

## Opposition to the Reclassification of External Bone Growth Stimulators

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### BGS Reclassification Opposition Group

- Comprised of the leaders in the BGS field: dj Ortho, EBI, and Orthofix.
- We represent 100% of the external electromagnetic BGS market. Petitioner RS Medical does not have a PMA-approved BGS device.
- Down-classification of BGS devices to Class II could
  - expose patients to ineffective or harmful treatments, i.e., ineffective devices could subject patients to further surgical interventions;
  - cause regulatory creep by permitting similar but unproven waveforms to enter the marketplace under 510(k) review;
  - stunt valuable research in this field, e.g., on new indications, cell response, etc.; and
  - undermine the integrity of BGS technology by permitting the influx of potentially unsafe and ineffective devices.

## External BGS Devices Included in RS Medical's Petition

- External BGS devices are currently classified as postamendments Class III devices.
- Capacitive coupling (“CC”) devices use a low voltage, high frequency oscillating current.
- Combined magnetic field (“CMF”) devices use a low frequency sinusoidal AC magnetic field overlaid onto a static DC magnetic field.
- Pulsed electromagnetic field (“PEMF”) devices use a time-varying (pulsed) electromagnetic field, with particular pulse trains, pulse shapes, pulse-repetition frequency (prf), and magnetic field strength.

## Reclassification Petition Requirements

- Petitioner must 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.” 21 C.F.R. § 860.3(i) (emphasis added).

## Reclassification Petition Requirements

- Petitioner must demonstrate that its proposed “special controls would provide reasonable assurance of the safety and effectiveness of the device and that general controls would not provide reasonable assurance of the safety and effectiveness of the device.” FDCA § 513(e)(2)(A) (emphasis added).
- Petitioner must rely only on publicly available “valid scientific evidence,” e.g., no trade secret or confidential commercial information, to support reclassification. FDCA § 520.
- Petitioner must include “representative data and information known by the petitioner that are unfavorable to the petitioner’s position.” 21 C.F.R. § 860.123(a)(7).

## Burden of Proof in Reclassifications

- Petitioner bears the burden of proof “regardless of whether those opposing reclassification can or do submit evidence showing that reclassification is not appropriate.” Contact Lens Rule, 48 Fed. Reg. 56778, 56783 (Dec. 23, 1983) (emphasis added).

## Deficiencies in RS Medical's Petition

1. Petition is deficient on its face.
  - (a) Petition fails to include representative unfavorable data.
  - (b) Petition contains 3 distinct proposals for reclassification.
2. Failure to identify a generic type of device for reclassification.
  - (a) Different technologies
  - (b) Different waveforms
  - (c) Different intended uses
3. Failure to propose adequate special controls that would provide a reasonable assurance of BGS safety and effectiveness.
  - (a) RS Medical's proposed special controls are inadequate.
  - (b) PMA requirements are necessary for BGS devices.
4. Failure to provide sufficient valid scientific evidence to support the petition.

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## 1(a). Petition is Deficient on Its Face

- RS Medical has failed to include representative unfavorable data.
  - Petition must include “representative data and information known by the petitioner that are unfavorable to the petitioner’s position.” 21 C.F.R. § 860.123(a)(7).
  - Examples of data that are unfavorable to RS Medical’s petition:
    - 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) (finding that a small deviation in frequency may adversely affect device effectiveness).
    - D. C. Fredericks, J. V. Nepola, J. T. Baker, J. Abbott, & B. Simon, *Effects of Pulsed Electromagnetic Fields on Bone Healing in a Rabbit Tibial Osteotomy Model*, 14 J. Orthopaedic Trauma 93-100 (2000) (describing a signal that worked in animal models but did not work clinically).

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## 1(b). Petition is Deficient on Its Face (cont'd)

- RS Medical has failed to identify the device for reclassification. The petition contains the following 3 distinct proposals:
  1. *Proposed reclassification regulation*
    - Proposes reclassification of BGS devices that use CC, PEMF, or CMF, regardless of specific waveform parameters.
  2. *Description of “Devices Covered by Reclassification Petition”*
    - Limits to currently marketed devices and RS Medical’s unapproved device.

## 1(b). Petition is Deficient on Its Face (cont'd)

3. *Proposed guidance document*
  - Limits to those devices that use the waveform parameters identified in RS Medical’s Table 1, which is inaccurate and incomplete.
    - Each BGS technology requires multiple parameters to define a waveform.

## 1(b). Petition is Deficient on Its Face (cont'd)

RS Medical's Table 1 (below) is an incomplete and inaccurate characterization of the waveforms.

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

RS Medical Petition, Table 1, at 5 and 107.

## 1(b). Petition is Deficient on Its Face (cont'd)

- **Deficiencies in Table 1:**
  - **Permits manufacturers to produce a variety of waveforms of unknown safety and effectiveness;**
  - **Provides inadequate information to generate waveforms that are identical or substantially equivalent to those used in currently marketed devices;**
  - **Specifies no tolerances; and**
  - **Relies on tissue electrical fields, which lack predictive value for signal effectiveness.**

## **2(a). Failure to Identify a Generic Type of Device: Different Technologies**

- **RS Medical has not defined a meaningful subset of BGS devices, i.e., the exclusion of ultrasound devices but inclusion of CC, PEMF, and CMF.**
- **RS Medical relies primarily on PEMF studies. PEMF studies, however, are not necessarily applicable to CC and CMF devices.**
  - **RS Medical cites 5 CC studies and 2 CMF studies.**
  - **Our independent literature search similarly found minimal literature on CC and CMF.**

## **2(a). Different Technologies (cont'd)**

- **In FDA's Draft Guidance on BGS devices, FDA concluded that CC, PEMF, and CMF raise different safety concerns and thus recommended testing "to address the safety issues related to the specific modality involved."**

*Guidance Document for Industry and CDRH Staff for the Preparation of Investigational Device Exemptions and Premarket Approval Applications for Bone Growth Stimulator Devices; Draft Document (1998).*

## 2(a). Different Technologies (cont'd)

- The mechanisms of action for these devices are different and not fully understood. Given that we do not fully understand the mechanisms of action for PMA-approved BGS devices, evaluating the safety and effectiveness of new devices under 510(k) review would present even greater difficulties.
  - C. T. Brighton et al., *Signal Transduction in Electrically Stimulated Bone Cells*, J. Bone Joint Surg. Am. 1514-23 (2001) (finding that CC, CMF, and inductively coupled modalities produced different responses in bone-forming cells in vitro).
  - R. K. Aaron et al., *Stimulation of Growth Factor Synthesis by Electric and Electromagnetic Fields*, 419 Clin. Orthop. Related Res. 30-37 (2004) (noting distinct differences between treatment modalities).
- Additional research on the disparate mechanisms of action is pending publication.

## 2(a). Different Technologies (cont'd)

- Different technologies present different design considerations that impact safe and effective use.
  - Coils: Petition does not address differences in coil designs.
    - In PEMF devices, different coils are required for different parts of the body and necessitate specific parameters.
  - Electrode materials: Petition does not address differences in electrode materials for CC devices.
    - Clinical studies are necessary to determine electrode safety and effectiveness.
  - Dosimetry: Petition does not provide dose thresholds.
    - Effectiveness of CMF and CC devices depend on the dose and frequency at which the dose is delivered.

## 2(b). Failure to Identify A Generic Type of Device: Different Waveforms

- As discussed earlier, RS Medical has inaccurately and incompletely described the waveforms used in BGS devices.
  - For example, RS Medical has attempted to define only the non-union parameters for PEMF devices.
- The precise definition of waveform parameters, however, is necessary to accurately reproduce a waveform.
- Waveform parameters differ significantly between the different technologies and different indications, and elicit different cellular responses.

## 2(b). Different Waveforms (cont'd)

- Studies show that any variation of waveform parameters may adversely affect device safety and effectiveness.
  - Examples:
    - Study by the Cleveland Clinic Foundation (publication pending) (finding that minor modifications to commercially available waveforms can render a signal ineffective, and may also negatively impact bone forming cells).
    - 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) (finding that a small deviation in frequency may adversely affect device effectiveness).
    - C. T. Brighton et al., *Fracture Healing in the Rabbit Fibula When Subjected to Various Capacitively Coupled Electrical Fields*, 3 J. Orthopaedic Research 331-340 (1985).

## **2(b). Different Waveforms (cont'd)**

- Only the waveform parameters of PMA-approved BGS devices have demonstrated safety and effectiveness.
- FDA has required extensive testing for even minor modifications to PMA-approved BGS devices.
- FDA has maintained that a change to one signal parameter in a BGS device results in a new signal that requires additional clinical study.

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## **2(b). Waveforms: Problem of Regulatory Creep**

- 510(k) review would permit similar—but unproven—waveforms to enter the marketplace.
  - The safety and effectiveness of BGS devices depend on a complex interrelationship of manufacturing, waveform, dose, mechanism of action, design, and intended use.
    - Alterations to these characteristics may pass 510(k) review while posing unknown effects on device safety and effectiveness.

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## 2(b). Waveforms: Problem of Regulatory Creep (cont'd)

- In rejecting the down-classification of RGP contact lenses, FDA concluded:
  - “The 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.”  
Contact Lens Rule, 48 Fed. Reg. at 56792.
- As with RGP contact lenses, “even minor changes . . . can significantly affect the safety and effectiveness” of BGS devices. *Id.* at 56780.

## 2(c). Failure to Identify a Generic Type of Device: Different Intended Uses

- FDA recognizes that non-union and lumbar spinal fusions pose different kinds of risks that necessitate different types of testing.
  - In FDA’s Draft Guidance on BGS devices, the agency noted 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.”
  - Citing the special safety concerns raised by spinal fusion, FDA required a BGS manufacturer to perform a clinical study on electrical stimulation of the cervical spine.

## **2(c). Different Intended Uses (cont'd)**

- Use different clinical measures
  - Non-unions – time-based definition
  - Spinal fusions – “This time-based definition of non-union may not be readily applicable to other fracture types and bones. . . . For example, in the case of spinal fusion, 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.”
- Require different patient follow-ups
  - Non-unions – follow for at least 1 year after end of stimulation
  - Spinal fusions – follow for more than 1 year

## **3(a). Failure of Special Controls to Reasonably Assure Device Safety and Effectiveness: RS Medical’s Special Controls are Inadequate**

- There is insufficient information to establish similar special controls that address the wide range of BGS devices described in the petition.
  - The International Commission on Non-Ionizing Radiation Protection (ICNIRP) has already concluded that there is insufficient information to establish a single set of safety controls to cover the range of frequencies used in electromagnetic field devices.

### **3(a). RS Medical's Special Controls are Inadequate (cont'd)**

- **IEC 60601-1 may not be sufficient to mitigate all risks for shock or burn.**
- **BGS devices require complex manufacturing processes and controls in order to produce devices that consistently produce the required signals.**
  - **Unlike 510(k) review, PMA requirements allow for the extensive review and inspection of a company's manufacturing process and facilities prior to device approval.**

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### **3(a). RS Medical's Special Controls are Inadequate (cont'd)**

- **RS Medical's special controls do not address:**
  - **the potential risks posed by electrical stimulation and bioactivity at the cellular level, i.e., carcinogenicity, mutagenicity, cell toxicity, and teratological effects;**
  - **the effect of duration of use on the risk for skin irritation;**
  - **the potential risk to patients who use electrical or metallic implants, i.e., cardiac pacemakers and neurological stimulators; and**
  - **the manufacturing tolerances for the petitioner's waveforms—a manufacturer must understand the entire signal in order to determine the tolerances.**

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### 3(b). Failure of Special Controls to Reasonably Assure Device Safety and Effectiveness: PMA Requirements Are Necessary for BGS Devices

- PMA clinical study requirements are necessary to provide a reasonable assurance of BGS device safety and effectiveness.
  - Preclinical studies of BGS devices are not always predictive of clinical success.
    - 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).
    - Studies on the BMD-Stim (although animal studies provided a reasonable assurance of efficacy, clinical studies showed no efficacy).

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### 3(b). PMA Requirements Are Necessary for BGS Devices (cont'd)

- 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.”

Contact Lens Rule, 48 Fed. Reg. at 56790 (emphasis added).

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### 3(b). PMA Requirements Are Necessary for BGS Devices (cont'd)

- Although FDA may require the submission of any information that is necessary to determine substantial equivalence, FDA may not convert the 510(k) process into a PMA.
  - Requiring PMA-type clinical studies as special controls under a 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.

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### 4. Failure to Provide Valid Scientific Evidence to Demonstrate Safety and Effectiveness

- Valid scientific evidence IS NOT:
  - “Isolated 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.” 21 C.F.R. § 860.7(c)(2) (emphasis added).
    - Unless used to identify “a device the safety and effectiveness of which is questionable.” *Id.*

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#### 4(a). Failure to Provide Valid Scientific Evidence to Demonstrate Safety (cont'd)

- RS Medical has not provided “valid scientific evidence” to “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.” 21 C.F.R. § 860.7(c)(2).

#### 4(a). Failure to Provide Valid Scientific Evidence to Demonstrate Safety (cont'd)

- “The phrase ‘presents a potential unreasonable risk of illness or injury’ has two significant features. First, the requirement that a risk be unreasonable contemplates a balancing of the possibility that illness or injury will occur against benefits from use. Second, the risk need only be a potential one. The risk may be one demonstrated by reported injuries or it may simply be foreseeable.” *General Medical Co. v. FDA*, 770 F.2d 214, 221 (D.C. Cir. 1985) (emphasis added).

#### **4(a). Failure to Provide Valid Scientific Evidence to Demonstrate Safety (cont'd)**

- Most of the studies cited by RS Medical do not report on device safety.
- The absence of reports in the published literature of serious, irreversible adverse events testifies to the success of the present Class III requirements, which ensure that only safe and effective BGS devices are marketed.
  - In rejecting the down-classification of RGP contact lenses, FDA concluded that the “mere absence of negative reports in this voluntary reporting system cannot establish the safety of a device.” 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.” Contact Lens Rule, 48 Fed. Reg. at 56783.

#### **4(b). Failure to Provide Valid Scientific Evidence to Demonstrate Effectiveness (cont'd)**

- RS Medical has not provided “valid scientific evidence” that shows “that in a significant portion of the target population, the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will provide clinically significant results.” 21 C.F.R. § 860.7(e).
- The cited evidence must “consist principally of well-controlled investigations.” *Id.*

#### **4(c). RS Medical Has Failed to Provide Valid Scientific Evidence to Demonstrate Safety and Effectiveness (cont'd)**

- **RS Medical has relied on studies that do not constitute valid scientific evidence to support reclassification.**
  - **The cited articles do not adequately describe the treatments that were studied.**
    - **Waveforms are not well-defined in any of the cited studies.**
  - **As discussed earlier, RS Medical relies primarily on PEMF studies that have limited, if any, applicability to CC and CMF devices.**
  - **Approximately half of the cited studies involved less than 60 patients.**
  - **Patient populations varied in age and demographics.**
  - **Some studies permitted previous surgeries, others did not.**

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#### **4. RS Medical Has Failed to Provide Valid Scientific Evidence to Demonstrate Safety and Effectiveness (cont'd)**

- **Some studies required treatment and no weight-bearing activities, others allowed patients with casts.**
- **Studies varied in their definitions of success and methods for evaluating success, i.e., radiographic evidence, “no pain,” absence of movement at fracture site, etc.**
- **Follow-up time frames varied. Several studies had follow-up 12 weeks after the end of treatment.**
- **Some studies inadequately describe the study treatment. Other studies describe treatment times ranging from 2 hours/day to 24 hours/day.**

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## **FDA Should Reject RS Medical's Petition for Reclassification**

- 1. Petition is deficient on its face.**
  - (a) Petition fails to include representative unfavorable data.**
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# Questions?