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Food and Drug Administration
5630 Fishers Lane
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Rockville, MD 20852

Re: FDA Docket 2005P-0121/CCP; Comments in Opposition to Reclassification Petition Amendment

Dear Sir or Madam:

On behalf of our client, EBI., L.P., we are submitting the following comments under 21 C.F.R. § 860.134(b) in opposition to RS Medical's amended petition for reclassification of noninvasive bone growth stimulators (2005P-0121/CCp1). We have had an opportunity to review the November 30, 2005, amendment submitted to the Food and Drug Administration ("FDA" or "the agency") by RS Medical (or "the company") in response to the agency's August 12, 2005, points to consider letter on the reclassification petition for the noninvasive bone growth stimulator. We believe that RS Medical continues to fail to demonstrate that special controls are sufficient to provide a reasonable assurance of the safety and effectiveness of noninvasive bone growth stimulators as required by 21 U.S.C. § 360c(e)(2). Further, in its amendment, RS Medical fails to constructively address the vast majority of substantive issues raised by FDA in the agency's August 12, 2005, letter.

Specifically, the company does not provide a rationale for pooling studies with disparate parameters, including treatment waveform, nor does it supply appreciable additional data to supplement its original submission. There is no meaningful response to the agency's question as to the scientific basis of information provided in the petition. The company's response to both safety and risk issues raised by FDA is unconvincing. Finally, RS Medical does not provide the

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complete output waveform parameters specifically requested by the agency. In such respects, RS Medical fails to provide direct and complete answers to FDA's questions. Thus, in no way may the company's amendment be considered a complete response to FDA's substantive concerns.

Given these continued deficiencies in RS Medical's petition for reclassification, we believe as a matter of both law and science that there is currently no basis for reclassifying noninvasive bone growth stimulators to class II.

Moreover, considering the current insufficiency of RS Medical's amendment, a panel meeting to discuss potential reclassification of noninvasive bone growth stimulators would be both premature and inconsistent with applicable agency regulations. Pursuant to 21 C.F.R. § 860.134(b)(3), a reclassification petition may only be referred to an advisory panel when, "that [] petition contains no deficiencies precluding a decision on it." Although this provision is specifically applicable to reclassification actions conducted under § 513(f)(2) of the Federal Food, Drug, and Cosmetic Act, reclassification under that section, like those conducted under § 513(e)(2) such as RS Medical's petition, involves the agency's evaluation of new information concerning a medical device. This data evaluation is essentially identical under either reclassification provision, and is directed at assessing whether those data are sufficient to support the regulatory standard for reclassification. The clear purpose of 21 C.F.R. § 860.134(b)(3) is to ensure that a reclassification petition is referred to an advisory panel only when data are reasonably adequate to allow reclassification. Given the substantially similar nature of the data analysis, it is entirely appropriate to apply the provisions found at 21 C.F.R. § 860.134(b)(3) to reclassification actions conducted under § 513(e)(2). Under the 21 C.F.R. § 860.134(b)(3) standard, the multiple substantive deficiencies of the RS Medical petition clearly preclude the agency's convening a panel meeting until such time as those deficiencies are resolved, if ever.

To more fully elucidate the deficiencies identified in our analysis of RS Medical's amendment, we have restated the six Items raised by FDA with regard to the company's original petition, followed by our analysis as to the adequacy of RS Medical's responses.

1. *In support of this petition, the sponsor has provided "new information", as described within § 513(e) - "publicly available, valid scientific evidence", which includes the following (42 Literature articles listed within Appendix A):*

    a. *sham-controlled, double-blinded, prospective studies,*
    b. *standard-of-care controlled (non-sham), prospective studies,*
    c. *historic-controlled, retrospective studies,*
    d. *and non-controlled studies.*

    These articles appear to differ considerably in respect to study size, drop-out rates, clinical/imaging evaluation, prior treatment, site of treatment, and concurrent treatment, etc. The petition does not appear to include an analysis of these disparate study parameters and their affect on the validity of the scientific evidence. The petition should be revised to include rationale for consolidating the provided literature studies as scientific evidence considering the studies inconsistencies. In addition, the petition does not appear to include literature articles which may be unfavorable to the petition. Additional research may be necessary to verify that the submitted summary literature is an adequate sample of the available scientific evidence and includes scientific evidence which may not support this petition.

The initial issue raised by FDA in this Item is that the original petition does not adequately explain the rationale for pooling studies with disparate parameters (for example inclusion/exclusion criteria, type of treatment, length of treatment, treatment site, and concurrent treatment) to produce scientifically valid data. RS Medical's response to this agency concern is clearly inadequate at multiple levels, as outlined below:

- RS Medical responds by defending the search methodology it used in selecting the 42 articles analyzed in the original petition. This defense does not, however, address FDA's substantive issue with the results of this search, namely the inconsistent and incomplete parameters specified by the studies. Furthermore, RS Medical provides no scientific justification for pooling the results of these disparate study populations. Accordingly, RS Medical has not met its burden of providing valid scientific evidence to support its reclassification petition, as defined by 21 C.F.R. § 860.7(c)(2).

- RS Medical attempts to defend the inconsistent study parameters by making the scientifically untenable argument that: (1) most significant study parameters were identified; and (2) citing studies with varying parameters provides additional scientific evidence by demonstrating that noninvasive bone growth stimulation is safe and effective under a variety of different treatment conditions. With regard to this latter argument, RS Medical states: "Seeing similar results from somewhat different study approaches reinforces, rather than calling into question, the conclusion that the Non-invasive bone Growth Stimulator can be a safe and effective type of device." This contention alone disregards the well-recognized and universally accepted scientific standards required for consolidating study results in a manner that produces valid and reliable data.

- RS Medical fails to explain how studies investigating devices with different waveform parameters can be reliably compared to one another. To the contrary, RS Medical discounts the impact of inconsistent, and sometimes unspecified, waveform parameters on data pooling, and argues that the specific waveforms featured by the devices are irrelevant if all of the devices are of the same "type". This argument is scientifically unsound and completely fails to address FDA's concern. Furthermore, RS Medical does not justify how studies of devices with unspecified or incomplete waveform parameters can produce reliable data in support of reclassification when it is impossible to determine whether the technology being tested is the same as that being proposed for reclassification.

- RS Medical argues that providing data from well-controlled trials that use specified and consistent study parameters is only necessary to support PMA review, and not reclassification. This argument does not address FDA's concerns and, furthermore, is flawed in that it mischaracterizes the requirements for reclassification. Under the reclassification standard, FDA may change the classification of a device from class III to class II "if [FDA] determines that special controls would provide a reasonable assurance of the safety and effectiveness of the device and that general controls would not provide a reasonable assurance of the safety and effectiveness of the device... ."

21 U.S.C. § 360c(e)(2). 1/ Thus, scientifically valid evidence must demonstrate the adequacy of special controls to assure the safety and effectiveness of a device in order to allow for reclassification. FDA has correctly raised concerns with regard to the adequacy and quality of RS Medical's supporting data, and the company clearly has failed to address these concerns.

- In addition to failing to explain how the data provided in its original petition constitutes valid scientific evidence, RS Medical does not provide significant additional data or data analysis to address FDA's concerns regarding the data the company originally submitted.

A second issue raised by the agency in Item 1 relates to the adequacy of the literature search that RS Medical performed to obtain the historical data cited in its original petition, and whether the company included in its search results data that were unfavorable to the reclassification petition. Similar to RS Medical's response to the first issue discussed above, the company's response to this agency concern is inadequate, and in several cases, inconsistent with assertions made in other portions of its November 30, 2005 amendment:

- RS Medical asserts that studies failing to demonstrate the safety and effectiveness of the bone growth stimulator tested are not necessarily unfavorable to the petition. The company attempts to support this rather novel position by noting that unsafe or ineffective output parameters are known risks of the device, and that a study suggesting the danger or ineffectiveness of a particular device does not necessarily suggest the danger and ineffectiveness of every device subject to the reclassification petition. This assertion is scientifically untenable, and is inconsistent with the company's original reclassification petition, which appears to encompass essentially all types of noninvasive bone growth stimulation devices and does not specify device parameters to the level of detail necessary to describe a useful waveform. Furthermore, the argument is inconsistent with regard to RS Medical's previous assertion that its pooled data constitutes valid scientific evidence,

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1/ Any device reclassified to class II must, by definition, meet the regulatory criteria for a class II device set forth at § 513(a)(1)(B) of the Federal Food, Drug, and Cosmetic Act.

even though particular devices or their waveforms are unspecified in most, if not all, of the cited studies. Specifically, in the case of favorable data, the company finds it unnecessary to specify the particular devices being tested. In contrast, in studies that produce unfavorable data, RS Medical attributes the results to a specific device, and does not generalize the results to all types of noninvasive bone growth stimulators.

- RS Medical describes an additional key word search conducted to identify unsuccessful clinical studies preceded by successful preclinical work. This search resulted in 16 references pertaining to preclinical investigations, including cell cultures, animal investigations, and investigations into mechanism of action. The search also produced 9 references containing general information on treatment with electrical stimulation. A mix of positive and negative results were reported in these studies, with RS Medical concluding that the data demonstrate the utility of preclinical testing and the knowledge it provides. However, RS Medical fails to mention that these studies also support the contention that only certain waveforms produce positive clinical results. Thus, this additional literature cannot be seriously considered to have fully addressed the agency's underlying concerns that certain types of noninvasive bone growth stimulation waveforms are either ineffective or unsafe.

- RS Medical also identified 6 additional clinical studies. Of these, only 2 were relevant to the indications being proposed for reclassification. The first study, by Barker, et al. (1984) 2/, included a randomized, double-blind, controlled design in which Pulsed Electromagnetic Field (PEMF) stimulation was used to treat tibial non-unions. The study included a small sample size of 16 patients. The waveform parameters specified were incomplete, and clinical and radiographic endpoints were undefined. Radiographic results were not reported. Clinical results showed no significant difference between the investigational and control groups. Notably, RS Medical attempts to discount these negative results by arguing that the Barker study may be unreliable because the device was not identified and the sample size may not have been large enough to make a clear assessment, criticisms that the company refused to apply to similar shortcomings seen in its more positive data. These

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2/ Barker, AT, et al. (1984) Pulsed magnetic field therapy for tibial non-union. Interim results of a double-blind trial. *Lancet*. 1(8384):994-996.

inconsistencies notwithstanding, the Barker study references a scholarly article to identify the type of noninvasive bone growth stimulator being evaluated 3/, meaning that RS Medical is incorrect in its assertion that the type of device studied was not identified. The second of the 2 studies relevant to the proposed indications was a retrospective review, by Dunn and Rush (1984) 4/, of patients treated with either an implantable bone growth stimulator or PEMF. Within the PEMF group, there was a relatively small sample size of 35 patients with confounding variables among the population, including non-uniformity of sites treated, prior or concurrent surgery, and prior or concurrent therapy. The evaluation methods for clinical and radiographic endpoints were unspecified. In summary, the additional clinical data offered by RS Medical in its amendment suffers from the same lack of scientific validity in terms of study design and specificity of the treatment waveform as do the previously cited studies. Accordingly, the new data cited provide essentially no additional scientific support to the reclassification petition.

2. *The petition appears to suggest that subsequent to the reclassification of noninvasive bone growth stimulators your proposed device would be "exempt from 510(k) requirements" (pg 89-90) (i.e. not require a 510(k) marketing submission). This is not acceptable. You do not currently own a legally marketed bone growth stimulator PMA device or a Pre-amendment device. Therefore, the submitted petition is considered to be a citizen's petition for the reclassification of the product group and NOT your proposed device. If the reclassification is granted, RS Medical must submit a 510(k) and receive a substantially equivalent determination prior to marketing your device.*

- RS Medical deferred a response to this Item, maintaining that is not relevant to the reclassification petition. This response ignores the fact that the scope of the reclassification proposed by RS Medical is a critical issue. FDA is entirely correct in raising the issue as to what generic device type would be included in

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3/ Barker AT. The Design of a clinical electromagnetic bone stimulator. (1981) *Clin Phys Physiol Meas.* 2:9-16.

4/ Dunn, AW and Rush, GA. Electrical stimulation in treatment of delayed union and nonunion of fractures and osteotomies. (1984) *South Med J.* 77(12):1530-1534.

the reclassification product group in as much as RS Medical itself does not have a specific device it is targeting for reclassification.

3. *The 33 literature articles submitted to support the indication for use, Treatment of established non-unions acquired secondary to trauma, includes 5 Capacitive Coupling (CC) and 28 Pulsed Electromagnetic Field (PEMF) studies. The petition does not appear to include valid scientific evidence to support the use of Combined Magnetic Field (CMF) devices for the treatment of established non-unions. Additional scientific evidence should be provided to support the use of CMF devices for this indication for use.*

- Rather than providing additional scientific evidence to support the use of CMF devices for the treatment of established non-unions, RS Medical removed CMF devices from its reclassification petition. This effectively removes one article from the group of 33 articles describing the treatment of established non-unions included in the original petition, leaving a total of 32 article to support device reclassification for the non-union indication. 5/ As discussed elsewhere, these remaining articles offer insufficient valid scientific data to support reclassification.

4. *The petition's risk analysis identified four general categories of health risk to the patient; electric shock, burn, skin irritation/allergic reaction, and inconsistent or ineffective treatment. The petition's risk analysis does not appear to adequately assess the risk of harm to the patient from the presence of metallic and/or electrical implants (including cardiac pacemakers, neurostimulators, and internal/external fixation). In addition, the petition's risk analysis does not appear to address risk associated with electrical stimulation at the biologic level, including carcinogenicity, mutagenicity, cell toxicity, and teratological effects. The risk analysis should be revised to include these risks.*

- **Potential Harm to Patients with Electrical Implants** (*e.g.*, cardiac pacemaker, cardiodefibrillator, neurostimulator). RS Medical's response fails to fully address the agency's concerns regarding this issue. The company suggests that adequate device labeling, including warnings, would mitigate these risks,

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5/ Linovitz, RJ, et al. (2002) Combined magnetic fields accelerate and increase apine fusion: a double-blind, randomized, placebo controlled study. *Spine.* 27(13):1383-1388.

and proposes verification and/or validation testing for manufacturers who do not wish to use such a warning in their device labeling. However, RS Medical does not offer any specific clinical data analyzing the potential effect of noninvasive bone growth stimulators on these electrical implants, nor does the company suggest any specific labeling or warnings that should be provided.

- **Potential Harm to Patients with Internal/External Fixation Devices.** RS Medical does not provide a complete response to this issue. The company notes certain studies provided in its original literature review that included patients with internal or external fixation devices, apparently to support the proposition that no injury to these patients resulted from the noninvasive bone growth stimulation. RS Medical cites an additional study by Bassett, et al., but does not provide a full citation. We have been unable to locate any such article or abstract in PubMed and related databases in order to perform a full analysis. However, with regard to the studies that the company provided in the original petition, these data continue to be suspect due to poor study design and lack of specificity with regard to the waveform being tested. With respect to risk analysis, the majority of these studies are uncontrolled for the particular risk factor being analyzed in response to FDA's concerns. Additionally, there is a high likelihood of investigator bias towards underreporting of adverse events, particularly in uncontrolled retrospective studies where the investigator's primary focus is on efficacy rather than safety.

- **Risk Associated with Electrical Stimulation at the Biologic Level – Carcinogenicity, Genotoxicity, Mutagenicity, and Teratology**. RS Medical does not meaningfully address FDA's concerns on this issue. Specifically, the company provides a literature review concerning research on the potential carcinogenicity, genotoxicity, mutagenicity, and teratology of electromagnetic fields. The cited research, however, does not address the risks associated with exposure to the specific frequencies of the electromagnetic fields generated by bone growth stimulators. Instead, as RS Medical itself notes, "[t]he majority of research involves frequencies associated with common environmental electromagnetic exposures (power lines, communication devices, and R.F.s, and microwaves.... Thus, the bulk of the available literature does not specifically pertain to these [PEMF] fields" and "the overwhelming [number] of studies reported using other exposures do[es] not necessarily apply

to the frequencies which are the subject of this petition." The same is true for the magnetic field studies cited by the company, which involve a variety of exposure conditions. Accordingly, the resulting data do not significantly contribute to a risk analysis of the potential harms from exposure to the particular fields generated by bone growth stimulators. As RS Medical itself notes: "Exposure conditions across the studies present the most confounding variable. Exposure conditions were not always uniform and cannot always be monitored accurately making it difficult to compare doses."

- RS Medical asserts that "the apparent lack of published clinical evidence" reporting adverse events related to the frequencies produced by bone growth stimulators "suggests that this type of electromagnetic energy/clinical exposure does not have adverse biological effects." The argument that an inability to identify adequate biological safety data for the relevant output waveforms constitutes affirmative proof of safety is obviously flawed and clearly fails to address FDA's request for a risk analysis.

- In its original petition, RS Medical correctly cited the risk of inconsistent or ineffective treatment as a risk associated with inconsistent or ineffective external bone growth stimulator treatment. Even as amended, RS Medical's reclassification fails to provide valid, scientific evidence that effective treatment can be consistently provided without the benefit of the premarket approval process. Notably, inconsistent or ineffective treatment may lead to a lack of fusion or nonunion, which may necessitate surgical intervention, with the morbidity and mortality that such intervention entails.

5. *The petition has identified thermal burns as a potential risk associated with this device. The petition has also recognized that the majority of burn-related, adverse events occur while the patient is using and recharging the device during sleep. To mitigate this risk the petition proposes appropriate warning labeling. Considering that treatment may be prescribed for up to 14 hrs per day, this mitigation may not be reasonable as a patient may not have the time to adequately charge and use the device during their wakeful hours. The petition should be revaluated to provide further mitigating activities to minimize the risk of thermal burns to the patient.*

- RS Medical proposed the use of labeling instructions, warnings, and design safeguards to minimize the risk of thermal burns. The company, however, addressed these proposed measures in a cursory manner. In particular, the company failed to offer specific language for instructions and warnings that could be effective in mitigating the risk of thermal burns. Additionally, the company's proposed design safeguards only address the risk posed by recharging the device during use, but not the potential risk of burn associated with, for example, duration of use, dosimetry, and coil design.

6. *The proposed special controls appear to outline a general set of output waveforms (burst length, pulse amplitude, pulse amplitude, and frequency) upon which substantial equivalence might be established. However, it is unclear if these parameters are adequate, in themselves, to assure safety and effectiveness. These device waveform parameters do not appear to provide a complete set of technical parameters which would be sufficient to assure the reproducibility of clinically effective treatment. The parameters do not address the distribution of the induced magnetic/electric fields, coil geometry, effective dosimetry of the resulting electrical gradient/magnetic field (magnetic field mapping), material and dimensions of the electrodes (capacitive plates), pulse rise/fall time, pulse width/shape, symmetry/asymmetry of waveform, and other technical parameters. In addition, the petition should include rationale to justify how the proposed technical specifications are sufficient to validate an effective clinical treatment signal. The petition should be revised to address what range of technical specification is necessary to ensure a clinically effective treatment signal/dose.*

- RS Medical entirely fails to provide an adequate response to this critical Item raised by FDA. The company initially acknowledges that its petition was deficient in identifying crucial parameters of the device being reclassified, and proceeds to list the type of descriptive information and performance data testing that should be provided for the subject device. However, rather than providing specific technical specifications for the device, as FDA requests, RS Medical only lists the general types of specifications that it asserts can be provided at a later stage to show substantial equivalence. RS Medical disregards the fact that there is presently no predicate device with which to claim substantial equivalence. Rather, the company continues to advance a reverse engineering argument that is inconsistent with the legal standards for

reclassification. The company states that "a new manufacturer can design a device that is virtually identical in characteristics and specification to a predicate." Here, as elsewhere in the amendment, RS Medical disregards the reclassification standard, which requires evidence that special controls provide a reasonable assurance of safety and effectiveness. As FDA recognizes in its question, without RS Medical delineating the range of technical specifications for which valid scientific evidence demonstrates safety and effectiveness, the agency is unable to determine whether the device being proposed for reclassification can provide a safe and effective treatment waveform.

- RS Medical completely fails respond to the agency request that the company provide a rationale justifying why the petition's proposed technical specifications are sufficient to validate an effective clinical treatment waveform. Rather than addressing FDA's concerns, RS Medical maintains that all noninvasive bone growth stimulators subject to the petition are of are the same "type"." The company further asserts that setting technological specifications for particular devices is unnecessary, "because enough is known about the safety and effectiveness of these devices." This is a circular argument that lacks scientific validity. Furthermore, as discussed in detail under Item 1 above, the clinical data provided in both the petition and the present amendment is inadequate to make a definitive determination as to the true safety and effectiveness of noninvasive bone growth stimulators.

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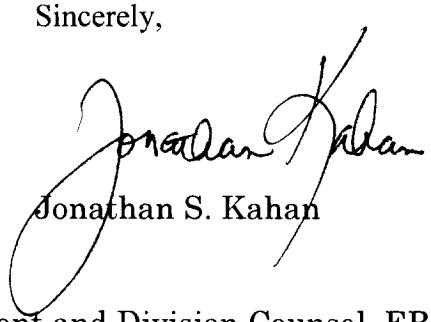
In sum, RS Medical's amendment is unresponsive to the vast majority of substantive concerns raised by the agency. RS Medical continues to offer insufficient support to establish that special controls are sufficient to provide a reasonable assurance of the safety and effectiveness of noninvasive bone growth stimulators.

Accordingly, we oppose RS Medical's petition to downclassify noninvasive bone growth stimulators. We firmly believe that a panel meeting to discuss potential reclassification based on the unreliable and inadequate support offered by RS Medical would also be inappropriate. A panel meeting at this time would be contrary to the agency's existing regulations for convening an advisory

panel to evaluate a reclassification petition under 21 C.F.R. § 860.134(b)(3), which as explained earlier, should be applied to reclassification actions conducted under § 513(e)(2) of the Federal Food, Drug, and Cosmetic Act. At this point, there no credible scientifically evaluable data in the docket to present to the panel or which can meet FDA's standard for reclassification. This lack of data constitutes a deficiency that precludes an agency reclassification decision and bars convening an advisory panel under 21 C.F.R. § 860.134(b)(3). We urge FDA to continue to require premarket approval for these devices as the only means of reasonably assuring their safety and effectiveness in clinical use.

Sincerely,



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