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BY HAND

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

Re: FDA Docket 2005P-0121/CCP 1;
Technical Comments in Opposition to the Proposed Reclassification of External Bone Growth Stimulator ("BGS") Devices from Class III to Class II

Dear Sir or Madam:

On behalf of the BGS Reclassification Opposition Group ("BGS Group"),[1] we submit the following comments in opposition to RS Medical's proposed down-classification of external bone growth stimulator ("BGS") devices from Class III to Class II. The comments contained in this document will focus on the scientific and technical deficiencies in RS Medical's amendment and will not reiterate all of the arguments presented in our earlier responses to the petition.[2]

RS Medical has failed to demonstrate that its proposed general and special controls would reasonably assure the safety and effectiveness of BGS devices. The petition does not merit consideration by an FDA advisory panel and the Agency should reject it. In an August 12, 2005 letter to RS Medical, FDA specifically requested a revised risk analysis and special control guidance document to address the potential risks posed by BGS devices. RS Medical's response is woefully inadequate. As discussed below, the only means of reasonably assuring the safety and effectiveness of these devices is through Class III designation and PMA review.

I. The Risk of Ineffective and Unsafe Waveforms

FDA requested that RS Medical revise its petition to address the range of technical specifications that are necessary to ensure a clinically effective and safe treatment signal/dose. RS Medical refused to provide these specifications, insisting that "it is neither necessary to describe all of the technological 'specifications' of the individual devices proposed for

[1] The BGS Group is comprised of the leaders in this device field—dj Orthopedics, Inc., EBI, L.P., and Orthofix, Inc.

[2] We have submitted two sets of comments on behalf of the BGS Group in response to RS Medical's proposed down-classification. On August 17, 2005, we submitted a critique of RS Medical's original petition ["BGS Group Response to Petition"]. On February 10, 2006, we submitted a legal critique of RS Medical's amendment ["BGS Group Response to Amendment"].

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reclassification, nor that it is necessary to impose, by regulation, any technological specifications on the specific devices within this type in order to reclassify them into Class II."[3] Only the waveforms of the current PMA-approved BGS devices have demonstrated safety and effectiveness. Consequently, only the specifications for these devices are proven to reproduce clinically effective signals. RS Medical argues that defining and replicating these specifications could be accomplished through testing and reverse engineering; yet, the petitioner entirely failed in its efforts to do so.[4]

The literature demonstrates that BGS devices require adherence to exacting waveform specifications and that insufficient valid scientific evidence exists to prove the adequacy of RS Medical's proposed special controls. The technical specifications for BGS devices are crucial to their safe and effective functioning. Studies show that seemingly minor changes in waveform specifications can render an ineffective signal. For example, Fitzsimmons et al. (1992, 1994) reported that a deviation in waveform frequency, as little as 2 Hz, resulted in an ineffective signal.[5] Brighton et al. (1985) similarly reported that increases in signal amplitude could adversely affect BGS efficacy.[6] Although RS Medical cites Leisner (2000) in support of the down-classification, this study actually reported similar callus formations in PEMF treatment and control (non-treated) groups for fresh ulnar fractures, with faster healing in the non-treated group.[7] RS Medical cites Brighton et al. (1992), but this study's results simply emphasize the precision required of BGS waveforms: "The pulse configuration and the duty cycle are also important, but only if the proper field strength is being applied to the cell."[8] BGS studies also show that the basic mechanisms of action for these devices remain unknown. The CC and PEMF modalities exhibit different biochemical pathways and produce different responses in bone-forming cells *in vitro*.[9] Even the same BGS signal may have varying clinical effects in different individuals.[10]

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[3] Amendment to RS Medical's Petition for the Reclassification of the Non-invasive Bone Growth Stimulator, FDA Docket 2005P-0121/CCP1 (Nov. 30, 2005) ["RS Medical Amendment"] at 25.

[4] RS Medical conducted testing on used and expired devices, limited testing to select models, and ignored a marketed BGS device intended for spinal fusion. Even after this testing, RS Medical was unable to replicate or define the waveforms of the PMA-approved devices. *See* BGS Group Response to Amendment at 4-5.

[5] *See* 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).

[6] *See* 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).

[7] *See* S. Leisner et al., *The Effect of Short-duration, High-intensity Electromagnetic Pulses on Fresh Ulnar Fractures in Rats*, 49 J. VET. MED. SERIES A 33-37 (2002).

[8] *See* C.T. Brighton et al., *In vitro bone-cell response to a capacitively coupled electrical field. The role of field strength, pulse pattern, and duty cycle*, 235 CLIN. ORTHOP. REL. RES. 255-62 (1992).

[9] *See* C.T. Brighton et al., *Signal Transduction in Electrically Simulated Bone Cells*, J. BONE JOINT SURG. AM. 1514-523 (2001); R.K. Aaron et al., *Stimulation of Growth Factor Synthesis by Electric and Electromagnetic Fields*, 419 CLIN. ORTHOP. RELATED RES. 30-37 (2004).

[10] *See* Aaron et al. (2004).

While acknowledging that a manufacturer could produce a BGS device with an unsafe or ineffective output, RS Medical illogically argues that these studies are irrelevant if they did not involve one of the marketed devices proposed for reclassification.[11] If RS Medical's petition is granted, however, all non-invasive BGS devices of the generic type will be reclassified, not just the currently marketed PMA-approved devices. Thus, new devices with varying designs and outputs could be found substantially equivalent through 510(k) review, without undergoing the rigorous PMA testing to demonstrate that the devices are safe and effective.

RS Medical implicitly recognizes that BGS devices require precise designs and thorough premarket testing. RS Medical would require a new BGS device either (1) to be an exact duplicate (i.e., same technological characteristics and specifications) of a current PMA-approved device, or (2) to undergo extensive PMA-type pre-clinical (animal) and clinical testing to validate that the device's signal is clinically safe and effective. Both of these options exceed the intent and capacity of 510(k) substantial equivalence analyses. We provide a detailed critique of the proposed 510(k) review for BGS devices in our previous comments on the reclassification.[12]

Moreover, given RS Medical's failure to identify the technical specifications for the PMA-approved BGS devices, all new BGS devices would be required to undergo animal and clinical testing. We do not believe that a 510(k) sponsor could demonstrate with certainty that the signal parameters of the new device were identical to those of the predicate. Although RS Medical asserts that reverse engineering and identification of signal parameters of predicate devices are common practice, the petitioner failed to accurately define and replicate the signals of the PMA-approved devices.

II. Potential Harm to Patients with Electrical Implants

New BGS devices may pose a risk to patients with electrical implants, such as cardiac pacemakers, cardiodefibrillators, and neurostimulators. To address this risk, RS Medical proposes that all BGS device labeling would incorporate a warning about the possible adverse interaction with electrical implants. FDA would exempt a BGS device from this requirement if the manufacturer submitted adequate validation/verification studies.[13]

RS Medical, however, has failed to identify the specific types of verification and validation testing that would support an exemption from this proposed warning requirement.[14] Performance of standard electrical testing (EMC, IEC 60601-1, etc.) would not sufficiently address this device interaction. The safety and efficacy of using a BGS device in patients with

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[11] RS Medical Amendment at 7.

[12] *See* BGS Group Response to Petition at 28-29; BGS Group Response to Amendment at 7-10.

[13] RS Medical Redlined Proposed Guidance Document, in RS Medical Amendment at 115.

[14] Under 21 C.F.R. § 820.3, "validation" is defined as "confirmation by examination and provision of objective evidence that the particular requirement for a specific intended use can be consistently fulfilled." "Verification" is defined as "confirmation by examination and provision of objective evidence that specified requirements have been fulfilled."

electrical implants can be demonstrated only through extensive animal and clinical studies—the types of testing normally required under a PMA, not a 510(k).

III. Potential Harm to Patients with Internal or External Fixation Devices

RS Medical proposes what it contends are "related precautions" in BGS labeling to address the potential risk to patients with internal or external fixation devices. The petitioner, however, offers insufficient valid scientific evidence to demonstrate that these vague "precautions" would reasonably assure the safety and effectiveness of new BGS devices. Without analysis, RS Medical asserts that "neither a CC nor PEMF Non-Invasive Bone Growth Stimulator is adversely affected in the presence of a non-magnetic, metallic fixation device" and that "CC . . . is not adversely affected in the presence of a magnetic, metal fixation device, whereas a PEMF device can be."[15]

The cited literature does not support RS Medical's assertion. As discussed in our other comments on the reclassification, RS Medical has failed to justify the pooling of results from studies that differ significantly in patient populations, pre-treatment conditions, etc.[16] The majority of articles that discuss BGS use in patients with fixation devices involve the treatment of spinal fusions. RS Medical, however, indiscriminately combines data on CC and PEMF technologies for spinal fusions with data on non-unions. The cited literature includes only one study that discusses the combination of CC and internal fixation devices for spinal fusion[17] and only four articles discussing the use of PEMF in the presence of fixation devices for spinal fusion.[18]

The few articles concerning BGS use with fixation devices for non-unions are insufficient to support any scientific conclusions. The majority of these studies failed to identify the number of patients with fixation devices and to stratify results according to the type of fixation device, e.g., internal or external.[19] Other studies lacked sufficient patient populations. For example, Brighton and Pollack (1985) examined a total of 7 patients with metal fixation devices, i.e., IM

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[15] RS Medical Amendment at 12.

[16] BGS Group Response to Petition at 27-30; BGS Group Response to Amendment at 6-7.

[17] C.B. Goodwin et al., *A Double-Blind Study of Capacitively Coupled Electrical Stimulation as an Adjunct to Lumbar Spinal Fusions*, 24 SPINE 1349-57 (1999).

[18] B. Bose, Outcomes After Posterolateral Lumbar Fusions with Instrumentation in Patients Treated with Adjunctive Pulsed Electromagnetic Field Stimulation, 18 ADVANCES IN THERAPY 12-20 (January/February 2001); L.G. Jenis et al., Prospective Comparison of the Effect of Direct Current Electrical Stimulation and Pulse Electromagnetic Fields on Instrumented Posterolateral Lumbar Arthrodesis, 13 J. SPINAL DISORDERS 290-96 (2000), V. Mooney, *A Randomized Double-Blind Prospective Study of the Efficacy of Pulsed Electromagentic Fields for Interbody Lumbar Fusions*, 15 SPINE 708-12 (1990); J.W. Simmons et al., Psuedoarthrosis After Lumbar Spine Fusion: Nonoperative Salvage with Pulsed Electromagnetic Fields, 33 AM. J. ORTHOP. 27-30 (January 2004).

[19] *See, e.g.*, C.A.L. Bassett et al., *Treatment of Ununited Tibial Diophyseal Fractures with Pulsing Electromagnetic Fields*, 63 J. BONE SURG. 511-23 (1981); H. Ito and Y. Shirai, *The Efficacy of Ununited Tibial Fracture Treatment Using Pulsing Electromagnetic Fields*, 2 J. NIPPON MED. SCH. 68 (2001); H.R. Gossling et al., *Review, Treatment of Ununited Tibial Fractures: A Comparison of Surgery and Pulsed Electromagnetic Fields (PEMF)*, 15 ORTHOP. 711-19 (June 1992).

rods, plate, and screws, at the treatment site.[20] Similarly, DeHaas et al. included information on only 6 non-union patients with internal fixation devices.[21]

Moreover, as RS Medical admits, some studies suggest that the use of BGS devices in the presence of fixation devices can be detrimental. For example, Mandronero et al. (1988) concluded that treatment with PEMF in patients with metallic fixation devices is ineffective.[22] Hisenkamp (1985) noted that further investigation is needed to clarify unknown parameters, such as mechanical or vascular interventions, that could have a determinant effect.[23]

Clearly, the body of literature does not establish the safety and effectiveness of BGS devices in the presence of fixation devices. The literature also does not demonstrate the sufficiency of any labeling to address the risks associated with this use. On the contrary, the literature supports that the safety and effectiveness of BGS devices under these conditions remain unknown and that extensive clinical studies are necessary.

IV. Biological Risks Associated with Electrical Stimulation

RS Medical's proposed special controls would not reasonably assure the safety of BGS devices. RS Medical dismisses the biological risks associated with electrical stimulation and suggests cursory labeling to address these potentially serious concerns.

A. Carcinogenicity, Genotoxicity, and Mutagenicity

RS Medical concedes that there is "concern regarding the possible relationship between exposure to electromagnetic fields and adverse biological effects, such as cancer development."[24] RS Medical further concedes that the majority of the data available on the risks of carcinogenicity and genetic mutation/alteration from electrical stimulation are based on stimulation frequencies that are not representative of the devices proposed for reclassification.[25] The only BGS-related article cited by RS Medical discusses a PEMF invasive device, which is not the subject of the proposed reclassification. RS Medical provides no evidence to address the biological risks potentially associated with CC devices.

RS Medical argues that the lack of published clinical evidence reporting these biological adverse events suggests that carcinogenicity, genotoxicity, and mutagenicity are not relevant

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[20] C.T. Brighton and S.M. Pollack, *Treatment of Recalcitrant Non-union with a Capacitively Coupled Electrical Field*, 47-A J. BONE JOINT SURG. 577-85 (April 1985).

[21] W.G. DeHaas et al., *The Canadian Experience with Pulsed Magnetic Fields in the Treatment of Ununited Tibial Fractures*, 208 CLIN. ORTHOP. REL. RES. 55-58 (1986).

[22] A. Mandronero et al., *Pulsed electromagnetic field treatment failure in radius non-union fracture healing*, 10 J. BIOMED. ENG. 463-66 (Oct. 1988).

[23] M. Hisenkamp et al., *Treatment of Non-unions by Pulsing Electromagnetic Field: European Multicenter Study of 308 Cases*, 19 RECONST. SURG. TRAUMAT. 147-51 (1985).

[24] RS Medical Amendment at 14.

[25] RS Medical only provides "example" articles on the genotoxic and mutagenetic potential of electrical and magnetic fields. *See* RS Medical Amendment at 71.

risks for BGS devices. In the Draft Guidance on BGS devices, however, FDA specifically recognized the potential for "teratogenesis, reproduction, genotoxic effects, cellular proliferation, and possible carcinogenic initiation/promotion effects."[26] In rejecting the down-classification of rigid gas permeable ("RGP") contact lenses, FDA also concluded that the "mere absence of negative reports . . . cannot establish the safety of a device."[27]

RS Medical proposes including a "warning/precaution that the long-term effects of electrical stimulation or magnetic fields have not been studied extensively in humans."[28] This language is in direct conflict with RS Medical's assertions throughout its original petition and amendment that the publicly available literature and the clinical history support the safety and efficacy of BGS devices. Moreover, the use of labeling to mitigate the potential genotoxic and mutagenetic risks is insufficient. Only comprehensive testing, as required under PMA review, would assure that patients do not use unsafe or ineffective BGS treatments.

B. Teratology

RS Medical recognizes that new BGS devices could pose teratological risks and that additional research on the teratological effects of BGS devices is necessary. In its amendment, RS Medical described:

> [L]imited information is available on the potential effects of prenatal exposure or postnatal behavior. . . . [W]ith respect to mammalian species (rats and mice), gross visceral, external, and skeletal anomalies were not observed in the reviewed studies, but there was evidence of minor skeletal alterations in several experiments. While these may be common findings in teratological studies and not always considered significant, subtle effects cannot be ruled out. This is significant [in] relation to the indications presented in the petition. Additional research is warranted.[29]

Despite this conclusion, RS Medical glibly proposes labeling as a special control to address these risks. By RS Medical's admission, there is insufficient valid scientific evidence to demonstrate that labeling would reasonably assure BGS safety and effectiveness. In fact, McGivern et al. reported that exposure to PEMF signals affected male scent-marking behavior and gonad size in rats.[30] RS Medical argues that this study is irrelevant because the PEMF pulses and exposure duration differed from those in clinical use. This study, however,

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[26] FDA 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"].

[27] *Reclassification of Daily Wear Spherical Contact Lenses Consisting of Rigid Gas Permeable Plastic Materials*; Withdrawal of Proposed Rule, 48 Fed. Reg. 56,778, 56,783 (Dec. 23, 1983).

[28] RS Medical Amendment at 115.

[29] RS Medical Amendment at 74.

[30] R.F. McGivern et al., *Prenatal exposure to a low-frequency electromagnetic field demasculinizes adult scent marking behavior and increases accessory sex organ weight in rats*, 41 TERATOLOGY 1-8 (1990).

underscores that only PMA-approved BGS devices have demonstrated safety and effectiveness. Since the 510(k) process requires a new device to be substantially equivalent, not identical, to a predicate device, new BGS devices with unproven waveforms and exposure durations could flood the market.

V. Potential Risk of Thermal Burns

In its petition, RS Medical proposed mitigating the risk of thermal burns through labeling that would instruct the user not to use the control unit and battery charger while sleeping and not to charge the battery while the device is in use. The petitioner failed to consider, as pointed out by FDA, that a patient may not have time to adequately charge and use the device while awake. RS Medical's solution is to require manufacturers to design BGS devices so that the battery cannot be charged while the device is in use (e.g., the battery pack must be removed from the device before charging) and to provide two battery packs with the device.

RS Medical's proposed special control is inappropriate and unenforceable. Mandating design requirements is beyond the scope of FDA's regulation of device manufacturers in general and is certainly not within the scope of a device reclassification. Guidance documents issued by the Agency, such as the special control proposed by RS Medical, are not binding on FDA or the public. Thus, FDA could not require a BGS manufacturer to design its device with dual battery packs; and FDA could find a new BGS device to be substantially equivalent without these design features. Moreover, even the currently marketed BGS devices—the proposed predicate devices—do not meet these design criteria. Thus, RS Medical has failed to identify a special control that would adequately address the risk of thermal burns and PMA review must be maintained.

VI. Conclusion

RS Medical's deficient petition should not proceed to an advisory panel. In the past, FDA has refused panel review for reclassification petitions that suffered from similar inadequacies.[31] Before a federal court, FDA "took the position that a lack of valid scientific evidence is an infirmity which obviates the need to send the application to a reclassification panel."[32] Here, RS Medical has provided insufficient valid scientific evidence to demonstrate that its special controls would reasonably assure BGS safety and effectiveness. The scientific literature shows that these devices require precise—not substantially equivalent—waveforms, and that the fundamental mechanisms of action for these devices remain unknown.

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[31] *See* Letter from Dr. Susan Alpert, Director, Office of Device Evaluation, CDRH, to Larry R. Pilot, McKenna & Cuneo, L.L.P. (Mar. 7, 1996) (refusing to convene a panel on a reclassification petition for obstetric data analyzers because of the petition's regulatory deficiencies, i.e., failure to provide specifications for the device proposed for reclassification, a lack of valid scientific evidence to support reclassification, etc.)

[32] *Lake v. FDA*, No. 88-6275, 1989 U.S. Dist. LEXIS 7179, *3 (E.D. Pa. June 27, 1989) (upholding FDA's refusal to refer a reclassification petition to panel because the petition lacked sufficient valid scientific evidence).

Substantial equivalence analyses should not require device identicality or the PMA-type clinical testing proposed by RS Medical. Down-classification would only straitjacket FDA's review of BGS devices by forcing the Agency's PMA requirements into a 510(k) paradigm. Furthermore, RS Medical offers nothing more than perfunctory labeling proposals to address the potential safety concerns raised by BGS devices. This petition does not warrant an investment of valuable panel resources. We urge FDA to reject the petition and continue the necessary PMA review of BGS devices.

Respectfully submitted,

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