KING & SPALDING LLP

Opposition to the Down-Classification of External Bone Growth Stimulators

March 14, 2006

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2005P-0121

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Background

- The BGS Reclassification Opposition Group is comprised of the leaders in the BGS field: dj Orthopedics, EBI, and Orthofix. We represent 100% of the external electromagnetic BGS market.
  - RS Medical does not have a PMA-approved BGS device.
- External BGS devices are currently classified as postamendments Class III devices.
  - Capacitive coupling ("CC") devices use a low voltage, high frequency oscillating current.
  - 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.

RS Medical Has Provided No Regulatory or Scientific Basis for Reclassification

- Despite FDA's requests for clarification and additional information, RS Medical has failed to:
  - Identify a generic type of BGS device for reclassification.
  - Provide sufficient valid scientific evidence to support reclassification.
  - Provide unfavorable data.
  - Demonstrate that PMA review is unnecessary and that its proposed special controls would reasonably assure the safety and effectiveness of new BGS devices.

RS Medical Has Provided No Regulatory or Scientific Basis for Reclassification

- RS Medical has fallen far short of its burden of proof. As the petitioner, RS Medical bears this burden "regardless of whether those opposing reclassification can or do submit evidence showing that reclassification is not appropriate." Contact Lens Rule, 48 Fed. Reg. 56,778, 56,783 (Dec. 23, 1983) (emphasis added).
- Indeed, RS Medical undercuts its own petition by simultaneously offering to abandon the reclassification in exchange for distribution agreements with current BGS manufacturers.
- FDA should not countenance a reclassification based on incomplete, inappropriate, and unscientific data. We urge the Agency to refuse panel review and reject the petition.

RS Medical Has Not Identified a Generic Type of Device for Reclassification

- Since there was inadequate scientific evidence to support the reclassification of CMF devices, RS Medical cavalierly eliminated this technology from its petition.
- RS Medical now proposes the down-classification of both CC and PEMF devices intended for non-unions and lumbar spinal fusions. These devices, however, do not constitute a "generic type of device."
  - A "generic type of device" is "a grouping of devices that do not differ significantly in purpose, design, materials, energy source, function, or any other feature related to safety and effectiveness, and for which similar regulatory controls are sufficient to provide reasonable assurance of safety and effectiveness." 21 C.F.R. § 860.3(i).

RS Medical Has Not Identified a Generic Type of Device for Reclassification

- **By contrast, the BGS devices proposed for down-classification have:**
  - **<u>Different technologies</u> -- CC devices deliver an electric field using skin-mounted electrodes; PEMF devices deliver a magnetic field using an external coil.**
  - **<u>Different mechanisms of action,</u> e.g., effects on cellular processes -- *See e.g.*, Brighton et al., *Signal Transduction in Electrically Stimulated Bone Cells*, J. Bone Joint Surg. Am. 1514-23 (2001) (finding that the different BGS modalities exhibited different biochemical pathways and produced different responses in bone-forming cells *in vitro*).**

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- **Different waveform parameters** -- Even after conducting testing on the PMA-approved devices, RS Medical was unable to fully and accurately define their waveform parameters. The precise definition of the parameters is necessary to consistently reproduce waveforms of proven safety and effectiveness. FDA has required extensive clinical testing for changes to a single waveform parameter.
- **Different dosimetries** -- CC devices may be used for 24 hours/day. Some PEMF devices for non-unions, 3-10 hours/day; other PEMF devices for spinal fusions, 2-3 hours/day

RS Medical Has Not Identified a Generic Type of Device for Reclassification

- <u>Different intended uses</u>, involving
  - *Different clinical measures* -- Time-based definitions for non-unions may not be applicable to spinal fusions.
  - *Different patient follow-ups* -- For non-unions, follow-up for at least 1 year after the end of stimulation; for spinal fusions, follow-up for more than 1 year. *See* FDA Draft BGS Guidance (1998).
  - *Different safety concerns* -- FDA has required different testing for different BGS intended uses, i.e., tests for the effects of stimulation on nervous tissue for spinal fusion uses.
    - These different safety concerns underscore that the devices proposed for down-classification do not constitute a generic type of device. In the preamble to the device classification regulation, FDA noted that "[b]y definition, all devices within the same generic type present the same or very similar risks to health."

RS Medical Has Not Identified a Generic Type of Device for Reclassification

- Even within the same BGS technology, i.e., PEMF, there are significant differences in device signals, dosimetries, and designs.
- The BGS devices are not substantially equivalent to each other. If they were substantially equivalent to each other --
  - then RS Medical would not need to specify each technology's distinctive risks, special controls, and relevant studies; and
  - RS Medical would not abandon the reclassification of the CMF devices but would offer the CC and PEMF literature to support CMF reclassification.

RS Medical Has Not Defined the Basic Technical Specifications for the BGS Devices

- RS Medical refused FDA's request for a "rationale to justify how the proposed technical specifications are sufficient to validate an effective clinical treatment signal" and the "range of technical specification . . . necessary to ensure a clinically effective treatment signal/dose."
- In an attempt to demonstrate that PMA-approved waveforms could be easily defined and replicated, RS Medical conducted limited testing on several used and expired BGS devices. This testing is inadequate.

RS Medical Has Not Defined the Basic Technical Specifications for the BGS Devices

- Even after this testing, RS Medical was unable
  - to replicate the waveforms of the approved CC and PEMF devices, or
  - to characterize a range of technical specifications with proven safety and effectiveness.
- RS Medical's inability to delineate these benchmarks of BGS safety and effectiveness undermines the company's suggestion that defining and reproducing these devices is readily accomplished.
- Consequently, unproven and potentially ineffective and unsafe devices could enter the market through the 510(k) process.

RS Medical Has Failed to Provide Sufficient Valid Scientific Evidence

- A reclassification petition must provide sufficient valid scientific evidence to demonstrate that the proposed special controls would reasonably assure device safety and effectiveness. *See* Federal Food, Drug, and Cosmetic Act § 513(a)(1)(B).
- RS Medical, however, relies on seriously flawed studies that have unknown and inconsistent study parameters.

RS Medical Has Failed to Provide Sufficient Valid Scientific Evidence

- RS Medical indiscriminately combines and compares:
  - studies with different inclusion/exclusion criteria, treatment regimens, durations-of-use, timeframes for follow-up, and definitions of clinical success,
  - PEMF studies to support the down-classification of CC devices,
  - non-union studies to support the down-classification of devices used in spinal fusion,
  - studies lacking safety data,
  - studies lacking sufficient patient populations, and
  - studies lacking clear characterizations of the waveforms or devices used.

The Proposed Special Controls Would Not Reasonably Assure BGS Safety and Effectiveness

Potential harm to patients with electrical implants, i.e., cardiac pacemakers, cardiodefibrillators, neurostimulators, etc.

- RS Medical proposes that BGS device labeling would incorporate a warning about possible adverse interactions with electrical implants. FDA would permit exemptions from this labeling requirement if the manufacturer submitted adequate validation/verification studies.
- RS Medical, however, fails to identify the specific types of validation/verification testing that would support an exemption from the warning labeling.
  - Certainly, standard electrical testing (i.e., EMC, IEC 60601-1, etc.) would not sufficiently address this device interaction.

The Proposed Special Controls Would Not Reasonably Assure BGS Safety and Effectiveness

Potential harm to patients with internal or external fixation devices

- RS Medical proposes vague "precautions" to address this risk.
- The scientific literature demonstrates that the safety and effectiveness of BGS devices, when used with internal or external fixation devices, remain unknown. Extensive clinical studies are necessary.

The Proposed Special Controls Would Not Reasonably Assure BGS Safety and Effectiveness

Potential risk of adverse biological effects

- In the Draft BGS Guidance, FDA explicitly recognized the potential for the following risks: "teratogenesis, reproduction, genotoxic effects, cellular proliferation, and possible carcinogenic initiation/promotion effects."
  - RS Medical also acknowledges concerns about "the possible relationship between exposure to electromagnetic fields and adverse biological effects, such as cancer development" and that the relevant data concern frequencies that are not representative of the devices proposed for reclassification.
- Yet, RS Medical proposes a cursory warning "that the long-term effects of electrical stimulation or magnetic fields have not been studied extensively in humans."

The Proposed Special Controls Would Not Reasonably Assure BGS Safety and Effectiveness

- For example, McGivern et al. (1990) reported that exposure to PEMF signals affected behavior and gonad size in male rats. RS Medical argues that this study is irrelevant because the PEMF pulses and exposure duration differed from those in clinical use.
  - However, since the 510(k) process only requires a new device to be substantially equivalent, not identical, to a predicate device, new BGS devices with unproven exposure durations and waveforms could be cleared.
- Yet, RS Medical proposes vague labeling as a special control. Only extensive clinical testing, as required under PMA review, would adequately address this risk.

The Proposed Special Controls Would Not Reasonably Assure BGS Safety and Effectiveness

Potential risk of thermal burns

- RS Medical proposes requiring manufacturers to design BGS devices so that the battery cannot be charged while the device is in use and to provide two battery packs with the device.
- This proposed special control is inappropriate.
  - Mandating design requirements is beyond the scope of FDA's regulation of device manufacturers in general and is not within the scope of a device reclassification.
  - Moreover, even the currently marketed BGS devices—the proposed predicate devices—do not meet these design criteria.

RS Medical Has Failed to Provide Data that Are Unfavorable to the Proposed Reclassification

- Rather than providing representative unfavorable data, RS Medical insists that any preclinical and clinical studies showing "unsafe or ineffective output parameters . . . are not pertinent to the reclassification," unless they specifically involve a marketed BGS device named in its petition.

RS Medical Has Failed to Provide Data that Are Unfavorable to the Proposed Reclassification

- The petition failed to include literature showing that:
  - Seemingly minor changes to BGS devices may render a device ineffective or unsafe. *See e.g.*, 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).
  - The basic mechanisms of action for these devices remain unknown. *See e.g.*, Aaron et al., *Stimulation of Growth Factor Synthesis by Electric and Electromagnetic Fields*, 419 Clin. Orthop. Related Res. 30-37 (2004) (describing differences in the mechanisms of action for different BGS modalities).
  - A BGS device was ineffective. *See* Barker et al., *Pulsed Magnetic Field Therapy for Tibial Non-Union*, 1 Lancet 993-96 (1984).

RS Medical Has Failed to Provide Data that Are Unfavorable to the Proposed Reclassification

- These studies are unfavorable to the petition because they demonstrate that:
  - The sensitivity and specificity of BGS devices make them ill suited for marketing clearance based on comparative determinations.
  - Insufficient information exists to support down-classification because the key performance parameters for BGS devices remain unknown.
  - BGS devices require PMA-type controls--rigorous preclinical and clinical testing and manufacturing oversight--to assure their safety and effectiveness.

RS Medical Has Failed to Demonstrate that PMA Review Is Unnecessary for BGS Devices

- BGS devices are unsuited for comparative determinations of substantial equivalence because ostensibly minor changes to these devices can result in ineffective or unsafe signals.
  - Under 510(k) review, however, the "piggybacking" of predicate devices would encourage a cascade of seemingly similar, but ultimately unproven, BGS devices to enter the market.
- There is no well-defined BGS predicate device, given the differences among the BGS technologies and the open questions about key parameters of these devices.

RS Medical Has Failed to Demonstrate that PMA Review Is Unnecessary for BGS Devices

- Comprehensive clinical data, the type of data normally required under a PMA, are necessary to reasonably assure BGS safety and effectiveness. Although FDA may require the submission of any information that is necessary to determine substantial equivalence, the Agency may not convert premarket notification into a quasi-PMA.
- PMA review also permits a crucial premarketing assessment of BGS device manufacturing.
  - It is imperative that a company reliably manufacture BGS devices within the specific tolerances for each waveform parameter. RS Medical has failed to identify these parameters and tolerances.

FDA Should Refuse Panel Review and Reject the Deficient Petition

- In the past, FDA has refused panel review for reclassification petitions that suffered from similar deficiencies. *See e.g.*, 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 refer a reclassification petition to panel because of the failure to provide specifications for the device proposed for reclassification, sufficient valid scientific evidence, etc.).

- 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." *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).

FDA Should Refuse Panel Review and Reject the Deficient Petition

- We urge FDA to refuse panel review and reject the petition for the following reasons:
  - RS Medical has failed to identify a generic type of BGS device for reclassification.
    - RS Medical's inability to define the technical specifications for CC and PEMF underscores that safe and effective BGS devices are difficult to define, let alone manufacture.
  - RS Medical has provided insufficient valid scientific evidence to demonstrate that its special controls would reasonably assure BGS safety and effectiveness.
    - RS Medical offers nothing more than perfunctory labeling proposals to address the potential safety concerns raised by BGS devices.

FDA Should Refuse Panel Review and Reject the Deficient Petition

- Substantial equivalence analyses should not require identicality to a predicate 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, i.e., extensive clinical testing, into a 510(k) paradigm.
- FDA regulations generally provide that petitions containing deficiencies should not be brought to panel.

Questions?