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Subject: FDA Docket 2005P-0121/CCP 1
Comments in Support of the Reclassification of
Non-invasive Bone Growth Stimulators
Orthopaedic and Rehabilitation Devices Panel Mtg. June 2, 2006

To whom it may concern:

I wish to convey my support for the reclassification of bone growth stimulators (BGS) from Class III to Class II. My reasons and my credentials follow.

I am Arthur Pilla, PhD, co-inventor of the first non-invasive BGS device to receive FDA approval for the treatment of non-union and delayed union bone fractures via the PMA process. I am also the co-founder of one of the current manufacturers of non-invasive BGS devices, with whom I severed all ties in the early 1980's. I have, however, actively continued my research on EMF effects of tissue growth and repair, which started in 1969, as a member of the faculty of the Departments of Biomedical Engineering at Columbia University, and Orthopaedics at Mount Sinai School of Medicine, both in New York, NY, as well as an industrial consultant.

In the early 1970's, we were, of course, overjoyed at the first clinical successes of non-invasive BGS treatments. However, there were many questions surrounding this success, particularly regarding the mechanism of action. Since that time the mechanism of action is much better understood, particularly for BGS devices which act via induced electric fields at the tissue target. In addition, hundreds of thousands of patients have been successfully treated with non-invasive BGS devices with no reported adverse effects over the past three decades.

I am attaching to this letter a final peer-reviewed preprint of my latest review article entitled "Mechanisms and Therapeutic Applications of Time-Varying and Static Magnetic Fields" (to appear in the Handbook of Biological Effects of Electromagnetic Fields, 3rd Edition, Barnes F, Greenebaum B, eds, CRC Press, 2006). Therein I report the latest clinical and basic research results on EMF tissue growth and repair. I have also attempted to provide enough evidence to

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allow the reader to understand which characteristics of BGS waveforms are important for adequate dosimetry.

All clinical and basic biological effects obtained with the currently approved BGS devices are due either to the induced electric field, whether inductively or capacitively coupled, or to a combined static and low frequency magnetic field operating via the Lorentz force. The mechanism of action of the former is much better understood than that for the latter magnetic field devices. These mechanisms are sufficiently well understood that it is now clear the waveform characteristics of the FDA-approved BGS devices are not so unique that they preclude the possibility other waveforms could provide equal or even better physiological effects. For example, one such waveform is delivered by a BGS device produced in Italy. This device induces a signal with a peak electric field in the same range as the FDA-approved BGS devices, but, instead of a pulse burst repeating at 15/sec, it consists of a single asymmetrical bipolar pseudo rectangular pulse ($\approx$ 0.3/7 msec) repeating at 75/sec. This BGS device has the necessary local regulatory approvals and has been extensively and successfully utilized for human fracture repair for at least 20 years in Europe. There are many double blind clinical studies showing efficacy with this device which are cited in my CRC review. There are also many failed clinical and basic studies using devices with waveform characteristics well outside those which are known, or could be predicted, to produce the desired biological and physiological effects. There are detailed analyses in my CRC review which can help explain why a given EMF waveform may or may not be effective, based, at least in part, on the degree to which the waveforms can modulate kinetics in the pertinent mechanistic pathways.

I have reviewed the draft of the Proposed FDA Guidance Document Entitled "Class II Special Controls Guidance Document: Contents of Premarket Notifications [510(k)s] for Non-invasive Bone Growth Stimulators" and am pleased to see it is already very comprehensive. I would like to offer the following suggestions to make it even more comprehensive. Documentation for all of the technical suggestions may be found in my CRC review.

1) **Section 4a *Identification***. The definition of BGS could be modified to the following in light of the various PMA approvals over the years: **A Non-invasive Bone Growth Stimulator provides stimulation through electrical and/or magnetic fields to promote osteogenesis to facilitate the healing of nonunion fractures, failed fusions, congenital pseudoarthroses and lumbar and cervical spinal fusions. A nonunion is considered to be established when the fracture site shows no visibly progressive signs of healing. BGS is used as a spinal fusion adjunct to increase the probability of fusion success and as a nonoperative treatment for salvage of failed spinal fusions, where a minimum of nine months has elapsed since last surgery, and as an adjunct to cervical fusion surgery in patients at high risk for non-fusion.**

2) **Section 4b *Classification*.** Table 1 is incomplete and contains several errors. It could be changed using the following considerations (refer to my review for supporting references).
   a) BGS devices which achieve their clinical results via induced electric fields do so whether the field is delivered via capacitive or inductive coupling.

b) Coils for inductive coupling are typically placed over the treatment site. Electrodes for capacitive coupling are typically placed either flanking the treatment site, if accessible, or at some distance proximal and distal to provide for adequate depth of penetration.

c) Peak induced current should not be used to define whether a signal is efficacious, only whether it is safe. This is because induced current/current density depends upon the electrical characteristics of the target which, in turn, depend upon individual anatomical factors, and which can change significantly during healing. The proposed Guidance Document does an excellent job to provide for the safety of BGS signals.

d) The rectangular-type induced electric field waveforms already have approved ranges as follows: pulse widths of 10 - 300 μsec; burst durations of 4 - 50 msec; and peak induced electric fields from 0.1-100 mV/cm.

e) Effective peak induced electric fields for both capacitively and inductively coupled BGS waveforms range from 0.1 – 100 mV/cm provided this is achieved with waveforms having primary frequency components in the 0.01 – 100 kHz range.

In light of 2 above, Table 1 could then look like the following:

Signal type	Waveform	Tissue electric field
Sinusoidal	10-100 kHz Sine wave Continuous 5-50 % Duty cycle	0.1 - 100 mV/cm
Pulse	Pulse duration: 1-300 μsec Burst duration: 0.1-50 msec Repetition rate: 1-20 Hz	0.1 - 100 mV/cm
Combined Magnetic Fields	76.6 Hz sinusoidal 40 μT peak-to-peak AC magnetic field superimposed on 20 μT DC magnetic field	NA Magnetic field effect

I realize the ranges of proposed waveform values extend somewhat beyond those for currently approved BGS devices. However, they are given with the knowledge that the frequency and amplitude ranges are all within effective ranges, based on the current understanding of the mechanism of action. These parameter ranges may offer the FDA the capacity to provide manufacturers the opportunity to propose new, and perhaps improved, waveform characteristics for a particular BGS device. Of course, this may result in the requirement for supporting animal or clinical evidence to show the proposed signal is efficacious, but this is certainly manageable in the 510(k) context.

The remainder of the proposed Guidance Document is clear and to the point. It already goes a long way to provide manufacturers proper and reasonable guidance to submit a BGS device for 510(k) clearance. In spite of this, I am aware of the many objections to this reclassification

process orchestrated by, much to my chagrin, the major suppliers of BGS devices in the US. I am particularly distressed by the attempt to prove science, safety and efficacy of BGS devices by legal arguments. Many of these arguments either have no basis in the published literature or are simply wrong. The promulgation of arguments that mystify the now reasonably clear scientific and clinical evidence that has accrued on the use of BGS devices and raise vague and unfounded concerns about safety is a misguided legal tactic. Such arguments will impede the further adoption and innovation of BGS technology in clinical practice. More worrisome, and hopefully unintended, is the possibility that this same tactic will push BGS technology back into the dark ages of EMF therapy, an age many of us have toiled mightily to enlighten. It would be a travesty for the industry itself, even inadvertently, to blunt the innovative momentum that should accrue to a non-invasive, non-pharmacologic therapy that is clearly without adverse effects. There is more to be said, but this is not the place to provide further details of my many objections. I would be glad to provide these in an appendix if the Panel so desires.

I am certain the applications of EMF for tissue growth and repair would advance much more rapidly if BGS devices were reclassified into Class II. I remember how proud we all were 25 years ago that FDA approval for our BGS device immediately rendered the care of recalcitrant fractures significantly safer because they were non-surgical, non-invasive, non-pharmacologic and out-patient, and significantly reduced the cost of health care for this indication as well. The decades since have proven these devices to be safe and efficacious, but, as the understanding of the mechanisms of action has progressed, the design and approval of new and potentially more effective BGS devices, as well as new clinical applications, has simply not followed.

I applaud the FDA for their quest to reclassify BGS devices and stand ready to aid in this process in any manner.

Sincerely

Arthur A Pilla

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