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

RE: Docket Number FDA-2014-D-0090 (product codes LOF and LPQ)

Dear Sir or Madam:

On behalf of the Bone Growth Stimulator ("BGS") Coalition, we submit the following comments in response to FDA's April 29, 2015 Federal Register notice identifying, among other devices, bone growth stimulators (product code LOF) ("electrical BGS Devices") and ultrasound muscle stimulators for uses other than applying therapeutic heat (product code LPQ) ("ultrasound BGS Devices") (collectively, "BGS Devices") as candidates for down-classification to Class II.[1] The BGS Coalition is comprised of the leaders in this device field.[2] Collectively, the BGS Coalition represents over 60 years of experience with BGS Devices and is responsible for 100% of the BGS market. FDA's April 29 Notice does not explain specific reasons for the listing of BGS Devices as candidates for down-classification. Nonetheless, as detailed below, these devices do not meet the criteria for down-classification established by the Federal Food, Drug, and Cosmetic Act ("FDCA"), and the BGS Coalition will strongly oppose any efforts to reclassify these devices.

Less than ten years ago, the BGS Coalition opposed a petition requesting that FDA down-classify these devices. The available scientific evidence on BGS Devices was closely considered by FDA and an Advisory Committee in 2006. That review resulted in the Advisory Committee's recommendation against down-classification, FDA's concurrence with this

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[1] *See* FDA, "Retrospective Review of Premarket Approval Application Devices; Striking the Balance Between Premarket and Postmarket Data Collection"; Notice and request for comments, 80 Fed. Reg. 23,798 (April 29, 2015) ("April 29 Notice").

[2] The BGS Coalition is comprised of leaders in the manufacturing, commercialization and/or development of BGS Devices, including Bioventus LLC, DJO Global, Inc., EBI, LLC d/b/a Zimmer Biomet Bone Healing Technologies, Electrostim Medical Services, Inc. d/b/a EMSI, and Orthofix International N.V.

recommendation, and subsequent withdrawal of the petition.[3] The BGS Coalition has reviewed the scientific literature that has been published since the original petition proceeding in 2006. As was the case when FDA considered the prior request for down-classification, the current scientific literature reflects a "bewildering array of model systems, clinical situations, and signal configurations"[4] and confirms that BGS Devices cannot be grouped into a generic type of device that qualifies for down-classification. Currently available information also continues to show that there is insufficient valid scientific evidence by which to establish special controls that can reasonably assure these devices' safety and effectiveness. Ultimately, the same issues that FDA and the Advisory Committee concluded precluded down-classification in 2006 continue to apply today. As such, BGS Devices must be maintained in Class III, and there is no basis to enable their down-classification under the FDCA.

I. Introduction

The FDCA recognizes three classes of medical devices that reflect (in increasing order of stringency) the extent of regulatory controls necessary to provide a "reasonable assurance" of device safety and effectiveness: Class I (general controls), Class II (special controls), and Class III (premarket approval). BGS Devices are currently classified as "postamendments"[5] Class III devices in accordance with FDCA section 513(f).

FDA classifies and reclassifies "generic types of devices."[6] For Class III devices, down-classification of a "generic type of device" is not permitted unless, at minimum, "there is sufficient information to establish special controls" that, together with general controls applicable to all devices, would be adequate to provide "reasonable assurance of the safety and effectiveness" of the device type.[7] As discussed further below, BGS Devices cannot be grouped into a single "generic type of device," and there is not necessary information, i.e., sufficient, publicly available "valid scientific evidence,"[8] to

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[3] *See* FDA Docket Nos. 2005P-0121 and FDA-2005-P-0052. The Panel recommendation and FDA's findings concurring therewith are summarized at FDA, "Orthopedic Devices; Reclassification of Non-Invasive Bone Growth Stimulator"; Notice of panel recommendation, 72 Fed. Reg. 1951 (Jan. 17, 2007).

[4] Haddad et al. *The Biologic Effects and the Therapeutic Mechanism of Action of Electric and Electromagnetic Field Stimulation on Bone and Cartilage: New Findings and a Review of Earlier Work.* The Journal of Alternative and Complementary Medicine. Vol. 13 2007. pp. 485-490.

[5] Postamendments devices are those devices that were not in commercial distribution prior to May 28, 1976, the enactment date of the Medical Device Amendments.

[6] 21 C.F.R. § 860.5(c)(3).

[7] FDCA § 513(a)(1)(B).

[8] FDA regulations define "valid scientific evidence" to include "evidence from well-controlled investigations, 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, from which it can fairly and responsibly be concluded by qualified experts that there is reasonable assurance of the safety and effectiveness of a device under its conditions of use." 21 C.F.R. § 860.7(c). Further, in accordance with 21 U.S.C. § 360j(c), "For the purpose of reclassification, the valid scientific evidence upon which the agency relies must be publicly available. Publicly available information excludes trade secret and/or confidential commercial information, e.g., nonpublic

establish special controls that would reasonably assure the safety and effectiveness of BGS Devices.

The need for Class III controls to assure the safety and effectiveness of BGS Devices was confirmed in June 2006 by FDA's Advisory Committee, which consisted of a panel of external experts in the BGS field. The Advisory Committee rejected the proposal to reclassify BGS Devices to Class II, citing a lack of valid scientific evidence to establish a single set of special controls adequate for all BGS Devices, the inability to define waveform parameters to ensure an effective signal, and the need for well-controlled clinical data to demonstrate safety and effectiveness for individual devices. For these reasons the Panel recommended that BGS Devices remain in Class III.[9] FDA concurred with the Advisory Committee's recommendation, finding that there "was not adequate evidence…to establish that…special controls could be used to adequately mitigate the risk of inconsistent or ineffective treatment."[10] As discussed below, the concerns cited by the Advisory Committee and FDA continue to be valid and prohibit reclassification of BGS Devices.

II. BGS Devices Do Not Meet the Statutory and Regulatory Criteria for Down-Classification

A. BGS Devices Cannot be Defined into a "Generic Type of Device"

FDA's April 29 Notice describes various factors the Agency considered in identifying devices as potential candidates for down-classification from Class III. Importantly, and of particular relevance to BGS Devices, the April 29 Notice did *not* acknowledge a factor essential to enable down-classification – that is, the ability to define a "generic type of device" to which down-classification would apply. A "generic type of device" is a "grouping of devices that do not differ significantly in purpose, design, materials, energy source, function, or any other feature related to safety and effectiveness, and for which similar regulatory controls are sufficient to provide reasonable assurance of safety and effectiveness."[11] BGS Devices do not comprise a "generic type of device" amenable to down-classification, as they differ significantly in terms of their modalities, mechanisms of action, waveforms, dosimetries, designs, and intended uses – all features related to safety and effectiveness. FDA has refused to reclassify devices where, as here, they "widely vary from model to model as well as from manufacturer to manufacturer."[12] Indeed, the BGS Devices identified in the April 29 Notice use four different types of technologies: pulsed electromagnetic fields ("PEMF"), capacitive coupled electric fields ("CCEF/CC"), combined magnetic fields ("CMF"), and low intensity pulsed ultrasound

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information in a pending PMA." FDA, Dental Devices; Reclassification of Root-Form Endosseous Dental Implants and Endosseous Dental Implant Abutments; Proposed Rule, 67 Fed. Reg. 34,416, 34,417 (May 14, 2002).

[9] Meeting of the Orthopedic and Rehabilitation Devices Advisory Committee (June 2, 2006).

[10] 72 Fed. Reg. 1951 at 1953 (Jan. 17, 2007).

[11] 21 C.F.R. § 860.3(i) (emphasis added).

[12] FDA, "Effective Date of Requirement for Premarket Approval for Cardiovascular Permanent Pacemaker Electrode"; Proposed Rule, 76 Fed. Reg. 48,058, 48,060 (August 8, 2011).

("LIPUS"). These devices differ significantly in design and signal generation.[13,14] The designs of BGS Devices also differ by intended use.

Moreover, as the April 29 Notice did recognize, a threshold factor to allow down-classification is whether "uncertainties about a technology have been alleviated."[15] This is not the case for BGS Devices. BGS Devices have varying mechanisms of action that are not well understood. The differing modalities among these devices affect cellular processes in different ways, and many uncertainties exist about how the various BGS signals positively affect bone growth. For example, with PEMF devices it remains unknown whether the treatment area responds positively to the electromagnetic field or to the induced current. Similarly, the exact nature of the effect of ultrasound energy on osteoblasts and vascular tissues involved in bone healing is not known. Even with the same field parameters, variable responses in different model systems illustrate that there are cell-specific and/or tissue-specific circumstances that mediate the cellular effects. Thus, a device shown to be effective in one clinical application may not be effective in another clinical application. The literature strongly supports this, and thus highlights the need for effectiveness to be established by well-controlled clinical studies for each device for each indication.[16] Relatedly, it also highlights that, in the absence of a complete understanding of the factors relevant to safety and effectiveness for any particular BGS Device, and given the variations among BGS Devices, it is impossible to define a "generic type of device" within which no significant differences in safety or effectiveness exist. Instead, device-specific clinical trials and FDA premarket review of manufacturing are necessary to establish that a new BGS Device is safe and effective.

Further, two other, crucial elements of BGS Device technology, dose and treatment time, also vary widely across the BGS Devices. Dosages vary by both device modality and intended use and cannot be established except through clinical studies specific to each BGS Device. Similarly, treatment times necessary for safe and effective treatment (as proven by device-specific clinical data) differ for different BGS technologies (e.g., ultrasound BGS Devices require treatment for 20 minutes/day whereas CCEF/CC BGS Devices require treatment for 24 hours/day). Even within the same modality, different intended uses may require different treatment times. For example, certain PEMF devices that are safe and effective for use with non-unions are indicated for 3 and 10 hours per day, while other approved PEMF devices for lumbar spinal fusions are indicated for 2 and 4 hours of use. In short, the dose and treatment time needed to yield a safe and effective signal is specific to each BGS Device and cannot be defined

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[13] Ramanujam et al. *Bone Growth Stimulation for Foot and Ankle Nonunions.* Clin Podiatr Med Surg. Vol. 26, 2009; pp. 607–618.

[14] Cook et al. *Healing in the New Millennium: Bone Stimulators. Where We've Been and Where We May be Heading.* Clin Podiatr Med Surg. Vol. 32, 2015; pp. 45–59.

[15] 80 Fed. Reg. 23,800 (April 29, 2015).

[16] *See, e.g.,* Aide et al. *Pulsed Electromagnetic Field Stimulation for Acute Tibial Fractures.* J Bone Join Surg. Am. 2011; pp. 1569-76, Massari et al. *Pulsed Electromagnetic Fields and Low Intensity Ultrasound in Bone Tissue.* Clinical Cases in Mineral and Bone Metabolism. 2009; pp. 149-154, Morone et al. *The Use of Electrical Stimulation to Enhance Spinal Fusion.* Neurosurgery. 2002; Focus, Art. 5, and Kahanovitz N. *Electrical Stimulation of Spinal Fusion: A Scientific and Clinical Update.* Spine. 2002; pp. 145-150.

class-wide by a single set of design specifications or parameters.[17] Rather, the appropriate dose and treatment time for any BGS Device can be determined only via extensive pre-clinical and clinical testing for that device.

The need for extensive and device-specific testing for BGS Devices underscores the fact that significant unknowns and variations among these technologies exist (e.g., mechanisms of action and safe and effective waveforms, doses, and treatment times) and thus preclude the devices from being grouped together to form a generic type of device for which a common set of Class II special controls would be adequate.[18] Instead, the safety and effectiveness of each BGS Device can be assured only through the rigorous panoply of pre- and post-market review and controls associated with the Class III/PMA framework.

B. Special Controls Cannot be Established to Assure the Safety and Effectiveness of BGS Devices

1. A single set of special controls cannot be established

The dissimilarities among the PMA-approved BGS Devices present different risks for which a similar set of regulatory controls would not reasonably assure safety and effectiveness for all devices. FDA has recognized that "[t]he similarity in health risks is fundamental to the concept of classification by generic type of device. If devices thought to be within the same generic type present different risks, it is likely that the devices are not really of the same generic type."[19] FDA's history of requiring testing to address safety issues specific to each BGS Device modality underscores the fact that different BGS Devices present different risks that cannot be mitigated by a single set of definable general and special controls; therefore, these devices cannot qualify for Class II classification.

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[17] Recent literature comments on the challenges associated with dosing: "The concept of an acoustic 'dose' for LIPUS that could be standardized is difficult to derive. Similarly to therapeutic thermal ultrasound, the dose should be related to the amount of bioeffect induced. However, given the lack of understanding of which parameters of the stimulation are responsible for any given bioeffects, the dose is so far a lacking concept in the field of LIPUS." Padilla et al. *Stimulation of Bone Repair with Ultrasound: A review of the Possible Mechanic Effects*. Ultrasonics. Vol 54, 2014; pp. 1125-1145.

[18] As discussed below, although FDA has flexibility under the FDCA to adopt a number of measures as special controls, as the Agency has recognized, this flexibility does not permit FDA to down-classify devices into Class II using a set of controls that are tantamount to Class III, PMA controls. *See* notes 66-69, *infra*, and related text.

[19] FDA, "Final Rule on Medical Device Classification Procedures," 43 Fed. Reg. 32987, 32992 (July 28, 1978).

More importantly, BGS Device waveforms are complex. A generic set of waveform parameters that will produce safe and effective treatment for all such devices cannot be identified. Rather, the different modalities and intended uses for BGS Devices require device-specific waveform parameters to be determined. In addition, the allowed waveform tolerances are important factors in assuring safety and effectiveness. These also vary among BGS Devices and cannot be defined generically across the class.

In addition to the waveform and design differences described above, BGS Devices have been approved for three distinct indications for use: fresh fractures, non-unions, and spinal fusion. The risks associated with BGS Devices for each indication are unique, and FDA has historically required different types of testing to demonstrate the safety and effectiveness of BGS Devices for each indication.[20] Consistent with this, even today members of the BGS Coalition continue to seek and receive Investigational Device Exemption ("IDE") approval to establish the safety and effectiveness of BGS Devices for new indications. It is thus impossible to define a single set of risks applicable across all BGS Devices and possible indications for use. As such, a single set of special controls cannot be established to mitigate the risks associated with all BGS Devices, as would be required for down-classification to Class II.

2. Insufficient valid scientific evidence exists to establish special controls

BGS Devices are not appropriate for reclassification because "insufficient information exists to determine that . . . special controls . . . would provide reasonable assurance of [their] safety and effectiveness."[21] The published literature on BGS Devices does not provide adequate evidence or information to establish special controls to provide this assurance.

Randomized, double-blind "well-controlled investigations"[22] are the gold standard in the hierarchy of valid scientific evidence and are required to demonstrate the effectiveness of a device[23]; yet, there is a dearth of such studies in the published literature on BGS Devices. Indeed, in 2011 Griffin et al. conducted a review of available data on electromagnetic field stimulation for the treatment of delayed union or non-union of long bone fractures and concluded the available evidence was "...insufficient to inform current practice" and that "more definitive conclusions on treatment effect await further well-conducted randomized controlled trials."[24,25] Similarly, a

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[20] For example, citing the unique risks associated with spinal fusions, FDA required a BGS Device manufacturer to perform a clinical study on electrical stimulation of the cervical spine. FDA explained, "Because the Cervical-Stim is intended for use in treating an area which includes the central nervous system (CNS), FDA has concerns regarding possible effects on the spinal nerves. You must discuss the possible risks involved when applying pulsed electromagnetic fields to the CNS and describe what provisions you have made to minimize such risks."
[21] FDCA § 513(a)(1)(C).
[22] 21 C.F.R. § 860.7(c)(2).
[23] FDA regulations require that "[t]he valid scientific evidence used to determine the effectiveness of a device shall consist principally of well-controlled investigations." *Id.* at § 860.7(e)(2) (emphasis added).
[24] Griffin et al. *Electromagnetic Field Stimulation for Treating Delayed Union or Non-union of Long Bone Fractures in Adults.* Cochrane Database Syst Rev. April 2011.

Cochrane review published in 2014 "highlights the limitations of the available [published] evidence on therapeutic ultrasound for acute fractures in adults," including inadequate "record[ing of] functional outcomes and follow-up [of] all trial participants," among other issues.[26]

Another fundamental deficiency of the majority of published studies on BGS Devices is a failure to include "sufficient details to permit scientific evaluation."[27] The published studies do not adequately define the waveforms used. As FDA has recognized, "the published literature do not always contain a complete, or entirely accurate, representation of the device design, performance, manufacture, clinical study plans, conduct, accountability, and outcomes."[28] In these cases, as is the case here, the "details provided in published literature may not be sufficient to establish that the device that is the subject of the published report is comparable in design, performance, and manufacture" to another device.[29] Without a sufficient description of the waveforms in each published study on BGS Devices, there is no rational basis for comparing the studies and concluding their adequacy to develop special controls sufficient for all BGS Devices.

Further, existing published studies on BGS Devices are characterized by heterogenicity among study design, variability in the outcome measures and small sample sizes.[30] For example, a Cochrane review published in 2014 "highlights the limitations of the available [published] evidence on therapeutic ultrasound for acute fractures in adults," with its inclusion of "12 quite different trials" that "varied substantially."[31] The heterogencity and variability among these studies, together with other issues like small sample sizes, further limit the publicly available literature's ability to serve as valid scientific evidence in support of a single set of special controls to reasonably assure the safety and effectiveness of BGS Devices.

Considering their limitations, current published studies do not constitute sufficient valid scientific evidence by which to establish a set of special controls that can reasonably assure the safety and effectiveness of BGS Devices.

C. Risks to Health Cannot Be Mitigated Through General and Special Controls

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[25] *See also* Ebrahim et al. *Low Intensity Pulsed Ultrasonography Versus Electrical Stimulation for Fracture Healing: A Systematic Review and Network Meta-Analysis.* Can J. Surg Vol. 57, June 2014; pp. 105-118.
[26] Griffin et al. *Ultrasound and Shockwave Therapy for Acute Fractures in Adults (Review).* The Cochrane Library. 2014; Issue 6.
[27] 21 C.F.R. § 860.7(c)(2).
[28] FDA, "Guidance for Industry, Supplements to Approved Applications for Class III Medical Devices: Use of Published Literature, Use of Previously Submitted Materials, and Priority Review" (May 20, 1998).
[29] *Id.*
[30] *See, e.g.*, Behrens et al. *A Review of Bone Growth Stimulation for Fracture Treatment.* Curr Ortho Pract. February 2013; pp. 84-91, Griffin et al. *Ultrasound and Shockwave Therapy for Acute Fractures in Adults (Review).* The Cochrane Library. 2014; Issue 6, and Dijkman et al. *Low-intensity Pulsed Ultrasound: Nonunions.* , IJO. Vol. 43, April-June 2009;Issue 2.
[31] Griffin et al. *Ultrasound and Shockwave Therapy for Acute Fractures in Adults (Review).* The Cochrane Library. 2014; Issue 6.

According to the April 29 Notice, in determining whether a device is an appropriate candidate for reclassification, FDA considered whether the risks associated with the device were "well known and low to moderate."[32] FDA has previously identified a number of significant risks associated with BGS Devices, including electric shock, burns, skin irritation, allergic reaction, damage to an implanted electrical device (e.g., a pacemaker), adverse biological effects of stimulation (e.g., carcinogenicity) and ineffective or inconsistent treatment.[33] These risks are certainly not low or moderate in nature. During the 2006 Advisory Committee meeting discussing potential reclassification of BGS Devices, the Advisory Committee confirmed these risks and agreed that PMA controls (i.e., Class III controls) were required to mitigate them. FDA concurred with this Class III recommendation.[34]

Today, BGS Devices continue to present these same risks and thus must be maintained in Class III. This is evidenced by FDA's recent review and approval of several IDE applications for clinical study of BGS Devices. By definition, an approved IDE is required for devices that present significant risk (i.e., risks that are not low or moderate).[35] Further, adverse events that have been reported in association with BGS Devices in the years since the 2006 Advisory Committee meeting include additional potential risks of a serious (not low or moderate) nature, including tumor and bone spur growth, seizure, cutaneous ulcers, and significant pain.[36] The BGS Coalition acknowledges that the frequency of reported adverse events for BGS Devices is minimal; however, the Coalition believes this is a direct result of - and not a reason or basis to discontinue - the present Class III controls, which ensure that only safe and effective BGS devices are marketed. This is similar to the view FDA established in declining to down-classify rigid gas permeable ("RGP") contact lenses. As FDA recognized there, to the extent devices subject to Class III controls demonstrate a strong safety record, it must be appreciated "that the safety record…to date represents the performance of [devices] for which there are approved PMA's."[37] (Emphasis added). Moreover, as FDA also noted, unlike controlled data required in a PMA that substantiate a device's safety, the infrequency of user reports of adverse reactions "do not constitute valid scientific evidence" on which down-classification can be based.[38]

In the past FDA has expressed serious concerns about potential risks associated with BGS Devices that must be addressed in clinical studies or PMA submissions, including the risk

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[32] 80 Fed. Reg. 23,800 (April 29, 2015).
[33] Meeting of FDA's Orthopedic and Rehabilitation Devices Panel (June 2, 2006); *see also* 72 Fed. Reg. 1951, 1952 (Jan. 17, 2007).
[34] 72 Fed. Reg. 1951 (Jan. 17, 2007).
[35] 21 C.F.R. § 812.20(a).
[36] These adverse events were identified by a search from 2005 through the present of FDA's MAUDE/Medical Device Reporting (MDR) database (available at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfMAUDE/search.CFM (last accessed June 11, 2015)) using product codes LOF and LPQ.
[37] FDA, "Reclassification of Daily Wear Spherical Contact Lenses Consisting of Rigid Gas Permeable Plastic Materials"; Withdrawal of Proposed Rule ["Contact Lens Rule"], 48 Fed. Reg. 56,778 at 56,783 (Dec. 23, 1983).
[38] *Id.* at 56,787.

of ineffective treatment.[39] There have been several recently reported incidences of ineffective treatment, signaling that this continues to be a significant risk.[40] Further, FDA regulations require that evidence submitted in a PMA to show safety must "adequately demonstrate the absence of unreasonable risk of illness or injury associated with the use of the device for its intended uses and conditions of use."[41] In General Medical Co. v. FDA, the D.C. Circuit concluded that an unreasonable safety risk "need only be a potential one. The risk may be one demonstrated by reported injuries or it may simply be foreseeable."[42] To address these serious potential risks (e.g., ineffectiveness or adverse biological effects), FDA has required an array of preclinical and clinical studies to support the PMA approval of BGS Devices, including data from long-term animal and clinical studies. General and special controls cannot be created to sufficiently mitigate these potential risks.

D. PMA Requirements Are Necessary to Reasonably Assure BGS Safety and Effectiveness

FDA's April 29 Notice explains that one factor that weighs against a device's appropriateness for down-classification is if PMA "review of annual reports and manufacturing changes have been important to maintain safety of the devices."[43] In the case of BGS Devices, FDA has long recognized the need to review design and manufacturing changes because modifications to the waveforms and other parameters, even if seemingly minor, may adversely impact device safety and effectiveness. Indeed, in practice, FDA has maintained the need for additional clinical evidence to accompany any changes to a device's signal.

In addition, numerous studies demonstrate that apparently minor alterations to BGS waveforms and other parameters (such as intensity, spatial average-temporal average ("SATA"), and MHz) can adversely affect device safety and effectiveness.[44,45,46,47] These studies thereby highlight the importance of FDA review of all changes to BGS Devices, which is achieved only

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[39] 72 Fed. Reg. 1951, 1953 (Jan. 17, 2007).
[40] *See* note 36, supra.
[41] Contact Lens Rule, 48 Fed. Reg. 56,778 at 56,787 (Dec. 23, 1983).
[42] *General Medical Co. v. FDA*, 770 F.2d 214, 221 (D.C. Cir. 1985) (quoting House Report) (emphasis added).
[43] 80 Fed. Reg. 23,800 (April 29, 2015).
[44] Fitzsimmons et al. *Low-amplitude, Low-frequency Electrical Field-stimulated Bone Cell Proliferation May in Part be Mediated by Increased IGF-II Release*. Journal of Cellular Physiology. 1992; pp. 84-89, and Fitzsimmons et al. *Combined Magnetic Fields Increased Net Calcium Flux in Bone Cells*. Calcif. Tissue Int. 1994; pp. 376-380.
[45] Brighton et al. *Fracture Healing in the Rabbit Fibula When Subjected to Various Capacitively Coupled Electrical Fields*. J. Orthop. Res. 195; pp. 331-340.
[46] Kesani et al. *Electrical Bone Stimulation Devices in Foot and Ankle Surgery: Types of Devices, Scientific Basis, and Clinical Indications for Their Use*. Foot & Ankle International. 2006; pp. 148-156.
[47] *See also* Wang et al. *Low Intensity Ultrasound Treatment Increases Strength in a Rat Femoral Fracture Model*. Journal of Orthopaedic Research. 1994; pp.40-47, Reher et al. *Ultrasound Stimulates Nitric Oxide and Prostaglandin E_2 Production by Human Osteoblast*. Bone. Vol. 31, July 2002; pp. 236-241, Reher et al. *The Stimulation of Bone Formation In Vitro by Therapeutic Ultrasound*. Ultrasound in Med. & Biol. Vol. 23, 1997; pp. 1251-1258), and Li et al. *Optimum Intensities of Ultrasound for PGE_2 Secretion and Growth of Osteoblasts*. Ultrasound in Med. & Biol. Vol. 28, 2002; pp. 683-690.

under Class III/PMA controls.[48] Significantly, FDA recently underscored this point in proposing to amend its classification regulations to make clear that "devices for which premarket review of any change that affects safety or effectiveness is necessary to provide RASE [reasonable assurance of safety and effectiveness] be classified into Class III."[49]

Close review of all device changes under Class III/PMA authorities is also important for ultrasound BGS Devices. In one recent study, an ultrasound BGS Device with similar output signal specifications as a PMA-approved ultrasound BGS Device failed to show a difference over placebo in lower limb stress fractures.[50] This further emphasizes the fact that purportedly minor differences between BGS Device waveforms can significantly impact the safety and effectiveness of these devices.

Furthermore, PMA premarket review of manufacturing is necessary to reasonably assure BGS Device safety and effectiveness. PMA oversight allows for the extensive review and inspection of a company's manufacturing process and facilities prior to device approval. Even with an accurate and complete description of the relevant parameters, it is difficult to build a BGS Device that consistently produces the required signal within an acceptable range. Establishing reliability in production is especially important for BGS Devices because of their sensitivity to even slight deviations from their designs or waveform parameters.[51] FDA has noted that a Class III classification is warranted where "safety concerns relate [to]...manufacturing processes and design changes," precisely because of constraints on FDA's authority, under a Class II, 510(k) framework, to perform premarket assessment of, or condition 510(k) clearance on, manufacturing compliance.[52] In its recent proposal to amend its classification regulations, FDA has further emphasized its view that "when a review of a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and, when relevant, packing and installation, of a device is necessary to provide

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[48] In the context of reclassification, FDA has specifically noted that its "oversight of postmarket changes to devices is very different in the 510(k) context as compared to the PMA context. Under 21 C.F.R. § 807.81, FDA requires 510(k)s for a change to a device only when the change "could significantly affect the safety or effectiveness of the device...." In contrast, under 21 CFR 814.39, FDA requires PMA supplements (including 30-day notices) for any change to a PMA-approved device that affects safety or effectiveness. These differences in authorities...warrant regulation of [applicable devices] in class III." FDA, "Effective Date of Requirement for Premarket Approval for Automated External Defibrillator Systems"; Final Order, 80 Fed. Reg. 4783, 4785 (Jan. 29, 2015).

[49] FDA, "Medical Device Classification Procedures"; Proposed Rule, 79 Fed. Reg. 16,252 16,256 (March 25, 2014).

[50] Gan et al. *Low-Intensity Pulsed Ultrasound in Lower Limb Bone Stress Injuries: A Randomized Controlled Trial.* Clinical Journal of Sport Medicine. November 2014; pp. 457-460.

[51] *See* 21 C.F.R. § 860.7(b).

[52] 80 Fed. Reg. 4783, 4785 (Jan. 29, 2015) (Class III is appropriate because "FDA does not generally conduct preclearance inspections under the 510(k) process because such information is not required in a 510(k) submission under the FD&C Act [FDCA] or FDA regulations. Further, under section 513(f)(5) of the FD&C Act...., FDA may not withhold a 510(k) "because of a failure to comply with any provision of this Act unrelated to a substantial equivalence decision, including a finding that the facility in which the device is manufactured is not in compliance with good manufacturing requirements....(other than a finding that there is a substantial likelihood that the failure to comply with such regulations will potentially present a serious risk to human health)"").

RASE [a reasonable assurance of safety and effectiveness] for a potentially high risk device, general and special controls are inadequate to provide RASE and the device thus meets the statutory definition of class III."[53]

In its April 29 Notice, FDA indicates that a device may be appropriate for reclassification if "non-clinical tests have been developed that could be surrogates for some clinical testing."[54] This echoes FDA's statement in endorsing the 2006 Advisory Committee recommendation against down-classifiying BGS Devices that, for these devices specifically, appropriate "preclinical test methods [would be needed] to mitigate the risk of inconsistent or ineffective treatment."[55] As discussed below, such tests do not exist for BGS Devices, as preclinical studies for these devices cannot reliably predict clinical success. It is well known that the models for animal fracture repair do not necessarily represent the human clinical situation. There are differences between animals and humans with respect to bone based cells themselves (e.g., osteoblasts, osteoclasts). For example, rats and mice possess a primitive bone structure without Haversian systems compared to humans.[56] Rats and mice also have a greater healing capacity as animals of a lower phylogenetic scale compared to humans.[57] Further, differences in cellular responsiveness exist between large animal models of bone repair and human models. A significant dose escalation as a result of animal size and species has been observed across animal models ranging from rodents, rabbits, dogs, sheep and non-human primates used to evaluate bone morphogenetic proteins.[58] In addition, the character of the periosteum (which serves as an important cellular source) surrounding the bone varies considerably between animals and humans.

More importantly, there are significant limitations in animal models with respect to the specific PMA-approved indications for BGS Devices:

- Fresh Fracture Model Limitations

  There is no known standardized fresh fracture model. A variety of different fracture models in rats and mice have been introduced during the last several years, but the devices used to achieve fracture stabilization differ from those used in human clinical studies. It is not clear which (if any) of these fixation methods is the most suitable to study the fracture healing process.[59] Additionally, animal fracture models typically induce the fracture by artificial means. For smaller animals this typically involves

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[53] 79 Fed. Reg. 16,252, 16,256 (March 25, 2014).
[54] 80 Fed. Reg. 23,800 (April 29, 2015).
[55] 72 Fed. Reg. 1951, 1953 (Jan. 17, 2007).
[56] Nunamaker DM. *Experimental Models of Fracture Repair.* Clin Orthop Relat Res. October 1998; pp. 56-65.
[57] Histing et al. *Small Animal Bone Healing Models: Standards, Tips, and Pitfalls: Results of a Consensus Meeting.* Bone. 2011;pp. 591-599.
[58] Martin et al. *Posterolateral Intertransverse Process Spinal Arthrodesis with rhBMP-2 in a Nonhuman Primate: Important Lessons Learned Regarding Dose, Carrier, and Safety,* J Spinal Disord. June 1999; pp. 179-186.
[59] Histing et al. *Small Animal Bone Healing Models: Standards, Tips, and Pitfalls: Results of a Consensus Meeting.* Bone. 2011; pp. 591-599.

breakage of the bone after it has already been stabilized with fixation, whereas fractures in larger animals are generally introduced through surgical means. The soft and bony tissue trauma from these controlled models differs from that of humans, resulting in differences in how a BGS Device signal is propagated through such damaged tissue and potentially in how the tissue responds on a cellular level.

- Non-union Model Limitations

  Fracture non-union is not an indigenous condition that arises in animals. Accordingly, bone growth in animal models must be retarded by other artificial means, such as cauterization, application of chemical agents, membrane barriers (e.g. silicone inserts), or intentionally not stabilizing the fracture. However, in mice and rats, even fractures with poor mechanical fixation or no fixation at all have been shown to heal without a significant delay of bony union.[60,61]

  Additionally, rodent definitions of a delayed union or non-union are lacking.[62] Thus, it is difficult to evaluate effectiveness in such studies when there are no baseline criteria to judge that the method used to stunt bone growth has indeed achieved a non-union in the model.

- Spinal Fusion Model Limitations

  The rabbit is the only known, generally recognized animal spinal fusion model; however, the recognition of this model is limited to posterior lumbar fusions ("PLF"). Other animal models have been used for PLF and interbody fusions, including canine, sheep, goat, and non-human primate models. The significant differences in the size of the bones, intervening soft tissues, soft tissue distances from the skin, and character of the soft tissues makes it difficult to correlate any of the findings in these models to human performance.

The lack of correlation of animal study results to results in humans is further evidenced in the published literature.[63] Based on the above, for any given BGS Device, only human trials can appropriately translate the complex character of the originating BGS Device signal to the actual clinical performance of the device.

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[60] Manigrasso MB, O'Connor JP. *Characterization of a Closed Femur Fracture Model in Mice*. J Orthop Trauma. 2004; pp. 687-695.
[61] Lu et al. *Effect of Age on Vascularization During Fracture Repair*. J Orthop Res. 2008; pp. 1384-1389.
[62] Garcia et al. *Rodent Animal Models of Delayed Bone Healing and Non-union Formation: A Comprehensive Review*. Eur Cell Mater. 2013; pp. 1-12.
[63] *See, e.g.*, Fredericks et al. *Effects of Pulsed Electromagnetic Fields on Bone Healing in a Rabbit Tibial Osteotomy Model*. J. Orthopaedic Trauma. 2000; pp. 93-100. In the context of LIPUS devices, recent literature has reported that "[i]n-vitro studies are not appropriate to identify the full complexity of biological effects..." Padilla et al. *Stimulation of Bone Repair with Ultrasound: A Review of the Possible Mechanic Effects*. Ultrasonics. Vol. 54, 2014; pp. 1125-1145.

The need for human data and other PMA controls discussed above to provide reasonable assurance of the safety and effectiveness of BGS Devices emphasizes that a Class III classification is necessary for these devices. Typically, for devices under a Class II classification, comparative descriptions and non-clinical testing are sufficient to support substantial equivalence (510(k) clearance), and clinical data are not required.[64] In very limited cases, clinical data may be included in a 510(k), but only to show substantial equivalence, and not to independently establish safety and effectiveness.[65] FDA has long made clear that, where clinical data are necessary to establish safety and effectiveness, and/or other Class III/PMA controls are needed for a device, the device must be regulated in Class III. In other words, FDA has recognized that its authority to impose special controls within a Class II, 510(k) framework is not so broad as to allow a device to be down-classified into Class II while, in effect, being subject to Class III requirements under the guise of special controls. FDA first articulated this point in 1983, when it rejected the down-classification of RGP contact lenses:

> [R]equiring so much information [in a 510(k)] would result in the submission of data so complete as to be indistinguishable from the data needed to determine the safety and effectiveness of a device in the first instance rather than on a comparison [i.e.,. substantial equivalence] basis. The data required in a premarket notification submission would then be indistinguishable from the data required in a PMA. FDA agrees that imposing such a requirement as an *a priori* condition for determining substantial equivalence would exceed the authority of section 510(k) of the act and Subpart E of Part 807.[66]

FDA recently reaffirmed this view. The Agency declined to down-classify automated external defibrillator ("AED") devices earlier this year. During Advisory Committee review, FDA noted that if all measures the Agency believed to be necessary to appropriately regulate these devices (including premarket manufacturing review and inspections and postmarket annual reporting and stringent change control) "were…to be incorporated into special controls under 510(k) it would substantially duplicate the requirements of the current PMA regulation and…the creation of a parallel regulatory paradigm would significantly blur the distinction of the regulation classifications [i.e., Class III versus Class II]. Hence [FDA's] recommendation was to regulate AEDs under Class III."[67] In its 2015 final order classifying AEDs into Class III and subjecting them to PMA requirements, FDA similarly rejected a comment "that several of the regulatory controls identified by FDA as consistent with PMA requirements – such as pre-market inspections, review of changes that could significantly affect the safety or effectiveness of the device, and postmarket surveillance – could also be conducted under the 510(k)

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[64] *See* FDA, The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications [510(k)] - Guidance for Industry and Food and Drug Administration Staff (July 28, 2014) ("510(k) SE Guidance") at 22-23.
[65] See 21 C.F.R. § 807.100(b); see also 510(k) SE Guidance at 23.
[66] Contact Lens Rule, 48 Fed. Reg. at 56,790 (emphasis added).
[67] FDA, Summary from the Circulatory System Devices Panel Meeting – January 25, 2011.

regime."[68] FDA emphasized this point generally as well in a notice issued last year: "FDA...believes...that the statutory classification scheme contemplates that certain regulatory controls are appropriately reserved to class III devices subject to [PMA] approval...."[69]

In short, the FDCA and FDA's regulations and interpretations thereunder clearly support continued regulation of BGS Devices in Class III. Down-classification of BGS Devices would eliminate crucial FDA premarket review and postmarket control authorities, thus wrongly jeopardizing the safety and effectiveness of these devices.

III. Conclusion

BGS Devices do not meet the statutory criteria for classification into Class II. The PMA-approved BGS Devices differ significantly in design and technology and cannot be grouped into a single "generic type of device" amenable to down-classification. Moreover, publicly available valid scientific evidence is inadequate to demonstrate that a common set of special controls can be established to assure the safety and effectiveness of these devices. Fundamentally, BGS Devices are used for potentially debilitating medical conditions, such as serious non-unions and spinal fusions, and, as FDA has previously acknowledged, their safety and effectiveness cannot be assured through general and special controls alone. It is known that even seemingly minor alterations to BGS Devices (e.g., to their waveforms or designs) may adversely impact their safety and effectiveness and that different BGS modalities and intended uses require proof by tailored testing, including clinical testing. In refusing to down-classify RGP contact lenses from Class III to Class II, FDA reasoned that "[t]he safety and effectiveness of contact lenses is a function of the complex interrelationship of material, design, and manufacture that results in a unique set of physical, chemical, mechanical, and optical characteristics."[70] Here, the safety and effectiveness of each BGS Device is similarly "a function of a complex relationship" of manufacturing, technological method, waveform, design, dosimetry, and intended use that must be closely regulated, evaluated, and controlled in a manner more stringent than possible under Class II authorities. As such, throughout the history of these devices, FDA has required clinical studies, premarket review of manufacturing, and rigorous annual reporting and postmarket change control under Class III/PMA authorities. For all of these reasons, BGS Devices must remain in Class III.

If BGS Devices were Class II devices (which they cannot be), new BGS Devices would come to market through the premarket notification [510(k)] process and a determination of "substantial equivalence." But in light of the concerns above, substantial equivalence determinations under 510(k) review would be inadequate to assure the safety and effectiveness of BGS Devices. For example, two ultrasound BGS Devices could have identical output

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[68] FDA, "Effective Date of Requirement for Premarket Approval for Automated External Defibrillator Systems"; Final Order, 80 Fed. Reg. 4783, 4785 (Jan. 29, 2015).
[69] 79 Fed. Reg. 16,252 16,256 (March 25, 2014).
[70] Contact Lens Rule, 48 Fed. Reg. at 56,792 (Dec. 23, 1983).

specifications but nonetheless deliver very different ultrasound signals to the treatment site, creating a potential for ineffective treatment. In short, effective treatment by these devices can be confirmed only through clinical testing. Yet, through the 510(k) process, which relies on a comparison of intended use and technological specifications (e.g., signal output), these devices would likely be found substantially equivalent to each other, thus allowing marketing clearance to be obtained even if one device is in fact ineffective. FDA previously recognized this precise concern of ineffectiveness as a fundamental deficiency in any effort to down-classify and regulate BGS Devices under a Class II/510(k) framework,[71] and there is no basis not to continue to do so now.

FDA erred when identifying BGS Devices in its April 29 Notice as potential candidates for down-classification. For the reasons above, the safety and effectiveness of BGS Devices can be assured only through Class III/PMA review and controls, and these devices must therefore be maintained in Class III.

The BGS Coalition appreciates FDA's careful consideration of these comments and the opportunity to provide them.

Respectfully submitted,

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[71] *See* 72 Fed. Reg. 1951, 1953 (Jan. 17, 2007).