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July 8, 2005

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

Re: FDA Docket 2005P-0121/CCP1;
Comments in Opposition to Reclassification Petition

Dear Sir or Madam:

The undersigned submits the following comments under 21 C.F.R. 860.134(b) in opposition to RS Medical's petition for reclassification of noninvasive bone growth stimulators (2005P-0121/CCP1).

I. Introduction

RS Medical has proposed the reclassification of noninvasive bone growth stimulators, products that utilize electromagnetic fields to stimulate bone growth. These products currently are approved for a variety of intended uses, including treatment of traumatic nonunion and congenital pseudoarthrosis, and as an adjunct to lumbar spinal fusion. Such devices are currently classified as class III devices in accordance with Section 513(f) of the Federal Food, Drug, and Cosmetic Act ("FDCA"). RS Medical's petition contends that special controls would be sufficient to provide a reasonable assurance of the safety and effectiveness for these devices as represented by the noninvasive bone growth stimulators currently approved by FDA through the premarket approval ("PMA") process and specifically cited in the petition. Consequently, RS Medical requests that the Food and Drug Administration ("FDA" or "the agency") reclassify these products to class II and regulate these devices as generic noninvasive bone growth stimulators.

2005P-0121¹

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We oppose RS Medical's petition to downclassify noninvasive bone growth stimulators from class III to class II as special controls are insufficient to provide a reasonable assurance of safety and effectiveness. RS Medical, in its proposed guidance document, "Class II Special Controls Guidance Document: Contents of Premarket Notification [510(k)s] for Noninvasive Bone Growth Stimulators" ("proposed guidance document"), has specifically identified "inconsistent or ineffective treatment" as a risk for this device. We agree with the petitioner that inconsistent or ineffective treatment represents a genuine risk of this technology. As outlined in detail in our comments, the literature cited by the petitioner clearly fails to demonstrate that consistent, effective treatment without PMA review is possible with the degree of scientific fidelity normally demanded by FDA.

There are myriad problems with the scientific data cited by the petitioner as support for reclassification. First, all the articles cited in the RS Medical petition fail to fully describe the treatment wave form utilized with the detail necessary for confident identification or reproduction. Similarly, study design is highly uneven, with most studies retrospective, uncontrolled, or involving few patients. Patient populations as described in the supporting studies are heterogeneous, with multiple potentially confounding variables, including concurrent, non-uniform surgical treatments and/or immobilization. Finally, both radiographic and clinical study endpoints are almost uniformly vague or nonexistent in most cited articles, and, where endpoints are defined, their evaluation is unexplained or seriously flawed.

II. Reclassification Standard

Under Section 513(e)(A), 21 U.S.C. § 360c(e)(2), of the FDCA, the 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"

Under Section 513(f)(1), 21 U.S.C. § 360c(f)(1), a device type, such as a noninvasive bone growth stimulator, that was not introduced for commercial distribution before May 28, 1976 is automatically designated as a class III device. However, section 513(f)(2), 21 U.S.C. § 360c(f)(2), states that "[a]ny person who submits a report under section 510(k) for a type of device that has not been previously classified under this Act, and that is [automatically] classified into class III under paragraph (1)," may request FDA to classify the device in accordance with the criteria established under the regulations. As noted, RS Medical argues for such a reclassification of

noninvasive bone growth stimulators from class III (Premarket Approval) to class II (Special Controls).

Section 513(a)(1)(B), 21 U.S.C. § 360c(a)(1)(B), sets forth the criteria for class II designation. It provides for class II designation if sufficient information exists to establish special controls that will provide a reasonable assurance of the safety and effectiveness of the device. Such special controls include “the promulgation of performance standards, postmarket surveillance, patient registries, the development and dissemination of guidelines (including those for the submission of clinical data in premarket notification submissions in accordance with section 510(k)), recommendations, and other appropriate actions as the Secretary deems necessary to provide such assurance.” 21 C.F.R. § 513(a)(1)(B), 21 U.S.C. § 360c(a)(1)(B). RS Medical has proposed certain special controls, relying on preestablished FDA standards and requirements, as well as proposing a draft of a guidance document for this particular device type that addresses design, labeling, and testing requirements.

We disagree with RS Medical’s assertion that such special controls would provide reasonable assurance of consistent, effective treatment. The literature that RS Medical relies upon to support this contention is flawed to the extent that it does not provided the required evidence that specials controls would provide reasonable assurance of safety and effectiveness. Given the lack of valid, scientific evidence in RS Medical’s petition, the continued class III designation for noninvasive bone growth stimulators as a class III device is appropriate.

III. Insufficient Publicly Available Information Exists To Provide A Reasonable Assurance Of Safety And Effectiveness Of Noninvasive Bone Growth Stimulators Based On Special Controls Alone

A. Significance of Wave Form Parameters in Demonstrating Effectiveness of Noninvasive Bone Growth Stimulators

Numerous clinical, animal and cellular studies have demonstrated that noninvasive bone growth stimulation waveform parameters (e.g. amplitude, frequency, etc) and the duration for which the resulting signals are applied exhibit specific thresholds and windows of

efficacy. Outside of these specific thresholds and windows, the signals do not elicit a biological response.^{1/}

For example, CC and CMF signals require very specific frequency windows in order to demonstrate efficacy. ^{2/ 3/ 4/} A deviation in the applied signal frequency of only 2 Hz can render a signal ineffective. ^{5/ 6/} Similarly, the amplitude of the applied signal is also crucial in achieving effectiveness. ^{7/ 8/} If signal amplitude is increased above an optimal range or window, it is no longer effective. Given the large variation in target tissue size, amplitude variation presents a serious constraint in the clinical applications of noninvasive bone growth stimulation. Specifically, varying target tissue size (*e.g.*, a femur fracture vs. a humeral fracture) results in a large range of electric field amplitudes within the tissue, some of which are effective and some of which are not. This greatly complicates scaling of a particular signal from cellular and/or animal studies to actual clinical application.

^{1/} See, *e.g.*, Pethica, B and Brownell J. (1988) The dose response relationship in PEMF therapy of ununited fracture. Bioelectrical Repair and Growth Society 8th Annual Meeting, Washington, DC.

^{2/} Brighton, CT, Hozack, WJ, Brager, MD, Windsor, RE, Pollack, SR, Vreslovic, EJ and Kotwick, JE. (1985) Fracture healing in the rabbit fibula when subjected to various capacitively coupled electrical fields. *J Orthop Res* 3:331-340.

^{3/} Fitzsimmons, R. J. Strong D.D., Mohan S. and Baylink, D. J. (1992) Low-amplitude, low-frequency electric field-stimulated bone cell proliferation may in part be mediated by increased IGF-II release. *J Cell Physiol* 150:84-89.

^{4/} Fitzsimmons, R. J., Ryaby, J. T., Magee, F. P. and Baylink, D. J. (1994) Combined magnetic fields increased net calcium flux in bone cells. *Calcif Tissue Int* 55:376-380.

^{5/} *Id.*

^{6/} Fitzsimmons, et al., *Cell Physiol.*

^{7/} Brighton, et al., *J Orthop Res.*

^{8/} Rubin, CT., McLeod, KJ. and Lanyon LE. (1898) Prevention of osteoporosis by pulsed electromagnetic fields. *J Bone Joint Surg Am* 71:411-417.

Signal exposure duration also significantly affects efficacy with different signals requiring differing minimal treatment durations to be effective. 9/ 10/ 11/ A fracture healing signal which was effective when applied for one hour per day in a rabbit fracture model (12/), a guinea pig osteoarthritis model (13/) and a rat ectopic bone formation model (14/), was ineffective at four and eight hours per day (15/). This sensitivity to signal exposure also substantially complicates development of clinically effective noninvasive bone growth stimulation wave forms.

B. Wave Form Parameters Are Unclear in the Petitioner's Articles

Complete, accurate information on the technology being evaluated is the foundation of clinical research. Without such information, there is simply no reliable way to determine what treatment is actually being tested or to reproduce an investigator's work. Thus, the results of any clinical trials conducted with inadequately described technology are meaningless, as what treatment is being evaluated is unknown.

9/ Aaron, R.K. and Ciombor, D.M. Personal Communication.

10/ Fredericks, D., Nepola JV., Baker, JT., Simon, B. and J Abbott. (2000) Effects of pulsed electromagnetic fields on bone healing in a rabbit tibial osteotomy model. *J Orthop Trauma* 14:93-100.

11/ Nepola JV., Fredericks, D., Simon, B. and J Abbott. (1996) Effect of exposure time on stimulation of healing in the rabbit tibial osteotomy model by a time varying pulsed electromagnetic field and by combined magnetic fields. Canadian Orthopaedic Research Society, 30th Annual Meeting. Quebec City, Canada.

12/ Fredericks, et al.

13/ Aaron, R.K., Ciombor, D.M., Capuano, A., Wang, S. and B.J. Simon. (2003) Modification of spontaneous osteoarthritis in guinea pigs: A morphological study. *Osteoarthritis and Cartilage* 11(6):455-62.

14/ Aaron and Ciombor, Personal Communication.

15/ *Id.*

As discussed in the previous section and described in the scholarly literature, the wave form parameters employed by noninvasive bone growth stimulators are complex, with multiple variables. ^{16/} Only a relatively specific set of these wave forms have demonstrated promise in promoting osteogenesis, as the petitioner acknowledges in their own cited literature. ^{17/} Certain of these fully characterized wave forms have been extensively tested in animals and humans, with the latter data largely confined to the PMA applications of EBI and other manufacturers of PMA-approved noninvasive bone growth stimulators. Outside of these well-defined wave forms, there is little evidence, proprietary or public, to demonstrate consistent, effectiveness treatment results.

The wave form most commonly described in the RS Medical petition's cited literature is the pulsed electromagnetic field ("PEMF"), which is utilized in 7 of 9 cited spine articles and 28 of 33 nonunion articles. The difficulty in characterizing these signals has been recognized by C.A.L. Bassett, a leading PEMF investigator who is the first author in 5 of the petitioner's cited articles. In a book chapter submitted as part of the petition, Dr. Bassett sounded a strong note of caution with regard to the descriptions of noninvasive bone growth stimulation wave forms found in the scholarly literature:

Until the pulse and other field characteristics (such as vector and uniformity) are precisely defined by all investigators, we shall continue to lack comprehensible communication. In order to reinforce this indictment, frequent reference has been made in the preceding sections [of this book chapter] to the high level of specificity of pulse characteristics required for effectiveness in augmenting bone formation and, probably, in any other given biological system. These characteristics are composed of pulse rise time, pulse amplitude, pulse width and shape, pulse "fall time," symmetry or asymmetry of energy

^{16/} Gupta T.D., Jain V.K., Tandon P.N. (1991) Comparative study of bone growth by pulsed electromagnetic fields. *Med Biol Eng Comput* 29(2):113-20.

^{17/} See, e.g., Bassett, C.A., Pilla, A.A., Pawluk, R.J. (1977) A non-operative salvage of surgically-resistant pseudarthrosis and non-unions by pulsing electromagnetic fields. A preliminary report. *Clin Orthop* 124:128-43 (noting that "it must be emphasized that the osseous responses [to the noninvasive bone growth stimulation] were obtained with only a relatively specific set of induced-current pulse parameters.").

distribution in the two phases of a pulse...and the repetition rate of the pulse []. 18/

To Dr. Bassett's point, the PEMF wave form utilized in EBI's own PMA-approved devices are characterized by more than 10 separate defining parameters. The wave form cannot be confidently characterized and reproduced with the 4 basic parameters cited in RS Medical's petition (burst length, pulse length, pulse amplitude, and frequency of repetition), and in its proposed guidance document.

The petition appears to rely heavily on a review article by Nelson, et al., for its description of noninvasive bone growth stimulator wave forms. 19/ Neither the Nelson article nor the information contained in any of the petitioner's 35 cited PEMF articles allows the accurate identification and/or duplication of the PEMF treatment wave form. Indeed, the lack of wave form specificity contained in these articles echo Dr. Bassett's own observations of the PEMF literature: "There has been little or no appreciation of the necessity to be specific in discussing the pattern of the energy." 20/ Furthermore, neither EBI or its competitor Orthofix, manufacturers of the only PMA-approved PEMF noninvasive bone growth stimulators cited in the petition, have ever published in the scholarly literature or otherwise placed in the public domain complete information on their respective wave form parameters. This includes the nonconfidential technical information supplied to clinical investigators who used the companies' products in the studies cited in the RS Medical petition.

There is little doubt that there is insufficient publicly available information to confidently ascertain the wave form employed in any of the petitioner's 35 cited PEMF articles, rendering the results described in those articles meaningless as reasonable evidence of consistent, effective treatment. Even assuming that this fundamental flaw is insignificant and allowing for the unscientific proposition that merely specifying a particular

18/ Bassett, C.A. (1978) Pulsing electromagnetic fields: A new approach to surgical problems. *In Metabolic Surgery*. 255-306 at 285. Edited by H. Backwald, R.L. Varco, Grune and Statton. This chapter may be found in the RS Medical petition at Attachment 8, Tab 4 [hereinafter "Bassett chapter"].

19/ Nelson F.R.T., et al. (2003) Use of physical forces in bone healing. *J Am Acad Orthop Surg* 11:344-54.

20/ Bassett chapter at 284.

PEMF device or providing a complete set of Nelson's four signal parameters adequately identifies a PEMF wave form, there are serious issues with the heterogeneity of devices described in the articles RS Medical cites to support its petition. In the 7 spine articles utilizing PEMF, there are no fewer than 4 different devices used, meaning that many of these disparate PEMF wave forms have only a single trial supporting their safety and effectiveness. Non-union PEMF data is even more disparate, with at least 7 different PEMF units identified and a total of 10 studies that did not identify a particular device or provide Nelson's four basic signal parameters. Accordingly, the actual clinical experience and publicly available clinical data cited by RS Medical for any given wave form is far smaller than implied in the petition.

Similar issues exist with the articles RS Medical cites to support the safety and effectiveness of the two competing methods of noninvasive bone growth stimulation, capacitive coupling ("CC") and combined magnetic field ("CM"). The petition cites only one article each for both CC and CM to support their use in lumbar spinal fusion, certainly not constituting overwhelming support for either technology. Furthermore, the only CM article provided for lumbar spinal fusion does not specify any wave form parameters, leaving its characterization completely uncertain. Nonunion data for CC and CM is equally sparse, with no articles whatsoever cited to support the use of CM in nonunion. Moreover, as described in detail below, all but one of the CC studies are small, with other experiment factors that call into serious question their scientific validity.

C. Clinical Trials Described in the Petitioner's Cited Articles Do Not Demonstrate That Special Controls Would Provide Reasonable Assurance of Safety and Effectiveness

The FDCA requires that medical devices be reasonably safe and effective for their approved indication(s). The valid scientific data necessary to demonstrate this safety and effectiveness is described at 21 C.F.R. § 860.7. Initially, this data is subject to a well-established hierarchy. 21 C.F.R. § 860.7(c)(2). At the top of this hierarchy are prospective, well controlled investigations, which are generally considered the "gold standard" of clinical research. These investigations are followed in descending order by partially controlled studies, studies and objective trials without matched controls, well-documented case histories conducted by qualified experts, and reports of significant human experience with a marketed device.

Under 21 C.F.R. § 860.7(e)(1), the valid scientific evidence contained in any study used for device classification must provide “reasonable assurance” that the device provides “clinically significant” results in a significant portion of the target population. The provisions found at 21 C.F.R. § 860.7(f) describe the principles that are recognized by both the scientific community and FDA as the essential elements of a well-controlled clinical investigation that provides valid scientific data. These elements include a method of subject selection that ensures that patients are suitable for the study, selected in a manner designed to minimize bias, and assures comparability between the test group and control. 21 C.F.R. § 860.7(f)(1)(ii). Furthermore, the methods of observation of results should be explained, including steps taken to minimize any possible bias on the part of observers or subjects. 21 C.F.R. § 860.7(f)(1)(iii). Comparison of treatment results with a control in a manner so as to facilitate quantitative evaluation is required. 21 C.F.R. § 860.7(f)(1)(iv). No treatment, placebo control, and active treatment controls are specifically described as suitable controls, as are historical controls. However, historical controls are specifically limited to instances “involving diseases with high and predictable mortality or signs and symptoms of predictable duration or severity.” Finally, echoing the very foundation of good science described earlier, namely the accurate identification of the treatment being evaluated, there is the requirement that “a well-controlled investigation shall involve the use of a test device that is standardized in its composition or design and performance.” 21 C.F.R. § 860.7(f)(2).

Further evidence of what constitutes valid science acceptable to FDA as reasonable evidence of safety and effectiveness, as these terms may be applied to the reclassification of a medical device, is found in two guidance documents: Clinical Data Presentations for Orthopedic Device Applications (“orthopedic guidance document”) and the Guidance Document for the Preparation of IDE’s for Spinal Systems (“spinal systems guidance document”). ^{21/} ^{22/} The spinal systems guidance document further expands on the study controls that are acceptable to the agency, specifically noting concurrent controls and literature controls. There is no indication that patients serving as their own controls is acceptable, with the agency observing that retrospective data has “many inherent limitations and,

^{21/} Guidance for Industry and FDA Staff. Clinical Data Presentations for Orthopedic Device Applications (December 2, 2004).

^{22/} Guidance for Industry and/or FDA Reviewers/Staff. Guidance Document for the Preparation of IDEs for Spinal Systems (January 13, 2000).

therefore disadvantages.” Furthermore, while literature controls are explicitly mentioned, the document notes specifically that:

[R]eferences from the literature are frequently incomplete in their reporting of relevant clinical parameters, such as indications for use, surgical techniques, and methods of evaluation. Therefore, comparison to the literature may be problematic with regard to specific endpoints.

While this statement is directed specifically at preparation of IDE’s for spinal systems, it has broad applicability to the use of the scholarly literature to demonstrate that special controls would provide a reasonable assurance of the safety and effectiveness of noninvasive bone growth stimulators, as will be outlined in our comments.

Both guidance documents indicate that any study used to establish safety and efficacy include sufficient subject numbers to adequately demonstrate the true effect of therapy, regarded as numbers sufficient to yield a statistically significant difference as compared to a control group. The orthopedic guidance document is specific in that for an IDE or PMA report, or an original PMA, FDA recommends a minimum of 85% follow-up of patients in each study cohort to maintain study power and avoid bias.

The orthopedic and spinal systems guidance documents indicate that both radiographic and clinical data be included as study endpoints. The spinal systems guidance document goes into considerable detail as to what the agency considers valid science in assessing study endpoints. For radiographic endpoints, the spinal systems guidance calls for specific definition of endpoints (evidence of fusion, lack of motion on flexion/extension radiographs) and the use of clearly defined imaging techniques to evaluate those endpoints. Actual image evaluation is to be performed by “at least two radiologists,” at least one of whom is masked (when possible) to avoid observation bias. The spinal systems guidance document is similarly demanding for clinical endpoint evaluation, emphasizing the need to assess both pain and function, and recommending several validated instruments to perform this somewhat subjective evaluation. The Oswestry Low Back Pain Disability Questionnaire, the Million Questionnaire, Waddell Disability Questionnaire, and the Quebec Disability Questionnaire are specifically noted. While the spinal systems guidance document may not be facially applicable to the trials supporting the use of noninvasive bone growth stimulators as described in the RS Medical petition, it is important to note that spinal systems trials often involve assessment of osseous fusion, the same radiographic endpoint used to evaluate success in nonunion. In any event, both guidance documents make it apparent that the agency expects

study endpoints to be clearly defined, the data used to evaluate those endpoints specified, and the evaluation of that data conducted in an objective manner.

As outlined in detail below, the literature cited in the RS Medical petition includes only 7 articles that describe prospective, controlled studies, with at least two of these articles unclear as to whether double-blinding was employed. Experimental design notwithstanding, the majority of petition articles describe studies with relatively few patients (30 studies with 100 or less patients enrolled, 18 studies with 50 or less patients) and a variety of confounding variables, such as pooling collections of disparate fusion or fracture sites, non-uniform previous therapy, and even a mixture of various concurrently conducted therapies, all of which may significantly impact the validity and broad applicability of study results. Even without these basic shortcomings in experimental design and study populations, there are serious issues in all the cited articles with undefined radiographic and clinical endpoints, no explanation of what data was used to assess these endpoints, and/or how this data was evaluated.

The significant issues with wave form characterization, experimental design, study population, and data collection and evaluation combine to destroy the scientific validity of all of the articles data cited by RS Medical in its petition. Thus, these studies are clearly inadequate to establish that special controls are sufficient to provide reasonable assurance of the safety and effectiveness of noninvasive bone growth stimulation as both an adjunct to lumbar spinal fusion and in nonunion of long and short bones.

1. Analysis of Lumbar Spinal Articles Cited by the RS Medical Petition

RS Medical cites 9 articles to support the safety and effectiveness of noninvasive bone growth stimulation to facilitate fusion in the lumbar spine following fusion surgery. A complete list of these articles is contained in the bibliography found in **Attachment 1** ("spine bibliography") and a summary of our analysis is contained in **Table 1**. All author citations in **bold font** in the following analysis refer to the spine bibliography in **Attachment 1**.

Table 1: Lumbar Spine Articles

Reference	Study Design	Randomized Placebo Controlled	Sample Size	Drop-Out	Device Type	Wave Form Type	No/ Incomplete Nelson Waveform Parameters ¹	Confounding Variables in Population ²	Radiographic Endpoint Issues ³	Clinical Endpoint Issues ⁴
1. Bose 2001	Retrospective		52 identified; 48 analyzed	n/a	Orthofix Spinal-Stim	PEMF	X		X	X
2. DiSilvestre and Savini 1992	Unclear; claimed as prospective in Petition but unclear from article		31	0	Unclear; article states "Igea-Stimulator"	PEMF	X	X	X	X
3. Goodwin, et al. 1999	Prospective	Randomized, double blind, placebo controlled	337 enrolled; 179 completed treatment	63 + 20 with only partial data	Bioelectron Spinalpak	CC		X	X	X
4. Jenis, et al. 1999	Prospective	Randomized	61 total; 22 control; 22 PEMF; and 17 Direct Current	0	Orthofix Spinal-Stim 8212 (PEMF) and EBI SpF-2T Stimulator (DC)	PEMF and Direct Current	X	X	X	X
5. Linovitz, et al. 2002	Prospective	Randomized, double-blind, placebo controlled	243 enrolled; 201 evaluated	42	Spina Logic/ OrthoLogic	CM	X	X	X	X
6. Marks 2000	Retrospective	Randomized	61	n/a	Orthofix Spinal-Stim	PEMF	X	X	X	X
7. Mooney 1990	Prospective	Randomized, double blind, placebo controlled	206	11	None specified; Petition states Orthofix, but this is unclear	PEMF	X	X	X	X
8. Simmons 1985	Prospective		13	0	EBI Bi-Osteogen	PEMF	X	X	X	X
9. Simmons, et al. 2004	Prospective		100	None specified	Orthofix Spinal Stim	PEMF	X	X	X	X

Definition of Column Headings

1. **No/Incomplete Nelson Wave Form Parameters.** The parameters for PEMF, CC, or CM wave forms as specified by Nelson are either absent or incomplete.
2. **Confounding Variables in Population.** Study population is non-uniform in terms of the mixture of sites treated, prior surgery or other therapy, and/or concurrent surgery or other therapy.
3. **Radiographic Endpoint Issues.** Endpoints for radiographic analysis are undefined, the techniques for obtaining those images not or incompletely defined, and/or evaluation methods not specified or potentially biased.
4. **Clinical Endpoint Issues.** Clinical endpoints are undefined, evaluation methods not or incompletely described, and/or evaluation methods potentially biased.

a. **Only Four Flawed Articles Describe Prospective, Randomized Studies**

Only 3 of the articles cited by RS Medical describe prospective, randomized, placebo-control studies; one additional article (**Jenis 23/**) employed a non-treatment arm apparently without placebo and did not specify whether a double-blind design was utilized. Important in any setting, randomization, placebo control, and blinding are crucial in the evaluation of low back pain, given the high potential for a placebo effect. 24/ 25/ Indeed, one of the petitioner's own uncontrolled spine articles noted only "moderate" concordance of 75.4% between radiographic and clinical findings. 26/ Given the high risk of bias, only these four prospective, randomized studies should be considered as possibly constituting evidence that special controls are sufficient to provide reasonable assurance of the safety and effectiveness of noninvasive bone growth stimulation as an adjunct to lumber spine fusion. These articles, by **Jenis, Goodwin, Linovitz and Mooney**, all have issues that seriously impact their applicability to reclassification of noninvasive bone growth stimulators. 27/

There are considerable issues in the study described by **Jenis**. As previously noted, no placebo control was utilized and it is unclear whether blinding was present, and if so, whether it was single or double blind. Apart

23/ Spine bibliography at 4.

24/ Brena, S.F., *et al.* (1980) Chronic back pain: electromyographic motion and behavioral assessments following sympathetic nerve blocks and placebos. *Pain* 8(1):1-10. [No difference in subjective pain reduction between active and sham injections.]

25/ Marchand, S., *et al.* (1994) Is TENS purely a placebo effect? A controlled study on chronic low back pain. *Pain* 56(1):99-106. [No difference in subjective pain reduction between active and sham TENS treatments.]

26/ Marks, R.A. (2000) Spine fusion for discogenic low back pain: outcomes in patients treated with or without pulsed electromagnetic field stimulation. *Adv Ther.* 17(2):57-67.

27/ Goodwin, Linovitz, and Mooney are found at citations 3, 5 and 7 of the spine bibliography, respectively.

from trial design, only 44 patients were involved in the trial's control and noninvasive bone growth stimulation arms (a third arm involved implanted bone growth stimulators), with only 22 patients in the PEMF treatment arm. These numbers are clearly inadequate by themselves to establish that special controls are sufficient to provide reasonable assurance of safety and effectiveness.

Three randomized, controlled spine studies had populations of more than 50 patients. **Goodwin** was the sole article to evaluate the use of CC as an adjunct to spinal fusion and analyzed 337 patients. However, 158 patients did not complete the trial and were not analyzed, raising a significant question of bias. In addition, the patients who did complete treatment were extremely heterogeneous with regard to prior surgeries and the surgical lumbar fusion procedure actually performed concurrent with the noninvasive bone growth stimulation treatment.

Linovitz reported a second sizeable randomized, controlled trial cited in the RS Medical petition. In the only cited trial to evaluate CM therapy, 243 patients were enrolled. Like **Goodwin**, **Linovitz** experienced a high drop out rate, with 42 patients failing to complete the trial and not included in the final analysis. Moreover, **Linovitz** looked exclusively at non-instrumented posterior lumbar fusion, an increasingly uncommon procedure in U.S. practice, severely limiting the applicability of the work to current practice. The trial was also heterogeneous with regard to the level (site) of lumbar fusion and the type of bone graft material employed. Given these considerations alone, **Goodwin** and **Linowitz** fail to provide the required evidence that special controls are sufficient to provide reasonable assurance of the safety and effectiveness of noninvasive bone growth stimulation that employ either the CC or CM treatment wave forms.

Mooney described the only large, prospective, double-blind placebo controlled trial focused on PEMF cited in RS Medical's petition. Unlike **Goodwin** and **Linowitz**, this trial of 206 enrolled patients had relatively low drop out, with only 11 patients failing to complete the trial. However, like the other prospective, controlled trials, **Mooney's** subjects had a wide variety of prior therapies and underwent a disparate collection of concurrent fusion treatments with regard to both level and technique. Particularly troubling is that 24 separate investigators took part in the trials, with a wide range of contributed cases (1 to 59 patients). Together, these confounding variables combine to impact scientific validity to the degree that no reasonable conclusion that special controls are sufficient to provide reasonable assurance of safety and effectiveness may be drawn.

b. The Remaining Non-Randomized, Uncontrolled Studies Cited Are Scientifically Inadequate to Support Reclassification

The 5 remaining articles in RS Medical's spine bibliography have significant issues with study design, patient population or both. The work described by **Bose, Di Silvestre and Simmons (1985 & 2004)** are non-randomized and do not employ a placebo control. ^{28/} **Bose and Mark** were both retrospective, with all the issues inherent in this type of experimental design. Three studies had low patient numbers, with **DiSilvestre and Simmons (1985)** reporting less than 40 patients each, and **Bose** reporting results on only 48 patients. Given the lack of placebo control alone, all of these articles fail to demonstrate that special controls are sufficient to provide reasonable assurance of safety and effectiveness. The retrospective nature and low numbers of several articles further impacts their scientific validity.

c. Essentially All Spine Articles Fail to Adequately Describe the Wave Form Used

At least 8 of the 9 spine articles suffer from a more fundamental flaw that was previously discussed, namely that the treatment wave form being evaluated is unknown. PEMF was the treatment wave form in 7 of the spine articles, including those by **Bose, Di Silvestre, Jenis, Marks and Simmons (1985 & 2004)**. In none of these trials were Nelson's four basic PEMF wave form parameters completely specified, let alone the more detailed information necessary to confidently identify and reproduce the signal. Similarly, the single article that describes the clinical use of a combined magnetic field (CM) fails to note a single wave form parameter, introducing complete uncertainty as what treatment was being administered. The lack of accurate knowledge of the treatment wave form being evaluated makes it impossible to determine that special controls are sufficient to provide reasonable assurance of safety and effectiveness from these trials.

^{28/} Bose, Di Silvestre, and Simmons (1985 & 2004) are found at citations 1, 2, 8, and 9 of the spine bibliography, respectively.

d. **All Cited Spine Articles Have Serious Shortcomings in the Evaluation of Radiographic and Clinical Endpoints**

In addition to shortcomings in experimental design, study populations, and wave form characterization, none of the lumbar spinal fusion articles cited by RS Medical provide a complete description of study endpoints, how data on those endpoints were acquired, and that how data were evaluated. Such information is crucial to a clinical trial's validity and is routinely required by FDA, as is evident from 21 C.F.R. § 860.7(f) and the spinal systems guidance document. Both studies described by **Simmons (1985 & 2004)** fail to provide precise radiographic endpoints. The techniques used to acquire radiographic data, such as imaging methods and views obtained, were not specified in the majority of spine studies cited, including those conducted by **Di Silvestre, Jenis, Mooney, and Simmons (1985 & 2004)**. The methods by which these images were evaluated, including information on the number, blinding and qualification of readers, were not addressed in the articles by **Di Silvestre** or **Marks**. Where these methods were specified, 3 studies had radiographic data interpreted by a single reader (**Bose, Jenis and Simmons (1985)**) and 4 additional studies (**Goodwin, Linovitz, Mooney, and Simmons (2004)**) had interpretation performed in part by the treating surgeon or other individuals with access to clinical data. Given these basic shortcomings, it is clear that none of the lumbar spinal fusion articles cited by RS Medical employ radiographic evaluations that would be acceptable to FDA in evaluating clinical trials for evidence that special controls are sufficient to provide reasonable assurance of safety and effectiveness.

The clinical evaluation of patients described in the RS Medical cited lumbar spinal fusion articles is, if anything, less rigorous than those employed in the radiographic evaluation. **Simmons (1985)** failed to specify any study-related clinical evaluation whatsoever, while articles by **Di Silvestre** and **Linovitz**, failed to precisely articulate their study's clinical endpoints. No article cited by the petitioner described the use of the validated clinical evaluation instruments specifically cited in the spinal systems guidance document. Who performed clinical assessments and how those assessments were performed was not specified in 6 of the 9 spine articles (**Bose, Di Silvestre, Jenis, Linovitz, Marks and Simmons (2004)**). Furthermore, in the 2 articles that did specify how the evaluation was performed (**Goodwin and Mooney**), the treating clinician assessed clinical outcome in both studies and one study further employed an undefined, retrospective telephone survey to assess clinical outcome (**Goodwin**). This clinical data does not meet scientific standards usually

employed by FDA in determining that that special controls are sufficient to provide reasonable assurance of safety and effectiveness.

2. Analysis of Nonunion Articles Cited by the RS Medical Petition

RS Medical cites 33 articles in its petition to support the contention that special controls are adequate to ensure the safety and effectiveness of noninvasive bone growth stimulation to facilitate union of fractures in long and short bones. A complete list of these articles is contained in the bibliography found in **Attachment 2** (“nonunion bibliography”). A summary of our analysis is contained in **Table 2**. All author citations appearing in **bold font** in the following analysis refer to the nonunion bibliography in **Attachment 2**.

Table 2: Nonunion Articles

Reference	Study Design	Randomized Placebo Controlled	Sample Size	Drop-Out	Device Type	Wave Form Type	No/Incomplete Nelson Wave Form Parameters ¹	Confounding Variables in Population ²	Radiographic Endpoint Issues ³	Clinical Endpoint Issues ⁴
1. Abced, et al. 1998	Prospective		16; tibia (6), radius (5), femur (3), and ulna (2)	0	Not specified	Capacitive Coupling		X	X	X
2. Adams, et al. 1992	Retrospective/ Case series		62 scaphoid fractures identified, 54 analyzed; proximal third in 10 patients, middle third in 41 patients, distal third in 3 patients	n/a	Not specified	PEMF	X	X	X	X
3. Bassett, et al. 1982 (JAMA)	Case series		1,078 selected from population > 6,000, 1007 available for final analysis; tibia (657), femur (189), humerus (52), radius and/or ulna (77), scapula (19), and others	0	Not specified	PEMF	X	X	X	X
4. Bassett, et al. 1982 (J Bone Joint Surg)	Retrospective		83; tibia (45), femur (25), humerus (8), radius and/or ulna (2), other (3)	n/a	Not specified	PEMF	X	X	X	X
5. Bassett, et al. 1977	Unclear; appears to be a case series		26 total; tibia (17), fibula (2), radius and/or ulna (3), femur (1), other (3)	0	EBI	PEMF	X	X	X	X

Reference	Study Design	Randomized Placebo Controlled	Sample Size	Drop-Out	Device Type	Wave Form Type	No/Incomplete Nelson Wave Form Parameters ¹	Confounding Variables in Population ²	Radiographic Endpoint Issues ³	Clinical Endpoint Issues ⁴
6. Bassett, et al. 1978	Unclear; appears to be a case series		108; tibia (52), femur (10), radius and/or ulna (5), congenital pseudoarthroses (35), wrist, ankle, and shoulder	0	Not specified	PEMF	X	X	X	X
7. Bassett, et al. 1981	Retrospective/ Case series		125; 127 tibia nonunions	n/a	EBI	PEMF	X		X	
8. Benazzo 1995	Prospective		21 patients, 25 stress fractures; navicular (13), 2 nd and 5 th metatarsal (7), tibia (2), fibula (2), talus (1)	0	Bioelectron Inc.	Capacitive Coupling		X	X	X
9. Brighton and Pollack 1985	Unclear; appears to be case series		20 patients, 22 nonunions; tibia (10), femur (4), radius (3), ulna (2), other (4)	0	Not specified	Capacitive Coupling		X	X	X
10. Brighton, et al. 1995	Retrospective		271; 167 Direct Current, 56 Capacitive Coupling, 48 bone graft; all tibia	n/a	Not specified	Capacitive Coupling and Direct Current		X	X	X
11. Caullay and Mann 1982	Unclear; claimed as prospective in Petition, but appears to be case series		4; tibial fracture (1) tibial/fibular fracture (1), pseudoarthrosis of the tibia (2)	0	EBI-supplied device "like Bassett's"	PEMF	X	X	X	X
12. Cheng, et al.	Retrospective		63 long bones, 50 non-unions; tibia (28), femur (10), humerus	n/a	"Bassett device"	PEMF	X	X	X	X

Reference	Study Design	Randomized Placebo Controlled	Sample Size	Drop-Out	Device Type	Wave Form Type	No/Incomplete Nelson Wave Form Parameters ¹	Confounding Variables in Population ²	Radiographic Endpoint Issues ³	Clinical Endpoint Issues ⁴
1985			(8), ulna (2), radius (2); 13 other							
13. Colson, et al. 1988	Prospective		32 long bones; tibia (22), femur (4), radius and/or ulna (4), humerus (3)	None noted	Not specified	PEMF	X	X	X	X
14. Delima and Tanna 1989	Unclear; claimed as prospective in Petition, but unclear from article		29; tibia and fibula (15), humerus (7), femur (6), radius (1)	1	Not specified	PEMF	X	X	X	X
15. Dhawan, et al. 2004	Prospective	Randomized, surgical control, no placebo	70 enrolled, various fusions of hindfoot; subtalar, talonavicular, and calcaneocuboid	6	EBI	PEMF	X		X	X
16. Fontanesi, et al. 1983	Unclear; claimed as prospective in Petition, but unclear from article		35 fractures, 33 patients; tibia (9), femur (6), humerus (4), ulna (4), radius (3), other (9)	0	BioStim	PEMF	X	X	X	X
17. Frykman, et al. 1986	Retrospective		50 scaphoid fractures, 44 analyzed; proximal third (8), middle third (33), distal third (3)	n/a	EBI, Bi-Osteogen	PEMF	X	X	X	X
18. Garland, et al. 1991	Prospective; 131 investigators		181 enrolled (193 fractures), 126 analyzed (135 fractures); tibia (50), femur (15), scaphoid (13), ulna (10), ankle (10), fibula (8), humerus (7), other (22)	55	Unclear; Petition states Orthofix	PEMF		X	X	X
19. Gossling, et al. 1992	Retrospective literature review		~2000 patients comprised the numerous studies analyzed; all tibia	n/a	Multiple	PEMF	X	X	X	X

Reference	Study Design	Randomized Placebo Controlled	Sample Size	Drop-Out	Device Type	Wave Form Type	No/Incomplete Nelson Wave Form Parameters ¹	Confounding Variables in Population ²	Radiographic Endpoint Issues ³	Clinical Endpoint Issues ⁴
20. Heckman, et al. 1981	Retrospective		174 identified, 149 analyzed; tibia (94), femoral shaft (31), humerus (9), radius and/or ulna (10), and others	n/a	EBI	PEMF	X	X	X	X
21. Hisenkamp, et al. 1985	Retrospective		308 cases reviewed; tibia (148), femur (55), humerus (19), ulna (16), other (34)	n/a	EBI	PEMF		X	X	X
22. Holmes 1994	Retrospective		9 selected from an indeterminate pool; all proximal 5 th metatarsal (Jones fractures)	n/a	Not specified (coil device)	PEMF			X	X
23. Ito and Shirai 2001	Prospective		30; all tibia	0	"Similar to the one described by Bassett"	PEMF	X	X	X	X
24. Madronero, et al. 1988	Unclear; claimed as prospective in Petition; claimed to be "pilot trial"		11 enrolled, 10 assessed; all radius	1	Not specified	PEMF	X	X	X	X
25. Marcer, et al. 1984	Retrospective		147 evaluated from a pool of ~9,000; tibia (102), femur (32), humerus (13)	n/a	EBI	PEMF		X	X	X
26. Meskens, et al. 1990	Retrospective		34 reviewed; tibia (15), femur (9), humerus (5), other (5)	n/a	"Apparatus used was described by Bassett (1977)"	PEMF	X	X	X	X
27. Meskens, et al. 1988	Retrospective		57; right and left tibia	n/a	"System used was that described by	PEMF	X	X	X	X

Reference	Study Design	Randomized Placebo Controlled	Sample Size	Drop-Out	Device Type	Wave Form Type	No/Incomplete Nelson Wave Form Parameters ¹	Confounding Variables in Population ²	Radiographic Endpoint Issues ³	Clinical Endpoint Issues ⁴
					Bassett (1977) ⁵					
28. O'Connor 1985	Prospective		54 enrolled; tibia (30), humerus (7), femur (9), radius (6), other (2); 32 completed treatment at time of writing	2	EBI, Bi-Osteogen	PEMF		X	X	X
29. Scott and King 1994	Prospective	Randomized, double blind, placebo controlled	23 enrolled, 21 analyzed; tibia (15), ulna (4), femur (2)	2	Bioelectron, Orthopak	Capacitive coupling		X	X	X
30. Sedel, et al. 1982	Prospective		39 enrolled; tibia (20), femur (11), humerus (4), radius and/or ulna (3), clavicle (1)	2	EBI, device created in collaboration with Bassett	PEMF	X	X	X	X
31. Sharrard 1990	Prospective	Randomized, double blind placebo controlled	51 fractures enrolled; all tibial shaft	6	Not specified	PEMF	X		X	X
32. Sharrard, et al. 1982	Retrospective		52 patients, 53 nonunions; tibia (30), femur (7), ulna (6), radius (4), humerus (1), other (5)	n/a	Not specified	PEMF	X	X	X	X
33. Simonis, et al. 1984.	Retrospective		15; tibia (11), ulna (1), radius/ulna (2), knee arthrodesis (1)	n/a	St. Thomas Hospital bone stimulator combined with Denham external fixator	PEMF		X	X	X

Definition of Column Headings

1. **No/Incomplete Nelson Wave Form Parameters.** The parameters for PEMF, CC, or CM waveforms as specified by Nelson are either absent or incomplete.
2. **Confounding Variables in Population.** Study population is non-uniform in terms of the mixture of sites treated, prior surgery or other therapy, and/or concurrent surgery or other therapy.
3. **Radiographic Endpoint Issues.** Endpoints for radiographic analysis are undefined, the techniques for obtaining those images not or incompletely defined, and/or evaluation methods not specified or potentially biased.
4. **Clinical Endpoint Issues.** Clinical endpoints are undefined, evaluation methods not or incompletely described, and/or evaluation methods potentially biased.

a. **Only Three Nonunion Articles Describe Prospective, Randomized Controlled Studies**

Only 3 of the 33 of the nonunion articles cited described prospective, randomized controlled studies and, among these trials, a number of serious deficiencies in the study design and conduct are evident. For example, **Scott** reported a sample of only 21 patients, 10 of whom received active treatment of a wide variety of fracture sites (tibia, ulna and femur). ^{29/} In addition to the small sample size and disparate treatment sites, of the 11 placebo-controlled patients, all but one was treated for a fracture of the tibia, calling into question the validity of the control group.

Similarly, the prospective, randomized controlled study by **Sharrard (1990)** analyzed only 45 patients. ^{30/} The cases were derived from 16 separate centers, with each center contributing only 1 to 11 cases over the course of 6 years. This wide dispersal of a small number of patients across numerous sites raises the risk of non-uniformity in both the treatment provided and evaluation methods used. More specifically, **Sharrard** does not specify the type of device used in the study or provide even the Nelson wave form parameters for the signal utilized. Moreover, this trial also suffered from significant issues of data collection and evaluation that impacted essentially all cited nonunion articles, as discussed further below.

Dhawan evaluated 64 patients in a prospective, randomized control study of hindfoot fusion. ^{31/} Though RS Medical apparently cites this work to demonstrate that special controls are sufficient to provide reasonable assurance of the safety and effectiveness of noninvasive bone growth stimulation for fracture nonunion, the trial was actually designed to evaluate whether bone growth stimulation would speed fusion following hindfoot arthrodesis. While the results indicated that noninvasive bone growth stimulation does indeed accelerate fusion, it is important to note that fusion occurred in all control patients as well, albeit several weeks after the treated group. Accordingly, this article appears to have demonstrated the validity of a scientific theory that is not directly applicable to the treatment the petition is attempting to support.

^{29/} Nonunion bibliography, citation 29.

^{30/} Nonunion bibliography, citation 31.

^{31/} Nonunion bibliography, citation 15.

b. RS Medical's Petition Inaccurately Characterizes Multiple Nonunion Studies As "Prospective"

While RS Medical cites several trials as "prospective" in its petition, we note that many of these articles actually describe case studies that lacked definitive evidence of an organized, prospective nature and even may have been subject to post hoc patient selection. *See, e.g., Caullay, Bassett (JAMA, 1982), Bassett (1978), Bassett (1977).* ^{32/} Only 10 of the studies involved actual prospective evaluations and, with the exception of the three controlled studies previously discussed, none used true control groups. The explanations offered by the authors for their lack of controls were weak. For example, **O'Connor** stated that use of a control group was unnecessary because "pertinent evidence on the failure of immobilization alone and its success in combination with PEMFs has already been generated in beagle dogs." ^{33/} **Bassett (1978)** purported that patients served as their own "controls" since each had experienced failure of a prior conservative or operative treatment of the fracture. Notably, the petitioner appears to agree with this unscientific proposition, classifying studies as controlled in the petition while specifically noting that the patient served as his or her own control.

c. The Majority of Nonunion Articles Describe Small Populations or Suffer From Confounding Variables

More than half of the nonunion articles (17 of 33) involved sample sizes of less than 50 patients analyzed. Better than two-thirds (24 of 33) of the articles involved sample sizes of less than 100 patients analyzed. In addition, the case mixes described in nearly all of the articles (29 of 33) was remarkably heterogeneous in terms of the type of fracture (open or closed), location of the fracture site, and/or number and type of prior surgeries involving that site. Thus, the fractures analyzed in each study may have reacted in very different ways to the treatment provided, limiting the broad applicability of the results. This non-uniform case mix compounds the

^{32/} Caullay, Bassett (JAMA 1982), Bassett (1978), and Bassett (1977) may be found at citations 11, 3, 6, and 5 of the nonunion bibliography, respectively.

^{33/} Nonunion bibliography, citation 28.

problems posed by a small sample size, as none or very few of the patients in each study might have had fractures truly comparable to one another.

Further obscuring the results was the existence of several confounding variables, such as concomitant treatments and variable time between the onset of injury and initiation of treatment. Over one-third of the articles (12 of 33) described subjects undergoing concomitant treatments, including bone grafting, cast immobilization, internal and external fixation. Of particular note is the fact that internal fixation is considered a treatment standard for nonunion and may well have contributed to union in these cases without the addition of noninvasive bone growth stimulation. In the vast majority of cases, investigators failed to control for these variables. Additionally, in some cases there was indication of a relatively short time between fracture onset and treatment with noninvasive bone growth stimulation, *e.g.*, 6 to 9 months. Fractures treated so soon after onset raise particular concerns in uncontrolled studies, as these fractures may well have healed spontaneously or with the concomitant treatment used regardless of the application of noninvasive bone growth stimulation.

In an article cited in the RS Medical petition, **Abeed** summed up, with respect to their study, the variety of weaknesses in experimental design that appear to exist in the vast majority of articles cited by RS Medical. ^{34/} As **Abeed** stated, “[t]he nature of the present study made it impractical to have a control group that did not receive CCEST [capacitively coupled electrical stimulation] or was given an alternative form of treatment because of the great differences in the history, treatment, and duration of the fracture nonunions of the individual subjects and the large numbers of subjects who would be required to verify that CCEST was or was not the most effective means of promoting healing.” Considering the poor experimental design inherent in the studies cited by RS Medical, these studies certainly fail to demonstrate that special controls would provide reasonable assurance of the safety and effectiveness of noninvasive bone growth stimulation for the treatment of nonunions.

Even studies that were ostensibly sound in certain respects, such as the use of a relatively large sample size, suffer from other serious deficiencies. For example, **Bassett (JAMA 1982)** conducted a case study analyzing the outcome of 1,078 patients treated at multiple institutions. Although RS Medical’s petition claims this study as having been prospective, the article describes a retrospectively selected, uncontrolled, multicenter case

^{34/} Nonunion bibliography, citation 1.

series evaluation. The authors state that the population of 1,078 patients represented "all confirmed final results" from over 6,000 patients who had been treated or were in treatment at the time of the study. However, the authors fail to explain how they selected this subset of patients for evaluation. Failure to explain how results for almost 5,000 patients were retrospectively excluded from analysis raises serious question as to the representative nature of the study population and, by extension, the validity of the data generated. Furthermore, most of the patients entered the program by referral from either the "responsible local orthopedic surgeon" or by private consultation at Columbia-Presbyterian Medical Center, one of the three major geographical categories established for the study. The article also is unclear as to what criteria were used to make these referrals, raising the issue of selection bias. Finally, the study analyzes a widely heterogeneous mix of fracture sites, including the tibia, femur, humerus, radius/ulna, scapula, clavicle, metatarsals, hip, knee, ankle, shoulder, and wrist, with considerable non-uniformity with regard to prior treatment.

Garland also reported on a relatively large sample of 193 nonunions in an uncontrolled study conducted by 131 investigators at 74 institutions. ^{35/} Apart from the obvious potential for bias with so many investigators and sites, the trial included a heterogeneous mix of long and short bone fractures, as well as failed fusions. A variety of prior surgeries were also performed on 81% of the fractures, with an average of 2 procedures per fracture. Thus, as with **Bassett (JAMA 1982)**, this study contains a widely heterogeneous case mix with various fracture sites and non-uniform prior and concomitant treatments.

Other studies with relatively large sample sizes demonstrated similar deficiencies in study design. For example, **Heckman** evaluated 149 patients in a retrospective, uncontrolled trial. ^{36/} Investigators evaluated fracture sites as varied as the tibia, femoral shaft, humerus, radius/ulna, ischium, metatarsal, and femoral neck. In addition, 19 of the patients had some form of surgery concurrent with the initiation of noninvasive bone growth stimulation treatment.

Together, the shortcomings in experiment design and study populations alone destroy the scientific validity of the nonunion data cited in the RS Medical petition. On these grounds alone, these clinical data do not

^{35/} Nonunion bibliography, citation 18.

^{36/} Nonunion bibliography, citation 20.

demonstrate that special controls are sufficient to provide reasonable assurance of safety and effectiveness as required for reclassification of noninvasive bone growth stimulators for treatment of nonunion.

d. Treatment Wave Forms are Unclear in the Vast Majority of Nonunion Studies

Like the articles cited by RS Medical to demonstrate the safety and effectiveness of noninvasive bone growth stimulation as an adjunct to surgical spinal fusion, it is unclear in most, if not all, of the nonunion articles as to what treatment wave form was being evaluated. Twenty-eight of 33 cited nonunion articles focus on the use of PEMF technology, none of which describe the treatment wave form in the detail that Bassett deemed necessary to fully characterize and reproduce treatment signals. ^{37/} Furthermore, 21 PEMF articles fail to cite even the 4 basic wave parameters described by Nelson and promoted by the petitioner as constituting adequate description parameters, while 14 articles contain no description of the PEMF device actually used. Given that confident identification of the treatment wave form is not possible in any of the petition's PEMF articles, they cannot possibly establish that special controls are sufficient to provide reasonable assurance of safety and effectiveness.

Five articles detail use of CC technology in noninvasive bone growth stimulation. All of these articles include the limited wave form parameters described by Nelson for CC technology. Even assuming that these wave forms are adequately characterized, issues with experimental design, study population, and endpoint definition and evaluation preclude the data from these trials from raising to the level required to support device reclassification.

As previously noted, no articles cited in the RS Medical petition address the use of CM wave forms in the treatment of nonunion. Given that the CM wave form has different characteristics and properties than either PEMF or CC, the petitioner clearly has failed to demonstrate that special controls are sufficient to provide reasonable assurance of the safety and effectiveness of CM technology for the nonunion indication.

^{37/} Bassett chapter at 285.

e. **All Nonunion Study Trials Have Flawed Evaluation of Radiographic and Clinical Endpoints**

Even if the experimental design, study population, and wave form characterization in the petitioner's cited nonunion articles are scientifically adequate, there are serious issues with all the trials' radiographic and clinical endpoints. Initially, 12 articles failed to clearly articulate the study's radiographic endpoint (**Abeed, Bassett (1977), Caully, Cheng, Colson, Fontanesi, Frykman, Gossling, Heckman, Hinsenkamp, Holmes, Madronero, and Simonis**), raising baseline questions as to what the investigators viewed as radiographic fusion. ^{38/} Even where radiographic endpoints were specified, there were serious shortcomings in descriptions in image data acquisition and interpretation.

As indicated in FDA's spinal systems guidance document, a document that address the radiographic assessment of osseous fusion, good science dictates that the imaging techniques and views obtained be specified when acquiring radiographic clinical data. In only 5 of 33 articles are the techniques used to obtain imaging data defined, leaving unacceptable ambiguity as to what was being interpreted in the overwhelming majority of the petition's cited clinical trials. Even where acceptable techniques are fully specified, good science requires image interpretation by at least two observers, preferably blinded and certainly without any bias to study outcome. FDA's spinal system guidance document reflects this concern, specifying that at least two radiologists, at least one of whom is blinded (if possible), should interpret imaging data. The rationale for this position is scientifically straightforward. Radiologists are specialists in the interpretation of medical images, having undergone extensive training to ensure their ability to objectively interpret radiographs and other imaging modalities. In addition, diagnostic radiologists do not typically engage in surgical or other types of therapeutic treatment, nor do they have a clinical practice where patients are seen, both factors minimizing the potential for bias when evaluating images in the course of clinical trials.

Only 4 of 33 cited nonunion articles describe how imaging data was interpreted, leaving insufficient information available to evaluate the science underlying the evaluation of images in 29 trials. Perhaps as

^{38/} Abeed, Bassett (1977), Caully, Cheng, Colson, Fontanesi, Frykman, Gossling, Heckman, Hinsenkamp, Holmes, Madronero, and Simonis may be found at citations 1, 5, 11, 12, 13, 16, 17, 19, 20, 21, 22, 24, and 33 of the nonunion bibliography, respectively

troubling, none of the 4 articles that do describe imaging evaluation techniques utilized evaluation methods that would satisfy the basics of valid science as illustrated in the spinal systems guidance document. Imaging data in **Scott** was interpreted by a single “senior investigator,” who may have had access to clinical data. In **Dhawan**, interpretation was performed by a single radiologist. **Sharrard** utilized a radiologist and an orthopedic surgeon, each using different scales. Not surprisingly, there was a substantial difference of opinion between the radiologist and the orthopedic surgeon, with the radiologist considering a total of 5 of 20 active subjects as “full” or “probable” union, and the orthopedic surgeon judging 9 subjects “united.” Though downplayed in the article, these different conclusions illustrate the danger of having individuals engaged in clinical practice interpret imaging, as such individuals may be more inclined to see positive results with a therapy they may hope to apply to their own patients. Similarly, **Garland** had three “independent” orthopedic surgeons evaluate the trial’s images, without the involvement of any radiologist whatsoever.

Clinical endpoints data in RS Medical’s cited nonunion articles is even more seriously flawed. Twelve articles fail to specify clinical endpoints, raising an issue of whether clinical data was even obtained (**Abeed, Adams, Brighton (1985 & 1995), Cheng, Colson, Delima, Dhawan, Fontanesi, Hinsenkamp, Holmes and O’Conner**). ^{39/} Of the articles that did describe clinical findings, little or no information was given on how these findings were measured and/or who obtained the data. Like the handful of radiographic evaluation methods described in the nonunion articles, the only clinical evaluations that were described also raise serious questions. For example, **Bassett (J Bone Joint Surg 1982)** gives clinical endpoints as lack of motion at the fracture site on stress, no local tenderness at that site, and no pain on ambulation. ^{40/} However, there are no criteria given for what constitutes motion and with what force, or how tenderness or pain were assessed. In **Scott**, clinical data was obtained by a “junior investigator” almost certainly involved in the clinical care of the subjects, raising questions of bias. **Simonis** described an examination of the affected site under anesthesia, but did not specify who performed this examination or what objective criteria constituted motion. Together with the serious issues with radiographic evaluation, the fundamental flaws in the evaluation of the clinical endpoints translate to an unequivocal lack of evidence that special controls could reasonably assure safety and effectiveness.

^{39/} Adams, Brighten (1985), Brighten (1995), and Delima may be found at citations 2, 9, 10, and 14 of the nonunion bibliography, respectively.

^{40/} Nonunion bibliography, citation 4.

IV. CONCLUSION

Reclassification of a class III medical device such as noninvasive bone growth stimulators to class II requires an FDA determination that special controls would provide reasonable assurance of safety and effectiveness. The clinical data contained in RS Medical's reclassification petition fail to provide the agency with the evidence necessary to make this crucial determination. To the contrary, objective analysis of trials described in the petition's literature reveals multiple scientific shortcomings that render the reported results unpersuasive as support for the reclassification of noninvasive bone growth stimulators from class III to class II.

RS Medical portrays the treatment wave forms of PEMF, CC, and CM as easily characterized and duplicated. This is simply not the case. The complexity of these signals, together with a lack of their full description in essentially all of the petition's cited articles, mean that it is uncertain what treatment was administered and analyzed. This ambiguity alone as to what device was actually evaluated makes the petitioner's data useless to demonstrate that special controls are sufficient to provide reasonable assurance of the safety and effectiveness.

Beyond this fundamental flaw, the science in the cited articles does not rise to the level generally recognized by FDA as constituting valid scientific evidence that special controls would provide reasonable assurance of safety and effectiveness. See 21 C.F.R 860.7(e)(2),(f). Only a handful of the cited trials describe large, prospective, randomized controlled investigations typically considered to constitute adequate, well-controlled studies by the agency. See 21 C.F.R. 860.7(c)(2). Of the large, non-randomized trials cited in the petition, many employ less than robust, and occasionally suspect, experimental design. Most of the smaller trials would constitute little more than pilot study data in a typical clinical trial setting. Virtually all articles describe potentially confounding, uncontrolled variables, such as various sites of injury or surgery, inconsistent prior treatment, and concurrent treatment. Like the fundamental issue with wave form characterization, the shortcomings in experimental design and study population are pronounced enough to destroy the validity of results for the purposes of RS Medical's reclassification petition.

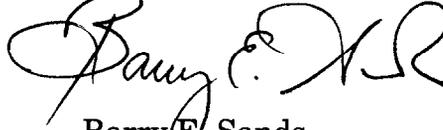
The pronounced impact of the uncertain wave form characterization, poor experimental design and confounding variables in the study populations notwithstanding, the literature cited by RS Medical fails to define and assess both radiographic and clinical endpoints in the sound scientific manner consistently applied by the agency. See 21 C.F.R. 860.7(f). Radiographic endpoints, acquisition of images used for evaluation, and/or interpretation of those images were either unspecified or scientifically flawed in every article cited by the petitioner. Similarly, clinical assessment was made without the use of fully described assessment instruments and/or a complete description of how those evaluations were obtained in every trial in RS Medical's petition. RS Medical recognizes the need for accurate, objective radiographic and clinical data in the evaluation of noninvasive bone growth stimulators in its petition, and there is little doubt that the articles cited to support these crucial assessments provide neither.

Overall, RS Medical has failed to demonstrate that special controls are sufficient to provide reasonable assurance of the safety and effectiveness of noninvasive bone growth stimulation as a treatment of established nonunion fractures acquired secondary to trauma (excluding vertebrae and flat bones), or as an adjunct to lumbar spine fusion. Furthermore, the special controls proposed by RS Medical based on this flawed data are clearly inadequate to ensure that an accurate treatment wave form is specified, much less delivered to patients. Given these realities, only the PMA process is adequate to continue to ensure the safety and effectiveness of noninvasive bone growth stimulators.

Compared to the 510(k) process, PMAs require a more detailed and thorough product evaluation, typically including extensive clinical data. This rigorous process can ensure that a fully characterized, uniform noninvasive bone growth treatment wave form is utilized in all patients in any given trial. In well-controlled trials to support PMA applications, experimental design and study populations can be crafted to minimize potential bias. Perhaps most important, radiographic and clinical endpoints can be developed and assessed in the manner necessary to ensure scientific validity. Allowing downclassification of noninvasive bone growth stimulators based on the special controls advocated in the RS Medical petition would destroy these essential protections and potentially lead to marketing of products whose true effects on bone growth are not completely known.

We, therefore, oppose RS Medical's petition to downclassify noninvasive bone growth stimulators and urge the Commissioner to require premarket approval for the device as the only means of reasonably assuring their safety and effectiveness in clinical use.

Sincerely,

A handwritten signature in black ink, appearing to read "Barry E. Sands". The signature is fluid and cursive, with a large initial "B" and "S".

Barry E. Sands
Vice President,
Regulatory, Clinical and Quality
Assurance

S/s

Enclosures

cc: Jonathan S. Kahan
John J. Smith, M.D., J.D.