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October 6, 2005

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

Re: Docket 2005P-0121: Reclassification of Non-Invasive Bone Growth Stimulator  
Devices From Class III to Class II

Dear Sir or Madam:

dj Orthopedics, Inc. (“dj Orthopedics” or the “Company”) submits the following comments in opposition to the above-referenced petition (the “Petition”) submitted by RS Medical pursuant to Section 513(e) of the Federal Food, Drug and Cosmetic Act (“FDCA” or the “Act”).<sup>1</sup> The Petition requests that the Food and Drug Administration (“FDA”) reclassify, from Class III to Class II, seven commercially available bone growth stimulator (“BGS”) devices that utilize three distinct technologies. Among these are dj Orthopedics’ OL1000™ and SpinaLogic™ devices, which utilize combined magnetic field (“CMF”) technology.<sup>2</sup> For the reasons set forth below, dj Orthopedics opposes the Petition.

On August 17, 2005, King & Spalding LLP submitted comments to the above-referenced docket opposing the Petition on behalf of several BGS device manufacturers, including dj Orthopedics.<sup>3</sup> dj Orthopedics fully supports and incorporates those comments herein. Due to the impact that the Petition would have on dj Orthopedics’ devices – and future BGS devices that may seek to utilize CMF technology – the Company submits these additional comments in support of the BGS Group Comments. In addition, these comments attach the statements of two recognized leaders in the field of BGS technology.<sup>4</sup> Both Dr. Ryaby and Dr. Zoltan oppose the reclassification of BGS devices. In their comments, these recognized experts detail the scientific and clinical bases underlying the need for premarket approval (“PMA”) of BGS devices.

<sup>1</sup> 21 U.S.C. § 360c(e).

<sup>2</sup> The Petition also identifies Bioeletron’s OrthoPak Bone Growth Stimulator; Bioeletron’s SpinalPak Fusion Simulator; EBI’s Bone Healing System; Orthofix’s Physio-Stim Lite; and Orthofix’s Spinal-Stim Lite. See Petition at 9.

<sup>3</sup> Comments of the BGS Reclassification Opposition Group, Docket 2005P-0121/C4 (the “BGS Group Comments”).

<sup>4</sup> See Comments of James T. Ryaby, M.D. (Attachment A) (“Dr. Ryaby Comments”) and Comments of Jon D. Zoltan, M.D. (Attachment B) (“Dr. Zoltan Comments”).

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## I. INTRODUCTION

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The Petition urges FDA to change the Class III designation of BGS devices pursuant to the procedure set forth in Section 513(e) of the Act.<sup>5</sup> As explained in the BGS Group Comments, the statutory and regulatory criteria governing the reclassification process require a petitioner to demonstrate to FDA that publicly-available, valid scientific evidence exists to: (1) specify and characterize the generic type of device; (2) identify and characterize the generic device's risks and efficacy profile (i.e., the device's performance parameters); and (3) identify and characterize "special controls" that will adequately address the defined risks and performance parameters of the generic device to assure the safety and effectiveness of devices within the generic class without the need for data from clinical testing in humans designed to support a PMA application.<sup>6</sup>

As demonstrated in the BGS Group Comments, the Petition falls far short of justifying the reclassification of BGS devices under the applicable statutory and regulatory framework. dj Orthopedics does not seek in these comments to restate all the grounds on which the Petition fails; instead, the Company wishes to emphasize the major flaws of the Petition. Primary among these is the Petition's failure to provide valid scientific evidence supporting the grouping of BGS devices within a single generic class. The BGS devices identified in the Petition are dissimilar and raise different issues of safety and effectiveness. They differ with respect to design parameters (e.g., coil shape, type of energy produced, magnitude of current, and electric or magnetic field properties), observed cellular and molecular effects (e.g., stimulation of growth factors, ion movement, and molecular signaling), and clinical parameters (e.g., duration of treatment and clinical indications). Due to these dissimilarities, no generic set of special controls could reasonably assure the safety and effectiveness of BGS devices as a class. The Petition is therefore fatally flawed.

In addition, the Petition fails to define and adequately characterize the performance parameters and waveforms utilized by the various BGS devices, including those that use CMF technology (which differs from other BGS technologies with respect to, among other things, its energy source and output, and its significantly shorter treatment time). RS Medical's proposed guidance document generally describes the waveform parameters of the BGS devices subject to the Petition without providing a sufficient basis on which to assess the safety and effectiveness of a future device pursuant to the 510(k) premarket notification process. For instance, even if an applicant files a 510(k) premarket notification for a BGS device that replicates one of the BGS waveforms described in the Petition, there will still be other, unaddressed factors that may impact the device's safety and effectiveness. Further, given the fact that the Petition seeks to apply the 510(k) review standard of "substantial equivalence,"

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<sup>5</sup> 21 U.S.C. § 360c(e).

<sup>6</sup> *See Ethicon, Inc. v. FDA*, 762 F.Supp. 382, 387 (D.D.C. 1991); *Contact Lens Mfrs. Ass'n v. FDA*, 766 F.2d 592, 600 (D.C. Cir. 1985); 21 U.S.C. § 360c(e)(1)-(2); 21 C.F.R. §§ 860.130(c)(1); 860.123(a)(1). Both *Ethicon* and *Contact Lens* review the statutory and regulatory framework governing the device reclassification process, and thus are relevant insofar as they articulate the legal criteria for reclassifying a device pursuant to a petition such as that filed by RS Medical. However, the current proceeding is a fact-specific inquiry. *See Ethicon*, 762 F.Supp. at 387 (holding that FDA's "...characterization of a generic class or type of device is fact-specific").

which does not require that the device under review be identical to a predicate,<sup>7</sup> numerous BGS devices could be commercialized that vary considerably with respect to performance parameters and waveforms. However, the available data indicate that even minor deviations in a BGS device's waveform can have significant (and unknown) effects on the device's safety and effectiveness. Thus, the Petition raises the prospect of new devices entering the market that satisfy the substantial equivalence criteria set forth in the proposed guidance document, but that are potentially ineffective or unsafe.

These failures of the Petition cannot adequately be addressed by RS Medical, due to the nature of BGS devices and the lack of publicly-available valid scientific evidence sufficient to support a reclassification. As a result, FDA must deny the Petition. Reclassification of BGS devices would likely result in a deterioration of the effectiveness of these devices. New devices and waveforms might satisfy the "substantial equivalence" criteria of Section 510(k) of the FDCA, but may nonetheless prove to be less effective than the currently approved devices in generating bone growth. The consequences of such diminished efficacy would have significant impacts on the health of patients with non-union fractures or requiring spinal fusion.

## **II. BGS DEVICE TECHNOLOGIES ARE DISSIMILAR AND SHOULD NOT BE GROUPED WITHIN A GENERIC CLASS OF DEVICE**

The reclassification of a particular device will result in the reclassification of all substantially equivalent devices within the generic class.<sup>8</sup> FDA regulations provide that "a petition for the reclassification of a specific device will be considered a petition for reclassification of all substantially equivalent devices within the same generic type."<sup>9</sup> There is no requirement that a device in a generic class be "essentially identical" to all other devices within the class.<sup>10</sup> However, the devices within the generic class must nevertheless be "substantially equivalent" to each other.<sup>11</sup> As detailed more fully in the BGS Group Comments, and as set forth in the Dr. Ryaby Comments,<sup>12</sup> the history of BGS device development and the characteristics of the approved devices identified in the Petition clearly demonstrate that CMF, Capacitive Coupling ("CC") and Pulsed Electromagnetic Field ("PEMF") technologies are not "substantially equivalent" and therefore devices employing these technologies should not be grouped within a single generic class.

The Petition posits that the identified BGS devices may be grouped into a single generic class because they "use a common mechanism of action; they deliver electrical and/or

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<sup>7</sup> See "Premarket Notification 510(k): Regulatory Requirements for Medical Devices," HHS Publication FDA 95-4158 (Aug. 1995), available at <http://www.fda.gov/cdrh/manual/510kprt1.html>.

<sup>8</sup> 21 C.F.R. § 860.120(b).

<sup>9</sup> *Id.*

<sup>10</sup> *Ethicon*, 762 F.Supp. at 387.

<sup>11</sup> *Id.*

<sup>12</sup> See Attachment A.

magnetic fields to cause a piezoelectric output.”<sup>13</sup> This statement is incorrect. The theoretical basis for BGS devices derives from the cellular response to strain-generated electric potentials, not causing a piezoelectric output. More importantly, this statement disregards clear differences among the CMF, CC and PEMF technologies that have been identified in the scientific literature and the mechanism by which each of these BGS devices influence cellular and molecular events required to stimulate bone growth. Although devices using each of these technologies have been shown to be safe and effective in preclinical and clinical trials, CC, PEMF and CMF technologies are not “substantially equivalent” in key respects. For example, these technologies differ with respect to their design parameters, modalities, mechanism of action, and intended use:

- **Design Parameters.** As described in the Dr. Ryaby Comments, “the currently approved CC, CMF, and PEMF devices are a group of heterogeneous and distinct devices, which differ significantly in coil shape, type of energy produced, magnitude of current, and electric or magnetic field properties.”<sup>14</sup> For instance, energy type is quite different between CC and CMF/PEMF technologies. CC delivers electric current through skin mounted electrodes and CMF/PEMF technologies deliver electromagnetic energy through externally placed copper coils. As another example, the magnitude of delivered energy is also different between technologies. For instance, CMF devices use a different energy configuration and two percent (2%) of the energy of a PEMF device. Further, as Dr. Ryaby concludes, “[m]inor deviations in these device characteristics can lead to significant alterations in effects on tissues.”<sup>15</sup>
- **Treatment Modalities.** The treatment modalities of the identified BGS technologies are substantially different, covering a broad continuum of potential electrical and electromagnetic waveforms. As discussed above, the different modalities – CC, CMF, and PEMF – represent specific waveforms spread out over an infinite spectrum of potential BGS waveform options. CC devices deliver 60 kHz sinusoidal, electrical energy. PEMF signals are highly complex electromagnetic pulse trains (large power spectrum, containing Hz to kHz frequencies) delivered at 15 Hz. CMF signals are a combination of specific, sinusoidal and constant electromagnetic fields, delivered at 76.6 Hz. Within any of the three technologies, a myriad combination of signal parameters could be generated. The Petition’s request that BGS technologies be reviewed as a generic class pursuant to the FDCA Section 510(k) standard of “substantial equivalence” raises the prospect that new types of signals and technologies with significant differences will enter the marketplace (for example, a low-frequency CC technology with a sinusoidal and constant electrical signal). However, there is little information concerning safety or effectiveness of treatment modalities with different characteristics.

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<sup>13</sup> Petition at 8.

<sup>14</sup> Attachment A at 3.

<sup>15</sup> *Id*

- **Mechanism of Action.** Several studies have demonstrated that the mechanism of action of different BGS devices may affect cellular processes in different ways that are not fully understood. In particular, the available data suggest that the different modalities may differentially affect signal transduction (activation of transmembrane channels, and stimulation of transmembrane receptors), growth factor gene expression, and growth factor synthesis.<sup>16</sup> However, the biological and biophysical mechanisms of these effects are not fully understood and remain an active area of research.
- **Intended Use.** The clinical use parameters of BGS devices, specifically dosage, vary widely between the BGS technologies. The amount and type of energy delivered per day during treatment is different between BGS technologies. Table 1 of the Petition illustrates the large dosage differences among the technologies.<sup>17</sup> The total energy dosage to the tissue differs considerably across the BGS technologies described in the Petition, which is a function of energy type (electrical or electromagnetic), signal characteristics (frequency or number of pulses), and treatment time. A comparison of the CMF and PEMF signals identified in Table 1 of the Petition illustrates this point. The energy-per-pulse delivered to the tissues for the PEMF signal is 45-times that of the CMF signal (18-G pulse versus 400-mG peak-to-peak). Further, the duration of treatment is different. The PMA-approved CMF BGS devices have a treatment time of 30-minutes per day, while the PMA-approved PEMF devices have a treatment time of 8-10 hours per day. As there currently is no known minimum effective dosage of electrical or electromagnetic stimulation that will result in bone healing, clinical trials conducted in support of a PMA application are needed to establish a specific device's safety and efficacy.

The distinctions among the CC, CMF and PEMF technologies, as well as the differences in the waveforms or field characteristics within a particular BGS modality, may have significant and dissimilar impacts on the safety and efficacy of the devices at issue. The Dr. Ryaby Comments note that “the development of [BGS] devices has demonstrated that the relationship between waveform parameters, cellular and molecular effects, and clinical safety and efficacy are not well understood.”<sup>18</sup> Thus, “as the precise mechanism that produces bone growth stimulation by exogenous signals is not known, there remains no means to accurately predict the effects of a new type of signal or modality . . . [and] the scientific evidence demonstrates that cellular and animal models cannot adequately predict the impact of [device] differences upon human physiologic systems. As a result, clinical testing is required to

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<sup>16</sup> Aaron, R.K. et al. (2004). Stimulation of growth factor synthesis by electric and electromagnetic fields. *Clin. Orthop. Related Res* 419:30-37; Otter, M.W. et al. (1998). Effects of electromagnetic fields in experimental fracture repair. *CORR.* 355S S90-S104.

<sup>17</sup> See Petition at 5.

<sup>18</sup> Attachment A at 3.

adequately protect against the potential for decreased safety and efficacy of substantially equivalent devices.”<sup>19</sup>

The Petition fails to adequately address the impacts that these dissimilarities among or within the CC, CMF and PEMF modalities may have on the safety and effectiveness of new BGS devices. RS Medical has made no attempt to demonstrate scientifically why its proposed generic special controls would assure the safety and effectiveness of each type of BGS technology. Indeed, RS Medical fails to support the Petition’s implicit contention that data on a PEMF device is relevant to a CC or CMF device, and vice versa. RS Medical has therefore attempted to compel reclassification of three distinct BGS technologies by inappropriately aggregating and generalizing data.<sup>20</sup>

### **III. THE PETITION FAILS TO ACCURATELY CHARACTERIZE THE PERFORMANCE PARAMETERS OF THE BGS DEVICES**

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A second major and fatal flaw in the Petition is its failure to identify and characterize the performance parameters of the BGS devices it seeks to reclassify. In order to meet its burden in justifying the reclassification of BGS devices, the Petition must provide valid scientific evidence adequate to define the performance parameters of the devices. As stated by the United States District Court for the District of Columbia in reviewing a previous reclassification proceeding, “. . . the question is whether the administrative record contains sufficient information for the agency to understand the device and sufficient evidence to demonstrate the factors determining the device’s safety and efficacy.”<sup>21</sup>

Here, the scientific evidence proffered in the Petition is scanty and flawed – particularly with respect to CMF technology.<sup>22</sup> As a result, it is wholly inadequate to “demonstrate the factors determining safety and efficacy” of the devices.<sup>23</sup> In fact, based on the public data, it is currently impossible to fully identify all the key performance parameters of the BGS devices identified in the Petition. While the BGS devices currently on the market are supported by extensive clinical data demonstrating that they are safe and effective for their intended uses, there is much that remains unknown regarding the mechanism by which they stimulate bone growth. As stated in the Dr. Ryaby Comments, “[d]espite over thirty years of development and research, the scientific community is unable to explain how and why or to

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<sup>19</sup> *Id.* at 3-4 (citing Fredericks, D.C. et al. (2000). Effects of a Pulsed Electromagnetic Fields on Bone Healing in a Rabbit Tibial Osteotomy Model. *J. Orthopedic Trauma* 14:93-100).

<sup>20</sup> Moreover, the literature cited by RS Medical is flawed in many respects, as more fully described in the BGS Group Comments and those filed to the docket by other manufacturers of BGS devices. *See* Docket 200P-0121/C2.

<sup>21</sup> *Ethicon*, 762 F.Supp. at 388.

<sup>22</sup> Indeed, the Petition cites a single study as supporting reclassification of devices using CMF.

<sup>23</sup> The BGS Group Comments detail, through a study-by-study critique of the scientific data on BGS devices, the ways in which the Petition fails to adequately describe the performance parameters of the BGS devices it seeks to reclassify.

predict when or under what conditions a particular electrical or magnetic signal will stimulate bone growth.”<sup>24</sup>

While the precise cellular mechanism that operates to produce bone growth stimulation remains subject to ongoing research, the available data suggest that physiologic systems are sensitive to variations in electrical or electro-magnetic signals, such that even a relatively minor variation in an electric or electromagnetic field or signal may have significant impacts on safety and effectiveness. An extensive body of research demonstrates that even minor alterations in a BGS device’s waveform parameters may affect ion movements, cellular activation, and clinical efficacy.<sup>25</sup> For instance, a recent review by Aaron et al. (2004) observed differential stimulation of growth factors among various BGS modalities and 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).”<sup>26</sup> Further, no means exist to predict the potential effects that minor variations in device parameters (e.g., amplitude, wavelength, field orientation, etc.) will have when utilized in humans. As noted in the Dr. Ryaby Comments, “as a consequence of this unpredictability, BGS devices have evolved through an incremental process, which has required continuous research regarding the effects of new or modified devices in cellular and molecular experiments, and evaluation of their efficacy in preclinical and clinical trials.”<sup>27</sup>

In light of the incomplete understanding of the effects of electric or electromagnetic currents on cellular processes, the differences associated with minor variations in wave characteristics, and the inability to reliably predict the effect of such variations, it is not possible to ensure the safety and effectiveness of a particular BGS device through the application of a generic set of special controls. Instead, as the Dr. Ryaby Comments conclude, in order to ensure that a particular electric or electromagnetic field is effective in promoting bone growth, and that it does not result in adverse effects on bone growth or other biologic processes, each new BGS device must undergo extensive safety testing in laboratory and animal models and human efficacy testing in clinical trials.

#### **IV. RECLASSIFICATION OF BGS DEVICES WILL INCREASE RISKS TO THE PUBLIC HEALTH**

The 510(k) premarket notification review standard of “substantial equivalence” cannot assure the safety and effectiveness of BGS devices. Instead, application of this standard may result in less-effective BGS devices entering the marketplace. This, in turn, would raise

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<sup>24</sup> Attachment A at 2.

<sup>25</sup> See, e.g., Smith, S. D. et al. (1987). Calcium cyclotron resonance and diatom mobility. *Bioelectromagnetics* 8(3):215-27; Fitzsimmons, R. J. et al. (1993). EMF-stimulated bone-cell proliferation. *Electricity and Magnetism in Biology and Medicine* (Blank, M. ed., San Francisco, CA, San Francisco Press, Inc.); Aaron, R.K. et al. (2004). Stimulation of Growth Factor Synthesis by Electric and Electromagnetic Fields. *Clin Orthop. Related Res* 419:30-37.

<sup>26</sup> R. K. Aaron et al. (2004). Stimulation of Growth Factor Synthesis by Electric and Electromagnetic Fields. *Clin. Orthop. Related Res.* 419:30-37.

<sup>27</sup> Attachment A at 3.

significant issues with respect to patient safety. The attached comments by Drs. Ryaby and Zoltan reflect their concerns, as clinicians and researchers with first-hand knowledge of BGS technology, regarding the impacts a reclassification may have on patient safety.<sup>28</sup>

BGS devices used to heal delayed or nonunion fractures are a non-surgical option for clinicians, and are often used when prior surgical intervention has failed, or surgery is contraindicated due to patient age or health reasons. As a result, a less effective device would increase the risk of an unresolved nonunion and associated complications. Such decreased efficacy would expose patients to increased risk of prolonged inactivity, loss of function, future surgery and surgery-related risks, and possible amputation. Thus, the risk that less-effective, but “substantially equivalent,” devices may enter the marketplace in the event BGS devices are reclassified would unnecessarily increase the risk of serious complications for patients. From the clinical perspective, these risks would be difficult to address. As the Dr. Zoltan Comments point out,

. . . physicians will not necessarily have access to data supporting the safety and efficacy of the actual device he or she is considering prescribing, and . . . some physicians will erroneously believe that the safety and efficacy of BGS devices marketed through the less-rigorous 510(k) process have been satisfactorily demonstrated through preclinical and clinical trials, although the device may be considered to be ‘substantially equivalent’ despite a decrease in safety or efficacy.<sup>29</sup>

Therefore, as the Dr. Ryaby Comments and the Dr. Zoltan Comments conclude, preclinical and clinical testing is necessary to ensure the safety of all new BGS devices. Without such testing, it is impossible to assess potential adverse effects of new devices, including unintended effects on processes associated with ion transport mechanisms on growth factors, as well as on hormone, cardiac and neurological functions. As discussed in the Dr. Ryaby Comments and the Dr. Zoltan Comments, minor variations in the parameters of BGS devices can produce significant, unpredictable effects on physiological processes. This raises the concern that use of untested devices may have unintended consequences, such as retarding bone growth or malignant transformation.

## **V. THE PETITION’S PROPOSED GUIDANCE DOCUMENT WILL NOT ASSURE THE SAFETY AND EFFECTIVENESS OF BGS DEVICES**

The Petition appends a draft guidance document that proposes “special controls” intended to ensure the safety and effectiveness of future BGS devices should they be reviewed through the 510(k) premarket notification process pursuant to a reclassification. As discussed herein and in the BGS Group Comments, it is not possible to promulgate a generic set of special controls that will adequately assure the safety and effectiveness of the different BGS technologies identified in the Petition. Therefore, the Petition’s proposed special controls fail to do so.

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<sup>28</sup> Attachments A-B.

<sup>29</sup> Attachment B.

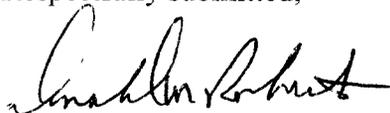
In addition to this fatal flaw, the proposed special controls fail to provide any tolerance or quality standards for the CMF signal parameters themselves. Such standards are necessary to produce a safe and effective BGS device using this type of technology. dj Orthopedics meets specific, proprietary testing standards on tolerance, calibration, and performance parameters for its CMF devices. These standards ensure that all of the BGS devices that dj Orthopedics manufactures have the same safety and efficacy profile demonstrated to the FDA in the Company's PMA clinical trials. These standards are not public; therefore, a substantial equivalence determination cannot be based on these important considerations.

As a result, based on the Petition's proposed guidance document, a device may be considered to be substantially equivalent to dj Orthopedics' CMF BGS devices without demonstrating the characteristics essential to the device's effectiveness. As a result, such a new device may in fact be less effective or ineffective in generating bone growth.

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dj Orthopedics respectfully requests that the FDA deny the Petition to reclassify BGS devices. The nature of BGS devices compels the conclusion that they are not suitable for grouping into a single generic class, and that a generic set of special controls will not be adequate to assure the safety and effectiveness of new BGS devices reviewed by FDA pursuant to the 510(k) premarket notification process.

Respectfully submitted,



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Senior Vice President and General Counsel  
dj Orthopedics, Inc.

Attachments