Bone-Cell Proliferation*, in *ELECTRICITY AND MAGNETISM IN BIOLOGY AND MEDICINE* (M. Blank, ed., 1993).

<sup>62</sup> S.D. Smith et al., *Calcium Cyclotron Resonance and Diatom Mobility*, 8 *BIOELECTROMAGNETICS* 215-27 (1987).

<sup>63</sup> S.D. Smith et al., *Effects of Resonant Magnetic Fields on Chick Femoral Development In Vivo*, 10 *J. BIOELECTRICITY* 81-99 (1991).

<sup>64</sup> M.C. Deibert et al., *Ion Resonance Electromagnetic Field Stimulation of Fracture Healing in Rabbits with a Fibular Osteotomy*, 12 *J. ORTHOP. RES.* 878-85 (1994).

- Using a slightly different electromagnetic signal, McLeod and Rubin (1992) found that frequency variations can adversely affect efficacy.<sup>65</sup> Using functionally isolated turkey ulnae, the authors compared sinusoidal EMF signals of 15, 75, and 150 Hz. The study found that as frequency decreased, bone area increased. For the 150, 75, and 15 Hz signals, the bone area gain/loss was -3%, +5%, and +10%, respectively.

### C. Intended Use Differences

In addition to waveform and design differences, BGS devices used for non-union and lumbar spinal fusion indications also differ in the types of testing required to demonstrate safety and effectiveness. For example, FDA's Draft Guidance suggested that "testing for effects on nervous tissue may be required for spinal fusion indications but may not be necessary for a study of tibial fracture non-union."<sup>66</sup> Citing the unique risks associated with spinal fusions, FDA required a BGS manufacturer to perform a clinical study on electrical stimulation of the cervical spine.<sup>67</sup> FDA explained, "Because the Cervical-Stim is intended for use in treating an area which includes the central nervous system (CNS), FDA has concerns regarding possible effects on the spinal nerves. You must discuss the possible risks involved when applying pulsed electromagnetic fields to the CNS and describe what provisions you have made to minimize such risks."<sup>68</sup> RS Medical's petition, however, identifies only one set of risks—e.g., electrical shock, burn, skin irritation, and allergic reaction, and inconsistent or ineffective treatment—for both non-union and lumbar spinal fusion uses.<sup>69</sup>

Furthermore, the clinical measures of device effectiveness differ for non-union versus lumbar fusion indications. For example, FDA has suggested that the time-based definition of non-unions, i.e., nine months, does not apply to the definitions of other indications such as spinal fusions.<sup>70</sup> The FDA Draft Guidance stated that for other bone conditions, "e.g., osteoarthritis, avascular necrosis, osteoporosis or spinal fusion, it is the responsibility of the [IDE] sponsor to propose the specific definitions of the medical indication."<sup>71</sup> For spinal fusion, FDA noted that "consideration should be given to the differences in rate of healing between the spine and bones of the appendicular skeleton in specifying the time to a healed fracture."<sup>72</sup> Different intended uses also require different clinical follow-ups. The FDA Draft Guidance stated that BGS devices used for non-union fractures should include patient follow-up for at least one year beyond the

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<sup>65</sup> B.R. McLeod et al., *Electromagnetic Gating in Ion Channels*, 158 J. THEOR. BIOL. 15-31 (1992).

<sup>66</sup> FDA Draft Guidance.

<sup>67</sup> Letter from FDA to Orthofix (Nov. 23, 1998).

<sup>68</sup> Letter from FDA to Orthofix (Nov. 23, 1998).

<sup>69</sup> RS Medical Petition, at 71-78.

<sup>70</sup> FDA Draft Guidance.

<sup>71</sup> *Id.*

<sup>72</sup> *Id.*

end of the stimulus treatment.<sup>73</sup> By contrast, BGS devices used for spinal fusions could require follow-up for more than one year.<sup>74</sup>

#### **D. Clinical Implications of Using Ineffective Devices**

The use of ineffective devices would create serious safety risks and economic waste. Patients who used ineffective devices, especially for the treatment of non-unions, would likely require subsequent surgeries. In addition to the risks inherent in surgical procedures, delaying surgery tends to hamper the recovery process. Thus, an ineffective BGS device could actually contribute to the worsening of a patient's condition if he declined effective therapies or delayed surgery. Along with prolonging the pain and discomfort of the original injury itself, ineffective BGS devices would also cause a significant waste in personal and medical resources.

#### **IV. RS Medical has failed to provide sufficient valid scientific evidence demonstrating that the proposed special controls would reasonably assure BGS safety and effectiveness.**

##### **A. RS Medical's proposed special controls inadequately address potential risks.**

RS Medical insists that the safety of BGS devices is demonstrated by the lack of adverse events reported in the literature and FDA's medical device reporting system. The absence of these reports, however, evidences the success of the present Class III controls, which ensure that only safe and effective BGS devices are marketed. In the final rule on RGP contact lenses, FDA concluded that the "mere absence of negative reports in this voluntary reporting system cannot establish the safety of a device."<sup>75</sup> FDA found "that the safety record of rigid gas permeable lenses to date represents the performance of lenses for which there are approved PMA's."<sup>76</sup> As with the RGP lenses, "[s]tatements by individual investigators that no adverse reactions were found do not constitute valid scientific evidence within the meaning of § 860.7 of the regulations."<sup>77</sup>

Indeed, FDA has expressed serious concerns about the potential safety risks associated with external BGS devices. FDA regulations require that the evidence on safety must "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."<sup>78</sup> In General Medical Co. v. FDA, the D.C. Circuit concluded that the safety risk "need only be a potential one. The risk may be one demonstrated by reported injuries or it may simply be foreseeable."<sup>79</sup> Thus, FDA has required an array of preclinical and clinical studies to support the PMA approval of these

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<sup>73</sup> *Id.*

<sup>74</sup> *Id.*

<sup>75</sup> Contact Lens Rule, 48 Fed. Reg. at 56783.

<sup>76</sup> *Id.*

<sup>77</sup> *Id.* at 56787.

<sup>78</sup> *Id.*

<sup>79</sup> General Medical Co. v. FDA, 770 F.2d 214, 221 (D.C. Cir. 1985) (quoting House Report) (emphasis added).

devices. The FDA Draft Guidance specifically noted the potential for “teratogenesis, reproduction, genotoxic effects, cellular proliferation, and possible carcinogenic initiation/promotion effects” and advised sponsors to “be cognizant of several epidemiological studies which have suggested some degree of association between electromagnetic field exposure and cancer incidence.”<sup>80</sup> The FDA Draft Guidance also emphasized “controlling excessive electromagnetic emissions” as “essential to the safety and effectiveness of medical devices.”<sup>81</sup> RS Medical’s proposed special controls, however, do not sufficiently provide for any of these potential risks.

These risks are more than theoretical. As discussed above, the mechanisms of action of electromagnetic stimulation on osteogenesis are not fully understood. Some data suggest that the osteoblastic effect is related at a cellular level to calcium ion transport.<sup>82</sup> The effects of changing this important cellular activity with an electromagnetic field remain largely unknown. Only laboratory and clinical data can assure that a particular field does not result in adverse effects in other physiological systems, e.g., cardiac, neurological, and endocrine systems.

In addition, RS Medical’s proposed special controls inadequately address the following:

- (1) as discussed *supra* Section III, dosimetry and coil designs;
- (2) the effect of duration-of-use on the risk for skin irritation, which may discourage patient compliance;
- (3) the risk to patients who use electrical or metallic implants, i.e., cardiac pacemakers and neurological stimulators,<sup>83</sup> and
- (4) manufacturing tolerances, test methods, and acceptance criteria. Since even minor alterations to waveform parameters may impact BGS safety and effectiveness, the adherence to manufacturing tolerances is critical. Each of the PMA-approved devices is manufactured to meet specific, proprietary testing standards on tolerance, calibration, and performance. These tolerances ensure that the marketed BGS devices satisfy the safety and efficacy profiles demonstrated to the FDA during the PMA clinical trials for these devices.

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<sup>80</sup> See FDA Draft Guidance; *International Commission on Non-Ionizing Radiation Protection, Guidelines for Limiting Exposure to Time-Varying Electric, Magnetic, and Electromagnetic Fields (Up to 300 GHz)*, 74 HEALTH PHYSICS 494-522 (April 1998).

<sup>81</sup> EMI [electromagnetic interference] testing should demonstrate that “the device performs as intended when subjected to radiated and conducted electromagnetic energy, magnetic fields, electrostatic discharge (ESD), transient bursts, and surges,” and that “nearby devices would not be subjected to excessive electromagnetic energy from the device, which could adversely affect the performance of those nearby devices.” FDA Draft Guidance.

<sup>82</sup> C.T. Brighton et al., *Signal Transduction in Electrically Stimulated Bone Cells*, J. BONE JOINT SURG. AM. 1514-23 (2001).

<sup>83</sup> The PMA-approved devices include warnings or contraindications against use in patients with electrical or metallic implants.

**B. While ignoring pertinent evidence that contradicts its petition, RS Medical has provided insufficient evidence to support down-classification.**

External BGS devices fall squarely within Class III designation because “insufficient information exists to determine that the special controls . . . would provide reasonable assurance of its safety and effectiveness.”<sup>84</sup> The International Commission on Non-Ionizing Radiation Protection (ICNIRP)<sup>85</sup> has cautioned that there is insufficient information to establish a single set of safety controls to cover the range of frequencies used in electromagnetic field devices:

There is insufficient information on the biological and health effects of EMF exposure of human populations and experimental animals to provide a rigorous basis for establishing safety factors over the whole frequency range and for all frequency modulations. In addition, some of the uncertainty regarding the appropriate safety factor derives from a lack of knowledge regarding the appropriate dosimetry.<sup>86</sup>

All of the marketed devices described in RS Medical’s petition exceed the thresholds established by this commission. Hence, the manufacturers of these PMA-approved devices have utilized an extensive battery of preclinical studies to establish the safety of their devices.

RS Medical has ignored the abundant evidence demonstrating that current PMA requirements are necessary to reasonably assure BGS safety and effectiveness. As discussed *supra* Sections II and III, RS Medical did not include studies demonstrating that: (1) small variations in waveform parameters may adversely impact BGS device safety and effectiveness; (2) preclinical studies on BGS devices are not always predictive of clinical success; (3) mechanisms of action for BGS devices differ among the modalities and are not fully understood; and (4) changes to device design and dosimetry impact BGS function. RS Medical disregarded all these data, contrary to FDA’s regulatory requirement to include representative unfavorable data.

RS Medical also has relied on seriously flawed studies to support reclassification. We have provided a table summarizing our critique of these studies in Appendix A and more detailed critiques in Appendix D. Randomized, double-blind “well-controlled investigations”<sup>87</sup> are the gold standard in the hierarchy of valid scientific evidence and are required for demonstrating the effectiveness of a device,<sup>88</sup> yet are noticeably absent from the studies cited by RS Medical. Although 21 C.F.R. § 860.7(c)(2) permits FDA to accept other types of studies as valid scientific

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<sup>84</sup> FDCA § 513(a)(1)(C).

<sup>85</sup> The ICNIRP develops international guidelines for non-ionizing radiation exposure. *International Commission on Non-Ionizing Radiation Protection, Guidelines for Limiting Exposure to Time-Varying Electric, Magnetic, and Electromagnetic Fields (Up to 300 GHz)*, 74 HEALTH PHYSICS 494-522 (April 1998).

<sup>86</sup> *Id.* (emphasis added).

<sup>87</sup> 21 C.F.R. § 860.7(c)(2).

<sup>88</sup> FDA regulations require that “[t]he valid scientific evidence used to determine the effectiveness of a device shall consist principally of well-controlled investigations.” *Id.* at § 860.7(e)(2) (emphasis added).

evidence, the regulations specify that “[i]solated case reports, random experience, reports lacking sufficient details to permit scientific evaluation, and unsubstantiated opinions are not regarded as valid scientific evidence to show safety or effectiveness.”<sup>89</sup> FDA may, however, consider such information “in identifying a device the safety and effectiveness of which is questionable.”<sup>90</sup>

The most fundamental deficiency in RS Medical’s cited studies is a failure to include “sufficient details to permit scientific evaluation.”<sup>91</sup> None of the studies adequately define the waveforms used. Without a sufficient description of the waveforms, RS Medical has no rational basis for comparing the studies and drawing conclusions as to the adequacy of its proposed special controls. FDA has recognized that “the published literature do not always contain a complete, or entirely accurate, representation of the device design, performance, manufacture, clinical study plans, conduct, accountability, and outcomes.”<sup>92</sup> Thus, the “details provided in published literature may not be sufficient to establish that the device that is the subject of the published report is comparable in design, performance, and manufacture” to the device that is the subject of the application.<sup>93</sup>

The petitioner’s cited studies also suffer from the following deficiencies:<sup>94</sup>

- Although proposing the reclassification of PEMF, CC, and CMF devices, RS Medical relies almost exclusively on PEMF studies—which have limited, if any, applicability to CC and CMF devices. RS Medical cites 6 CC studies and a single CMF study.
- Although proposing the reclassification of BGS devices for both non-unions and lumbar spinal fusions, RS Medical provides minimal data on the lumbar spinal fusion indication. Only 9 of the cited references are on lumbar spinal fusion, of which 1 study used CMF and 1 study used CC.
- To support the non-union indication, RS Medical provided the following:
  - For CC — 1 randomized study, 3 prospectively controlled studies (primarily using the subject as his own control), and 1 retrospective study;
  - For CMF — no studies; and
  - For PEMF — 1 randomized study, 17 prospectively controlled studies (primarily using the subject as his own control), and 10 retrospective studies.
- To support the spinal fusion indication, RS Medical provided the following:

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<sup>89</sup> 21 C.F.R. § 860.7(c)(2) (emphasis added).

<sup>90</sup> *Id.*

<sup>91</sup> 21 C.F.R. § 860.7(c)(2).

<sup>92</sup> *Guidance for Industry, Supplements to Approved Applications for Class III Medical Devices: Use of Published Literature, Use of Previously Submitted Materials, and Priority Review* (May 20, 1998).

<sup>93</sup> *Id.*

<sup>94</sup> See Appendices A and D for further detail.

- For CC — 1 randomized study;
  - For CMF — 1 randomized study; and
  - For PEMF — 1 randomized study, 4 prospectively controlled studies, and 2 retrospective studies.
- More than half of the cited studies involved less than 60 patients, which does not allow for scientifically or clinically valid conclusions to be drawn. For effectiveness, FDA regulations require that the valid scientific evidence show “clinically significant results.”<sup>95</sup>
  - Most of the studies cited by RS Medical do not report on device safety.
  - Study parameters varied, making cross-study comparisons or aggregation of study results impossible. Based on the cited studies, RS Medical cannot draw conclusions about the sufficiency of its special controls for assuring the safety and effectiveness of new BGS devices.
    - The inclusion/exclusion criteria for the studies were not consistent. For the lumbar spinal fusion studies, Simmons et al. (2004) enrolled patients with radiographic documentation of pseudoarthrosis and clinical symptoms indicative of pseudoarthrosis at 9 months and who had no radiographic evidence of progressive healing for 3 months. In contrast, Bose (2001) did not describe the inclusion/exclusion criteria for the patients.

Similarly, the studies supporting the non-union indication varied greatly in their inclusion/exclusion criteria. Benazzo et al. (1995) enrolled only athletes who sustained a non-union injury during training and had a history of training 3 times/week. Sharrard et al. (1982) included patients as young as 13 years of age, while others required patients to be at least 18 years old. Studies such as Adams et al. (1992) did not describe the patient selection criteria while other studies generically stated “delayed union or non-union tibial fractures” (Ito and Shirai, 2001).

- Some studies permitted previous surgeries; others did not. For example, in Brighton and Pollack et al. (1985) patients could have received previous bone grafting plus electrical therapy, bone grafting alone, or electrical therapy alone. In Dhawan et al. (2004), patients underwent elective triple arthrodesis or subtalar arthrodesis prior to treatment with the BGS device. Other studies, such as Fontenesi et al. (1983) and Meskens et al. (1990), did not discuss or specify previous treatments.
- The treatment regimen varied between the studies. Some studies restricted weight-bearing (Heckman et al. 1981), whereas other studies allowed

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<sup>95</sup> 21 C.F.R. § 860.7(e)(2).

limited weight-bearing (Holmes et al., 1994) or progressive weight bearing (Sharrard et al., 1982). Some studies used internal or external fixation devices (O'Connor, 1985) or immobilizing casts during treatment (Ito and Shirai, 2001).

- The duration-of-use varied between studies. In the non-union studies, duration of the electrical stimulation treatment ranged from 8 hours/day (Garland et al., 1991) to continuous stimulation (Brighton and Pollack, 1985). In the lumbar fusion studies, treatment duration ranged from 2 hours/day (Jenis et al., 2000 and Simmons et al., 2004) to 24 hours/day (Goodwin et al., 1999). Some studies inadequately describe the study treatments altogether.
- Studies varied in their definitions of clinical success and methods for evaluating success—i.e., radiographic evidence, “no pain,” absence of movement at fracture site, etc. For example, Meskens et al. (1990) defined success as mechanical stability on clinical testing, an absence of local tenderness, and obliteration of fracture gap on the radiograph. By contrast, Scott and King (1994) defined success as clinical assessment of pain and motion and radiographic assessment of callus; Adams et al. (1992) employed standard radiographic evaluation to determine success. Several studies did not describe methods for evaluating success at all.
- Follow-up time frames varied from 12 weeks to 2 years. Often, follow-up was conducted “until union,” or “the fracture healed,” or was unspecified.

These flawed and assorted studies certainly do not constitute sufficient valid scientific evidence to demonstrate the adequacy of RS Medical’s special controls. See Appendix A for a summary critique of the studies cited by RS Medical and Appendix D for more detailed critiques of these studies.

**C. PMA requirements, e.g., rigorous clinical trials and FDA premarket review of manufacturing, are necessary to reasonably assure BGS safety and effectiveness.**

PMA clinical trials are necessary to assure BGS device safety and effectiveness. In the final rule on RGP contact lenses, FDA noted that it had “regulated contact lenses as new drugs or class III devices for more than a decade, and is unaware of any combination of nonclinical laboratory studies capable of predicting the performance of any contact lens on the human eye.”<sup>96</sup> Similarly, for BGS devices, preclinical studies are not always predictive of clinical success. For example, Fredericks et al. (2000) reported a preclinical success in a rabbit model that could not be replicated in a clinical study.<sup>97</sup> In a different study, the BMD-Stim PEMF device demonstrated

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<sup>96</sup> Contact Lens Rule, 48 Fed. Reg. at 56792.

<sup>97</sup> D.C. Fredericks et al., *Effects of Pulsed Electromagnetic Fields on Bone Healing in a Rabbit Tibial Osteotomy Model*, 14 J. ORTHOPAEDIC TRAUMA 93-100 (2000).

increased bone strength and stiffness in two animal models.<sup>98</sup> In a subsequent clinical study of 77 patients, however, the BMD-Stim device resulted in no significant improvements in bone mineral density or T-scores during 12 months of treatment.<sup>99</sup> The BMD-Stim is a high-frequency PEMF signal that is a variation of the PMA-approved Spinal-Stim signal. The two signals are identical except for differences in two signal parameters.

While FDA may require the submission of any information that is necessary to determine whether a device is substantially equivalent,<sup>100</sup> the agency may not convert the premarket review process into a quasi-PMA.<sup>101</sup> Requiring PMA-type clinical studies as special controls under 510(k) is inconsistent with substantial equivalence requirements and FDA guidance. Typically, comparative descriptions are sufficient and clinical data are not required to support substantial equivalence. In rejecting the down-classification of RGP contact lenses, FDA recognized

that requiring so much information would result in the submission of data so complete as to be indistinguishable from the data needed to determine the safety and effectiveness of a device in the first instance rather than on a comparison basis. The data required in a premarket notification submission would then be indistinguishable from the data required in a PMA. FDA agrees that imposing such a requirement as an *a priori* condition for determining substantial equivalence would exceed the authority of section 510(k) of the act and Subpart E of Part 807.<sup>102</sup>

Upholding FDA's decision, the D.C. Circuit added that "reviewing evidence 'on a comparison basis' rather than for the purpose of 'determining the safety and effectiveness of a device in the first instance,' would be both difficult and constraining. . . . the exacting character of the comparisons involved might discourage innovation by requiring the manufacturer of a new RGP lens to demonstrate 'substantial equivalence' almost to the point of patent infringement."<sup>103</sup>

Furthermore, PMA premarket review of manufacturing is necessary to reasonably assure BGS safety and effectiveness. PMA oversight allows for the extensive review and inspection of a company's manufacturing process and facilities prior to device approval. Even with an accurate and complete description of the relevant parameters, it is difficult to build a BGS device that consistently produces the required signal within an acceptable range. Reliability is an especially important trait for BGS devices because of their sensitivity to seemingly minor changes to their designs or waveform parameters.<sup>104</sup>

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<sup>98</sup> P.A. Glazer et al., *Use of Electromagnetic Fields in a Spinal Fusion: A Rabbit Model*, SPINE 2351-56 (October 1997).

<sup>99</sup> These studies were conducted by Orthofix for the treatment of osteoporosis. After a 12 month follow-up period revealed no significant improvement, the study was terminated due to a lack of demonstrable effectiveness.

<sup>100</sup> 21 C.F.R. § 807.87(l).

<sup>101</sup> See *Contact Lens Mfrs Ass'n*, 766 F.2d 592; Contact Lens Rule, 49 Fed. Reg. at 56790.

<sup>102</sup> Contact Lens Rule, 48 Fed. Reg. at 56790 (emphasis added).

<sup>103</sup> *Contact Lens Mfrs Ass'n*, 766 F.2d at 601.

<sup>104</sup> 21 C.F.R. § 860.7(b).

RS Medical's proposed special controls would not compensate for the proprietary verification and validation criteria currently employed by BGS manufacturers to ensure safety and effectiveness. For example, simply mapping the field of CMF devices, as RS Medical suggests, does not ensure device effectiveness. The magnetic fields of PMA-approved CMF devices have been thoroughly mapped, are held to specific tolerances, and have proven their clinical safety and effectiveness. For a new device to provide an efficacious treatment, the magnetic field treatment volume within tolerance and location must be equivalent. Down-classification of BGS devices would eliminate FDA's crucial premarket review, thus jeopardizing the safety and effectiveness of these devices.

## V. Conclusion

RS Medical's reclassification petition for external BGS devices contains the following fatal deficiencies:

1. The petition is deficient on its face. First, RS Medical's petition flouts the regulatory requirement to provide representative data that are unfavorable to its reclassification petition. Second, the petition wavers between three inconsistent proposals for reclassification, one of which depends on an inaccurate and incomplete description of BGS waveform parameters.
2. RS Medical has not identified a generic type of device for reclassification. The external BGS devices described in the petition include a diverse—not generic—array of modalities, mechanisms of action, waveforms, dosimetry, designs, and intended uses. Studies demonstrate that the slightest alteration of any one of these variables may adversely affect the performance of these devices. Rather than recognizing the exacting specifications required for BGS devices, RS Medical provides an inaccurate and incomplete list of BGS waveform parameters. Furthermore, the basic characteristics of these devices, i.e., their mechanisms of action and effects at the cellular level, are not yet fully understood. Without an identification of a generic type of BGS device, there is no foundation for RS Medical's proposed down-classification.
3. RS Medical has failed to provide sufficient valid scientific evidence demonstrating that its proposed special controls would reasonably assure BGS safety and effectiveness. RS Medical ignores manufacturing tolerances and the crucial premarket review of manufacturing provided by a PMA. RS Medical's proposed controls inadequately address several known risks posed by BGS devices. RS Medical also relies on studies that suffer from a variety of deficiencies and do not constitute the valid scientific evidence necessary for down-classification. The literature on BGS devices indicates that both PMA clinical trials and FDA premarket review of manufacturing are necessary to reasonably assure the safety and effectiveness of these devices.

For these reasons, we urge FDA to continue its successful Class III oversight of external BGS devices. Only the rigors of the PMA process will reasonably assure that new BGS devices provide safe and effective options for bone healing.

Respectfully submitted,

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