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

Re: Docket No. 2005P-0121

Dear Sir or Madam:

I am an Associate Professor in the Department of Molecular Medicine at the Cleveland Clinic Lerner College of Medicine in Cleveland, Ohio, and have over 20 years experience in basic research, much of it focused on how bone forms, develops, grows and regenerates. On June 2, 2006 I provided a public statement to the Food and Drug Administration Panel on Orthopaedic and Rehabilitation Devices that recommended disapproval of the petition to reclassify Non-Invasive Bone Growth Stimulators from Class III to Class II devices. It is my understanding that on January 17, 2007 the FDA published its notice of the Panel recommendation to deny the petition. I write to you again to voice my support for this Panel decision and recommendation. I would like to submit further comments to support this view based on the findings from our research over the last nine months.

In its Notice, the FDA pointed out "the Panel believed that there was insufficient evidence presented by the petitioner to control for the risk of inconsistent or ineffective treatment because there is *a lack of knowledge about how waveform characteristics (e.g. pulse duration,*

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amplitude, power, frequency) affect the clinical response to treatment." The FDA also pointed out that the Panel was concerned with potential device modifications because "it is not known *how a change to the device output due to device modifications may impact the clinical response to treatment.*" This situation has not changed since the Panel meeting. There is still a lack of a complete understanding how cells respond to these biophysical energy fields.

At this June 2nd Panel meeting evidence was presented by RS Medical Corp. to suggest that transient fluctuations in intracellular calcium concentrations were the primary mechanism to alter cellular metabolism and functional fate. While the data on which RS Medical relied are an important contribution to the research efforts in this field, they are not comprehensive. Data I presented at the meeting suggest that this mechanism was not representative of the entire spectrum of intracellular signaling effects that bone growth stimulator devices can impart. We have recently published these findings in the peer-reviewed literature: Patterson, TE, Sakai, Y, Grabiner, MD, Ibiwoye, M, Midura, RJ, Zborowski, M, and Wolfman, A., *Exposure of Murine Cells to Pulsed Electro-Magnetic Fields Rapidly Activates the mTOR Signaling Pathway*, *Bioelectromagnetism* 27:535-544 (2006). I am now providing a copy of this article for FDA review.

Our very latest research findings further indicate that bone growth stimulators may activate several intracellular signaling molecules. In this report, signaling pathways activated by acute parathyroid hormone (PTH) or insulin treatments were compared to those activated by pulsed electromagnetic field (PEMF) treatments in osteoblast-like cells. Some signaling molecules like the extracellular response kinases 1/2 and the cAMP response element binding protein were activated by insulin and PTH, respectively, but not by PEMF treatment. Other signaling molecules like insulin receptor substrate-1 (IRS-1), S6 ribosomal subunit kinase,

and endothelial nitric oxide synthase (eNOS) were phosphorylated by PTH, insulin and PEMF to the same relative extent and within the same time frame. IRS-1, eNOS and S6 have been implicated in bone anabolism, and these results suggest that the anabolic effects of PEMF may be mediated, in part, through the activation of these proteins. The manuscript presenting these findings has recently been accepted for publication in the Journal of Orthopaedic Research: Matthew Schnoke and Ronald J. Midura, "*Pulsed electromagnetic fields rapidly modulate intracellular signaling events in osteoblastic cells: comparison to parathyroid hormone and insulin*". I am now providing a copy of the pre-print article for FDA review.

The ultimate goal of on-going research in this area is to develop a scientific understanding of the biological reactions to BGS stimulation sufficient to be able to predict in advance how particular specified waveforms will affect human bone healing. To reach this level of knowledge, we need to understand and be able to explain at least four phenomena. First, we need to understand the precise, cellular-level processes stimulated by known human effective BGS devices. Second, we need to understand what characteristics of the BGS signal are predominant in causing the biological response. Third, we need to understand how any particular variation in the spectral characteristics or energy output of BGS devices would affect these cellular-level processes. And fourth, we need to understand how a particular change observable at the cellular level would affect human bone healing.

While our recent studies, and those of others, provide valuable data points upon which future research can build, they do not suggest the complete answer to any of these questions, let alone provide the level of understanding necessary to be able to make safety and effectiveness determinations with any degree of confidence. Moreover, because of the

complexity of the issues, which need to be studied, and the extensive research that remains to be done, I do not expect this situation to change in the near future.

Based on my own research, as well as the findings of other researchers, it is my opinion that the information available today does not provide a sufficient basis to assure the safety and effectiveness of new BGS devices through any means other than tried and true PMA clinical trials. I therefore recommend that the Panel's findings be accepted and that the classification of bone growth stimulators as Class III devices remain unchanged.

Thank you,

A handwritten signature in black ink that reads "Ronald J. Midura". The signature is written in a cursive style with a long horizontal line extending to the right.

Ronald J. Midura, Ph.D.