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INTRODUCTION

I, Dr. James T. Ryaby, submit the following comments to the RS Medical petition for the reclassification of external bone growth stimulators ("BGS") devices from Class III to Class II.[1] For the reasons described in more detail below, I oppose this reclassification.

I am the Senior Vice President of Research and Chief Technology Officer for OrthoLogic Corp., the original premarket approval ("PMA") applicant and manufacturer of two Combined Magnetic Field ("CMF") BGS devices, the Orthologic 1000 and the SpinaLogic. I have over 20 years of experience studying the cellular effects of electromagnetic fields and have directed research that has led to clinical application of BGS devices in a variety of contexts. I have published over 40 articles and study reports that examine the effects of external stimulation on bone growth. In addition, I am a regular presenter at academic and industry seminars on BGS device technology. I am extensively involved in academic medicine, and have served as an Adjunct Professor in the Department of Bioengineering at Arizona State University since 1992. I remain active in the orthopedic research community, holding leadership positions in several national organizations. Please refer to my attached *Curriculum Vitae* for additional information.

For the past twenty years, my career has focused on the development and advancement of bone growth stimulator technology. I have participated in the development of CMF BGS devices from the initial design stages to experiments with *in vitro* and animal models, clinical testing in humans, and eventual use in patients. I have first hand knowledge of the complexities and obstacles associated with the development of a safe and effective BGS device. There are many factors which must be considered, altered, and tested in order to assure that a BGS device is safe and clinically effective for patients. I believe that preclinical and clinical data are key aspects of this determination. I do not believe that the Class II pre-market clearance process and special controls will adequately protect patients from ineffective and unsafe BGS devices. I therefore oppose RS Medical's proposal to abandon the PMA application process. I strongly support the continued maintenance of Class III controls to ensure the safety and efficacy of BGS devices.

I believe there are three fundamental flaws in the RS Medical petition: (1) RS Medical's "generic class" is not supported by the scientific literature; (2) provisions in the petition are inadequate to ensure the safety and efficacy of BGS devices; and (3) the proposed reclassification paradigm would result in increased risks for patients. Each of these issues is discussed below.

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1 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 2005-0121/CCP 1 (filed Feb. 9, 2005).

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I. THERE ARE SIGNIFICANT DIFFERENCES AMONG THE VARIOUS BGS TECHNOLOGIES THAT PRECLUDE THEIR EVALUATION AS A GENERAL CLASS

Bone growth stimulation may be achieved through several different technologies, including Capacitive Coupling (CC), Pulsed Electromagnetic Fields (PEMF), and Combined Magnetic Fields (CMF). While the approved devices in these categories have been shown to stimulate bone growth, they differ significantly in terms of device design, underlying physics, and mechanisms of action. The BGS devices have very different design parameters (e.g., coil shape, type of energy produced, magnitude of current, and electric or magnetic field properties), observed molecular and ionic effects (e.g. stimulation of growth factors, ion movement, and molecular signaling) and clinical parameters (e.g. duration of treatment and clinical indications). These differences have significant impacts on the safety and efficacy of the particular device. RS Medical states, generally, that the devices may be considered as a generic category because they "use a common mechanism of action; they deliver electrical and/or magnetic fields to cause a piezoelectric output."[2] As BGS devices do not cause a piezoelectric output, this statement is scientifically inaccurate. In addition, RS Medical's conclusion regarding consideration of the different BGS technologies as a generic category fails to account for the differences among the BGS technologies identified in published and unpublished research, and the mechanism by which each of these BGS devices causes the cellular and molecular events required to stimulate bone growth.

Despite over thirty years of development and research, the scientific community is unable to explain how and why or to predict when or under what conditions, a particular electrical or magnetic signal will stimulate bone growth. The development of BGS devices for clinical use began with the discovery of the electrical properties of bone tissue in the 1950s and 1960s. Early studies reported the generation of electrical potentials upon bone deformation. These studies led to the hypothesis that strain-generated electric potentials may be the signal for the regulation of cellular processes in bone. [Ref 1] This body of work led to the hypothesis that all tissues which are subject to dynamic mechanical stress (bone, cartilage, tendon, etc), may employ electrical signaling as regulatory component in the maintenance and repair of tissue function. Although there were no direct experiments equating these stress-generated potentials with fracture healing, in the 1970s, scientists and physicians began developing therapeutic devices, which employed electrical signals similar to those seen in the early experiments. The efficacy of several of these signals to promote healing of nonunion fractures or spinal fusion has subsequently been demonstrated in well-controlled prospective, multicenter clinical trials conducted in support of PMA applications.

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2 Petition at 8.

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Over the past thirty years, researchers have tried simultaneously to understand the cellular and molecular events which cause BGS devices to promote bone growth while developing new modalities which could be clinically useful. However, 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. [Ref. 2] This inability to predict, and therefore translate, preclinical studies to definitive clinical effects underscores the need to continue to utilize the PMA process in the development and regulatory review of new BGS technologies.

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. The development of these devices has demonstrated that the relationship between waveform parameters, cellular and molecular effects, and clinical safety and efficacy are not well understood. [Ref. 2] This lack of understanding of the relationship between these different parameters is best demonstrated by the different exposure times required to observe a positive effect on fracture healing, which ranges from 30 minutes to 24 hours per day. In fact, basic science data demonstrate that BGS devices differ in dose-response and signal transduction pathways [Ref. 3], both of which are clinically relevant parameters affecting safety and efficacy. Moreover, the scientific evidence regarding the various approved BGS technologies highlights the differences in their functional characteristics, cellular and molecular effects, and clinical uses. As a result, the safety and efficacy of each BGS technology must be evaluated individually on the basis of evidence derived from clinical trials on that technology, and not as part of a more general category of devices.

There are significant differences in physical characteristics and design among the BGS devices described.

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. CC utilizes surface electrodes that are placed on the skin, between which a high-frequency, oscillating electrical current is placed. PEMF devices utilize copper coils and induce electric current by creating a time-varying magnetic field, with particular pulse trains, pulse shapes, pulse repetition frequency, and magnetic field strengths. CMF devices use a low-power, low-frequency sinusoidal AC magnetic field overlaid onto a static DC magnetic field. Minor deviations in these device characteristics can lead to significant alterations in the effects on tissues. For example, C.T. Brighton *et al.* (1992) demonstrated that field strength plays a critical role on bone cell proliferation. [Ref. 4] Other studies, such as that by Smith *et al.* (1987), have shown that minor alterations in AC or DC field orientation, or frequency employed, can produce significant changes in efficacy. [Ref. 5] These critical differences in design characteristics are particularly important when one considers the effects of such minor changes on cellular and molecular events.

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The different BGS modalities have the varied effects on cellular and molecular events.

Several studies have shown differences among BGS modalities on ion movement, growth factor stimulation, and cellular activity. For example, Brighton *et al.* (2001) examined the cellular effects of CC, PEMF, and CMF on bone cells and demonstrated that the devices resulted in dramatically different cellular effects. [Ref. 3] In this study, Brighton and colleagues evaluated the DNA content for mouse MC3T3-E1 bone cells exposed to CC, PEMF, and CMF signals. The investigators exposed other cultures to the three signals in the presence of known metabolic inhibitors to signal transduction pathways. The authors found that the signal transduction pathways differed among the different BGS signals. Specifically, CC appeared to affect calcium ion transport through cell-membrane voltage-gated channels, whereas CMF and PEMF signals affected intracellular calcium release. This study also examined the dose-response effects of these three signals. Cultures exposed to CC, CMF, or PEMF signals for 0.5, 2, 6, or 24 hours showed that these signals affect cellular pathways differently. The results indicated that CC exhibited dosage dependency, exhibiting substantially more DNA/dish when exposed to the CC signal for 24 hours, compared to 30 minutes exposure. Conversely, cultures exposed to CMF and PEMF signals result in very similar amounts of DNA/dish after 24 hour and 30 minute exposures. As a result of the differing responses, the authors concluded that the different BGS devices resulted in different cellular effects mediated through distinct signaling pathways.

The three BGS modalities have different clinical use parameters.

Clinical use parameters, such as duration of treatment, tolerance, and clinical indications, vary widely among the CC, CMF and PEMF BGS device. These factors are critical to the device's safety and effectiveness, particularly because one cannot know in advance the effects of subtle changes. The approved BGS devices vary in their duration of use from 30 minutes per day to up to 24 hours per day. Similarly, the tolerances of various BGS waveforms are quite different, as the devices employ various forms and magnitudes of energy. In addition, the clinical indications for which these devices are approved vary widely.

Considerable scientific evidence demonstrates that the substantial differences among BGS devices may pose different safety and efficacy concerns. Furthermore, the scientific evidence demonstrates that cellular and animal models cannot adequately predict the impact of such differences upon human physiologic systems. As a result, clinical testing is required to adequately protect against the potential for decreased safety and efficacy of substantially equivalent devices.

II. THERE MAY BE SIGNIFICANT DIFFERENCES IN EFFICACY AND SAFETY AMONG SUBSTANTIALLY EQUIVALENT BGS DEVICES

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Even minor variations in BGS devices that share similar characteristics may result in decreased efficacy and safety. 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 a result, extensive preclinical and clinical testing adequate to support a PMA application is required to ensure that future devices will be as safe and effective as existing PMA-approved devices. In contrast, the waveform parameters in the special controls proposed by RS Medical are incomplete and inaccurate, and would not necessarily generate waveforms that are as safe and effective as currently approved BGS device waveforms. They also do not address issues associated with the dosage and tolerance of each particular waveform, which may significantly impact the safety and effectiveness of the device.

Several studies have demonstrated that minor alterations in device parameters may affect ion movements, cellular activation, and clinical efficacy. For example, Smith *et al.* (1987) conducted a study utilizing a marine diatom model for calcium ion transport to examine the effects of variations in CMF signals. [Ref 5] The study gave strong support for ionic resonance effects of CMF signals where odd harmonics (odd multiples of 15Hz) effectively stimulated calcium transport; however, even harmonics were ineffective and did not differ significantly from the control. The study also found that a CMF signal that lacked either an AC or a DC component was ineffective. Third, the authors concluded that improper alignment of the AC and DC fields may result in an ineffective signal. And finally, the peak-to-peak amplitude of the AC component affected calcium ion transport, where certain amplitudes above and below 20.9 μT resulted in reduced calcium transport.

Several investigators have also demonstrated the highly sensitive nature of BGS waveforms. For example, R.J. Fitzsimmons *et al.* (1993) demonstrated that small deviations in frequency may adversely affect device effectiveness. [Ref. 6] Fitzsimmons exposed TE-85 osteoblast (bone) cells to CMF signals at 72.6, 74.6, 76.6, 78.6, and 80.6 Hz and determined that the 76.6 Hz CMF signal resulted in the largest increase in IGF-II production, an approximate 10-fold increase over the control. The data also suggested that IGF-II production dropped by nearly 50% for the 74.6 and 78.6 Hz signals. Similarly, R.K. Aaron *et al.* (2004) observed differential stimulation of growth factors among various BGS modalities and concluded that, "transmembrane 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)." [Ref. 2] Animal models also suggest similar sensitivity to device parameters for bone growth. McLeod and Rubin (1992) utilized a model of isolated turkey ulnae and observed incremental improvements in bone growth where decreasing EMF signals from 150 Hz to 75 Hz to 15 Hz led to bone area gain/loss of -3%, +5%, and +10% respectively. [Ref. 7]

In light of the incomplete understanding of the effects of electric currents on cellular processes, the differences associated with minor variations in waveform characteristics, and the inability to reliably predict the effect of such variations, the safety and effectiveness of a

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particular BGS device cannot be assured through the application of a specific set of special controls. To ensure that a particular electric or electro-magnetic field is effective in promoting bone growth and does not have adverse effects on bone growth or other biologic processes, each device must undergo extensive safety testing in laboratory and animal models and human efficacy testing in clinical trials. In my opinion, clearance of devices without such safety and efficacy testing would clearly expose patients to increased risk.

III. RECLASSIFYING BGS DEVICES WILL EXPOSE PATIENTS TO INCREASED RISK

My extensive research experience and the available scientific studies with BGS technology lead me to the conclusion that the only way to determine whether a BGS device is safe and effective for treating nonunions and spinal fusion is through preclinical and clinical studies. As minor changes to a BGS device can result in a significant decrease in the device's safety and effectiveness, only clinical testing of a BGS device with defined parameters for waveform, signal type, field size, manufacturing controls, and clinical usage can adequately ensure the device's efficacy and safety. BGS devices that are not subject to the extensive preclinical and clinical testing requirements of the PMA process will pose additional risks for patients, including inferior bone growth stimulation and healing, as well as other safety concerns. In addition, the scientific rigor of clinical studies conducted to support PMA applications provides reassurance to the medical and patient community that the safety and efficacy of a device has been demonstrated, thereby providing clinical benefit to the patient.

BGS devices are currently approved for the treatment of diseases of delayed union and nonunion, and to achieve lumbar spinal fusion. BGS devices are offered as an alternative to surgery, and are often the sole treatment patients receive to treat a nonunion. As a patient may utilize a BGS device for 3 to 6 months with only periodic physician follow-up, 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. This is particularly relevant in light of studies that have demonstrated that the longer a non-union or delayed union remains untreated, the less effective future treatments will be, regardless of the modality employed. [Ref. 8] Spinal fusion patients would be at an increased risk of pain, disability, and functional loss. The potential for apparently "substantially equivalent" devices to be less efficacious would unnecessarily increase the risk of serious complications for patients.

Preclinical and clinical testing is also necessary to ensure the safety of new BGS devices. Such testing serves as a means of ruling out potential adverse effects of new devices including among others, unintended effects on processes associated with ions transport mechanisms on growth factors, as well as on hormone, cardiac and neurologic functions. Minor variations in the parameters of BGS devices can produce significant, unpredictable effects. For example, studies

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such as those by Smith *et al.* (1987) demonstrate that calcium ion movement can be affected by minor alterations in field orientation or frequency. [Ref. 5] Such findings raise concern about the effects of non-PMA-approved devices on calcium responsive cells such as heart tissue, nerve and brain cells, and muscle. Furthermore, without extensive preclinical and clinical testing, the effect of a particular device on any ion dependent cells or tissues is unknown. [Ref. 9] Similarly, the varied effects on growth factor stimulation, mRNA production, and cellular proliferation observed in cellular and animal models similarly raises concerns about the potential for unintended consequences, such as retarding bone growth or malignant transformation.

CONCLUSION

Evaluating the safety and effectiveness of BGS devices as a generic class is not consistent with the body of experimental data and underestimates the potential for an apparently "substantially equivalent" device to be considerably less effective and safe than those devices whose safety and effectiveness has been demonstrated in clinical trials conducted pursuant to the PMA process. As a result, RS Medical's proposed reclassification would result in potentially significant risks to patients if less efficacious and unsafe devices are provided to patients. As a result of the risks associated with less rigorous testing and review of new BGS devices and the excellent record of safety BGS devices have enjoyed under the current PMA-approval paradigm, I strongly urge the FDA to reject the proposed reclassification.

Respectfully Submitted,

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