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via Electronic Transmission

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Orthopaedic and Rehabilitation Devices Panel
Center for Devices and Radiological Health
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RE: Comments of Bone Growth Stimulator Coalition opposing potential reclassification of Non-invasive Bone Growth Stimulator Devices (product codes LOF and LPQ)

Dear Mr. Garcia:

On behalf of the Bone Growth Stimulator ("BGS") Coalition, we submit the following comments regarding the September 8, 2020 meeting of FDA's Medical Devices Advisory Committee, Orthopaedic and Rehabilitative Devices Panel ("Panel"), to consider the potential reclassification of non-invasive 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") from Class III to Class II.[1] The BGS Coalition is comprised of the leaders in this field of bone healing devices and is collectively responsible for all of the BGS Devices that have been approved by FDA.[2] The BGS Coalition supports maintenance of BGS Devices in Class III.

I. Introduction

The BGS Coalition understands FDA's efforts to reclassify devices to Class II where warranted and recognizes that Class II classification is appropriate for many devices. Coalition members support the Class II/510(k) pathway where applicable and market

[1] See FDA, Orthopaedic and Rehabilitation Devices Panel of the Medical Devices Advisory Committee; Notice of Meeting, 85 Fed. Reg. 45642 (July 29, 2020).
[2] The BGS Coalition is an informal group comprised of the following BGS Device manufacturers: Bioventus LLC, DJO Global, Inc., Orthofix Medical Inc., and Zimmer Biomet.

several devices under this pathway. However, the BGS Coalition does not believe that Class II is appropriate for BGS Devices. At this time the Coalition wishes to highlight for the Panel and the administrative record key reasons BGS Devices do not meet the statutory and regulatory criteria for reclassification.[3] Among these are reasons that FDA and the Panel previously agreed preclude reclassification of BGS Devices, including the necessity of Class III controls to avoid the substantial adverse effects on patient health when these devices are ineffective. The BGS Coalition addresses below aspects of FDA's recently issued proposed order for BGS reclassification[4] and will promptly submit further comments on the proposed order and/or discussion at the upcoming Panel meeting following the meeting.

In 2006 FDA convened a meeting of the Panel ("2006 Panel Meeting") to consider a petition seeking reclassification of electrical BGS Devices to Class II. The Advisory Committee recommended against reclassification, and FDA concurred. In particular:

> [T]he Panel believed that there was insufficient evidence…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, amplitude, power, frequency) affect the clinical response to treatment. This concern was also expressed by the Panel regarding potential modifications made to the device. It is not known how a change to the device output due to device modifications may impact the clinical response to treatment. The Panel requested additional clinical data and/or special controls to control for the risk of inconsistent or ineffective treatment….
>
> …FDA believes that there was not adequate evidence in the petition to establish that the petitioner's proposed special controls could be used to adequately mitigate the risk of inconsistent or ineffective treatment. Additional evidence is required to establish special controls, including preclinical test methods, to mitigate the risk of inconsistent or ineffective treatment. ... Therefore, based on the currently available information, FDA concurs with the Panel's recommendation to retain the non-invasive bone growth stimulator as a class III device.[5]

As discussed below, FDA and the Panel's findings remain true today and, thus, the conditions to permit reclassification of BGS Devices continue to be unmet. In particular, effective performance of new, unproven bone growth stimulator technologies cannot be

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[3] The BGS Coalition incorporates by reference comments it has previously submitted to FDA on the topic of BGS Device classification (see BGS Coalition Comment to FDA Docket 2005P-0121 (August 17, 2005) and BGS Coalition Comment to FDA Docket FDA-2014-D-0090 (June 29, 2015)), as well as the presentation it will make to the Panel at the September 8, 2020 Panel meeting, reflected in the slides attached.

[4] See FDA, Physical Medicine Devices; Reclassification of Non-Invasive Bone Growth Stimulators; Proposed amendment; proposed order; request for comments, 85 Fed. Reg. 49986 (Aug. 17, 2020) ("proposed order").

[5] FDA, Orthopedic Devices; Reclassification of Non-invasive Bone Growth Stimulator; Notice of Panel Recommendation, 72 Fed. Reg. 1951, 1953 (Jan. 17, 2007) (published following June 2, 2006 Panel Meeting).

established without high-quality (Level 1 and 2) clinical data of the type that FDA has insisted upon for all BGS Devices approved to date and that is typically required in Class III PMAs generally. As also detailed below, the retention of Class III status is necessitated by several other factors as well, including variations among BGS Devices that preclude the development of a single, generic set of special controls adequate class-wide; the need for Class III controls to ensure pre-market FDA review of key, device-specific manufacturing processes, as well as the quality and integrity of clinical and nonclinical data essential to establish the safety and effectiveness of BGS Devices; and the need for FDA review of all post-market device modifications. Continuing classification in Class III is further warranted to avoid adverse impacts that reclassification to Class II would present in terms of quelling vital research and innovation for BGS Devices.

It is important to appreciate that approved BGS Devices have been marketed safely and effectively under Class III controls since FDA granted the first approval for these devices more than 40 years ago. Though several reclassifications of Class III devices have involved devices that, though Class III, were marketed via the 510(k) pathway and related controls (those typically associated with Class II), and thus had a demonstrated history of safe and effective performance under the 510(k) regime prior to reclassification, BGS Devices are different.[6] The robust record for BGS Devices is a direct result of the rigorous Class III controls that have always been, and continue to be, in place for these products. As well, over the years, the Class III framework has incentivized and enabled BGS Coalition members to engage in extensive and important research, including high-level clinical research, on BGS Devices. This research has resulted in vital evidence generation that has promoted innovation in these devices and helped improve treatment and outcomes for vulnerable patients. To ensure that the longstanding, successful experience with BGS Devices continues, going forward, all new technologies should be held to the same high standards that the BGS Devices approved today have met: Class III standards for manufacturing review, clinical evidence, and change control to ensure safety and effectiveness. Given the nature of BGS Devices, no Class II special controls can substitute for these standards. Any new BGS Device authorized for marketing with less scrutiny would present greater potential to introduce risks to patients, many of whose health is severely compromised. This is simply unnecessary and unwarranted.

[6] Class III devices marketed via 510(k) are so-called "preamendments" devices. Over the years, including recently, FDA has completed the reclassification of a number of these devices, such as thoracolumbosacral pedicle screw systems (including semi-rigid systems), electroconvulsive therapy devices (certain indications), and cranial electrotherapy devices (certain indications). These and other examples of reclassified, formerly Class III preamendments devices are identified at https://www.fda.gov/about-fda/cdrh-transparency/515-project-status.

II. BGS Devices and Reclassification Standards

A. Device Classification and BGS Devices

Under the Federal Food, Drug, and Cosmetic Act ("FDCA") and FDA regulations, three classes of medical devices exist 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 (low risk/general controls), Class II (moderate risk/general and special controls), and Class III (high risk/premarket approval). BGS Devices are and always have been regulated in Class III, which has ensured their safety and effectiveness.[7] Among other indications, all BGS are approved for treatment of non-unions. As the Panel and even the petitioner that previously sought down-classification readily affirmed, BGS Devices are "of substantial importance in preventing impairment of human health," thus meeting a critical statutory criterion for Class III status.[8,9] Indeed, a recently published literature review notes that "[p]seudarthrosis is an exceedingly common, costly, and morbid complication in the treatment of long bone fractures and after spinal fusion surgery" that can "prolong musculoskeletal disease and physical disability" and "contribute to poor functional outcomes…and quality-of-life metrics."[10] Experts have also observed that "[f]ailure or delays in bone healing often require further intervention and may result in serious morbidity such as increased pain and functional limitations."[11]

Underscoring the importance of BGS Devices in preventing severe harm to human health, research studying the effects of long bone non-unions on patients' physical health, mental health, and quality of life has revealed that their impact in these respects is "comparable with the reported impact of end-stage hip arthrosis and worse than that of congestive heart failure"[12] and other severe conditions including "type-1 diabetes mellitus, stroke, and acquired immunodeficiency syndrome."[13] From data on tibia shaft fractures, fracture patients who experience non-unions are more likely to suffer with serious co-morbidities, experience additional fractures within two years, and depend on strong use of

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[7] BGS Devices are "postamendments" Class III devices, i.e., devices that were not in commercial distribution prior to May 28, 1976, the enactment date of the Medical Device Amendments.
[8] FDCA § 513(a)(1)(C)(ii)(I) (21 U.S.C. § 360c(a)(1)(C)(ii)(I)) and 21 CFR § 860.3(c)(3).
[9] See Transcript of Orthopaedic and Rehabilitation Devices Panel Meeting of June 2, 2006 ("2006 Panel Transcript") at 301-302 (remarks of Panel members).
[10] Khalifeh JM et al., Electrical Stimulation and Bone Healing: A Review of Current Technology and Clinical Applications. IEEE Reviews in Biomedical Engineering Vol. 11, 2018: 217-232.
[11] Aleem, IS et al., Efficacy of Electrical Stimulators for Bone Healing: A Meta-Analysis of Randomized Sham-Controlled Trials. Sci. Rep. 19;6:31724; doi: 10.1038/srep31724 (2016).
[12] Brinker MR et al., The devastating effects of tibial nonunion on health-related quality of life. J Bone Joint Surg Am. 2013 Dec 18;95(24):2170-6. Doi:10.2106/JBJS.L00803; see also Brinker MR et al. Debilitating Effects of Femoral Nonunion on Health-Related Quality of Life. J Orthop Trauma. 2017 Feb;31(2):e37-e42. Doi: 10.1097/BOT.0000000000000736.
[13] Schottel PC et al., Time Trade-Off as a Measure of Health-Related Quality of Life: Long Bone Nonunions Have a Devastating Impact. J Bone Surg Am. 2015 Sep 2;97(17):1406-10. Doi: 10.2106/JBJS.N.0190.

opioids.[14] Researchers have thus stressed the "devastating" and "debilitating" nature of non-unions.[15] In this context, it is crucial that the effectiveness and safety of BGS Devices be rigorously assured, and, given the unknowns about BGS Devices and the high variability of waveform characteristics, this can be achieved only under Class III controls.

Notably, FDA has up-regulated several devices to subject them to PMA/Class III requirements because important risks or harms have materialized under less stringent controls. For example, as FDA explained in the context of metal-on-metal total hip implants, "[R]eports [of risks and harms], as well as recent recalls of devices from the U.S. market, have indicated that preclinical testing currently used to support [510(k)] marketing clearance of these devices has not been sufficient to mitigate the risks associated with these devices and identify potential clinically-relevant failure modes."[16]

By contrast, all BGS Devices approved by FDA have been authorized for marketing on the basis of data from Level 1 and Level 2 clinical trials substantiating their safety and effectiveness. These devices have also been strictly regulated post-marketing with ongoing FDA review of all design, labeling, and manufacturing changes under Class III controls. Under this regime, the approved BGS Devices have a long and strong record of safe and effective performance. As FDA recognized in considering and rejecting another down-classification effort, it must be appreciated "that the safety record…to date represents the performance of [devices] for which there are approved PMA's" and Class III controls.[17]

As detailed below, in light of the significant potential risks and harms associated with BGS Devices, the consistently safe and effective performance of approved technologies since they were first authorized by FDA over four decades ago manifests the importance of their Class III classification. Further, though few adverse event reports has been one factor FDA has cited in down-classifying certain devices in recent years, FDA has also recently affirmed that "a low number of MDRs [Medical Device Reports]" does not support reclassification where, as FDA and the Panel previously recognized for BGS Devices, "there is insufficient information to establish special controls that…will provide a reasonable assurance of safety and effectiveness…."[18]

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[14] Antonova E et al. Tibia shaft fractures: costly burden of nonunions. BMC Musculoskeletal Disorders 2013, 14:42. http://www.biomedcentral.com/1471-2474/14/42

[15] See Brinker et al., *supra* n. 12.

[16] FDA, Effective Date of Requirement for Premarket Approval for Two Class III Preamendments Devices; Proposed Order, 78 Fed. Reg. 4094, 4097 (January 18, 2013); this proposal was finalized in 2016. See FDA, Effective Date of Requirement for Premarket Approval for Total Metal-on-Metal Semi-Constrained Hip Joint Systems; Final Order, 81 Fed. Reg. 8146 (February 18, 2016) (emphasis added).

[17] FDA, Reclassification of Daily Wear Spherical Contact Lenses Consisting of Rigid Gas Permeable Plastic Materials; Withdrawal of Proposed Rule, 48 Fed. Reg. 56778, 56783 (Dec. 23, 1983) ("Contact Lens Rule").

[18] FDA, Neurological Devices; Reclassification of Cranial Electrotherapy Stimulator Devices Intended to Treat Anxiety and/or Insomnia; Effective Date of Requirement for Premarket Approval for Cranial Electrotherapy Stimulator Devices Intended to Treat Depression; Final Amendment, Final Order, 84 Fed. Reg. 70003, 70008 (December 20, 2019).

To change the classification of BGS Devices, FDA bears the burden of proving that down-regulation is warranted. On this point, "FDA has consistently maintained that proponents of reclassification assume the burden of demonstrating – through "publicly available, valid scientific evidence" – that the device's present classification is inappropriate and that the proposed classification will provide reasonable assurance of the device's safety and effectiveness."[19] To date, no such evidence has emerged to enable Class II classification of BGS Devices. To the contrary, the scientific limitations that the Panel and FDA previously identified as barriers to reclassification persist today. FDA has not identified information otherwise, and the Coalition – which generates and assiduously monitors scientific developments in this space – is aware of none. Absent changes in the fundamental realities precluding reclassification that the Panel and FDA previously cited, Class III remains the only appropriate classification for these devices.

B. Standards for Reclassification

To reclassify devices, FDA must identify a "generic type of device" for which "there is sufficient information to establish special controls" that, together with general controls applicable to all medical devices, would be adequate to provide "reasonable assurance of the safety and effectiveness" ("RASE") of the generic device type. In other words, FDA must be able to define a "generic type of device" whose safety and effectiveness can reasonably be assured by a common set of special controls. A "generic type of device" is a "grouping of devices that do not differ significantly in purpose, design, energy source, function, or any other feature related to safety and effectiveness, and for which similar regulatory controls are sufficient to provide [RASE]."[20]

As earlier noted, information FDA may rely on to reclassify a device must generally be valid scientific evidence that is publicly available.[21] By statute, FDA may also rely for reclassification on certain information in PMAs that have been approved for six or more years; however, the permissible information does not include methods of manufacture, product composition, or other trade secrets.[22] FDA has previously noted that waveform parameters – including a description of "what range of technical specification is necessary to ensure a clinically effective treatment signal/dose" – would be critical to support down-classification.[23] Yet, as discussed at the 2006 Panel Meeting, the BGS Coalition member companies maintain as trade secrets these parameters integral to each BGS Device, and, accordingly, have not publicly identified all necessary parameters.[24] Absence of such

[19] Contact Lens Manufacturers Association v. FDA, 766 F.2d 592, 599-600 (D.C. Cir. 1985) (internal citations omitted).
[20] 21 CFR § 860.3(i) (emphasis added).
[21] See FDCA § 520(c) (21 U.S.C. § 360j(c)) and 21 CFR § 860.7(c)-(g).
[22] See FDCA § 520(h)(4) (21 U.S.C. § 360j(h)(4)).
[23] Letter from Donna Bea-Tillman, Ph.D., FDA, to William Carroll, RS Medical re: RS Medical's reclassification petition for Non-invasive Bone Growth Stimulators (August 12, 2005), at 3.
[24] See 2006 Panel Transcript at 195, 199, 236 (remarks of Dr. Bruce Simon (member of BGS Stimulator Opposition Group (precursor to BGS Coalition)).

information in the public domain further complicates the ability to establish special controls for this product class.

Moreover, special controls that would enable devices to qualify for Class II classification include the promulgation of performance standards, postmarket surveillance, patient registries, special labeling requirements, and the development of guidelines for premarket 510(k) submissions.[25] While special control guidelines may include guidelines for the submission of clinical data in 510(k)s to help establish substantial equivalence, FDA rarely requires clinical data to support 510(k) submissions, and in several of those cases, clinical data is required only in certain 510(k)s where proposed devices do not meet listed performance parameters, as opposed to being routinely required for each device proposed for clearance.[26] Additionally, 510(k)s supported by clinical data can include devices with clinical performance testing short of randomized, controlled clinical trials. Put simply, devices whose performance must always be substantiated by data from well-controlled clinical trials are not typically classified in Class II.

Further, a device cannot be classified into Class II – even with a special control requiring clinical trials – if other regulatory controls characteristic of Class III (e.g., review of all post-approval changes, pre-market inspection and review of manufacturing compliance) are necessary to reasonably assure the device's safety and effectiveness, and/or information is not available or adequate to establish additional special controls necessary to provide RASE. This is the case for BGS Devices, as further explained below. Although FDA has authority to implement a broad range of controls under its special controls authority, the Agency itself has made clear on multiple occasions that where controls needed to provide RASE for a device include multiple measures solely or primarily associated with Class III, they cannot be collectively adopted as Class II special controls for purposes of enabling down-classification. Making the Class II/510(k) framework functionally "indistinguishable" from the Class III/PMA framework "would exceed the authority of section 510(k) of the [FDCA]"[27] and would improperly "blur the distinction of the regulation classifications [Class III versus Class II]."[28]

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[25] See FDCA § 513(a)(1)(B) (21 U.S.C. § 360c(a)(1)(B)).

[26] See, e.g., FDA, Guidance for Industry and Food and Drug Administration Staff; Class II Special Controls Guidance Document: Repetitive Transcranial Magnetic Stimulation (rTMS) Systems (July 26, 2011), at 4 ("You should indicate whether your device falls within the limits listed in Table 2. If your device does not fall within these parameters, FDA may recommend that you provide data from a clinical study to demonstrate that your device's output parameters are as safe as those of the predicate device"). Very few 510(k)s cleared for rTMS devices have required clinical data.

[27] Contact Lens Rule, 48 Fed. Reg. at 56, 790.

[28] FDA, Summary from the Circulatory System Devices Panel Meeting (January 25, 2011), at 2; see also FDA, Effective Date of Requirement for Premarket Approval for Automated External Defibrillator Systems; Final Order, 80 Fed. Reg. 4783, 4785 (January 29, 2015).

III. BGS Devices Do Not Satisfy the Standards for Reclassification into Class II

A. BGS Devices Do Not Constitute a "Generic Type of Device" for Which a Single Set of Special Controls Would be Adequate

FDA has proposed to reclassify ultrasound BGS Devices and all types of electrical BGS Devices together under a unitary set of special controls. Doing so would not be warranted. [29] As earlier noted, a "generic type of device" subject to down-classification must be a "grouping of devices that do not differ significantly" in "design,…function, or any other feature related to safety and effectiveness…."[30]

Contrary to this, there are substantial differences between, and even within, the electrical and ultrasound BGS Device categories that directly bear on the devices' safety and effectiveness. As such, BGS Devices do not comprise a "generic type of device" that can be grouped together for down-classification. There are 18 approved BGS Devices, and they are substantially heterogeneous. Key differences among the devices include differences in device modalities, mechanisms of action, waveforms, dosimetries, designs, and intended uses. For each approved device, these differences manifest in unique dosed responses promoting osteogenesis. Each device has unique specifications related to therapeutic field specifications, effective treatment volumes, and ambient magnetic field operating compensation parameters. As FDA has determined in other cases, devices cannot be grouped together for down-classification where, as here, they "are widely variable from model to model as well as from manufacturer to manufacturer" and this "limit[s] the ability to develop comprehensive performance standards which would apply to all aspects of [device] design, testing, and use."[31]

The different modalities of electrical BGS Devices (pulsed electromagnetic fields ("PEMF"), capacitive coupled electric fields ("CC"), and combined magnetic fields ("CMF")) and ultrasound BGS Devices (low intensity pulsed ultrasound ("LIPUS")) represent significantly different device designs and signal generation.[32,33] CC devices use surface electrodes placed on the skin with a high-frequency, oscillating electric current passed between them. CMF devices use a low-frequency sinusoidal AC magnetic field overlaid onto a static DC magnetic field. PEMF devices use conducting coils and induce electric current by creating a time-varying (pulsed) electromagnetic field with particular

[29] As FDA acknowledges in the proposed order, ultrasound BGS Devices were not included in the reclassification effort considered at the 2006 Panel Meeting.
[30] 21 CFR § 806.3(i).
[31] FDA, Effective Date of Requirement for Premarket Approval for Cardiovascular Permanent Pacemaker Electrode; Proposed Rule, 76 Fed. Reg. 48058, 48060 (Aug. 8, 2011). In its 2014-2015 retrospective review of PMA devices, FDA determined that these devices should continue to be maintained in Class III.
[32] Ramanujam et al. Bone Growth Stimulation for Foot and Ankle Nonunions. Clin Podiatr Med Surg. Vol. 26, 2009: 607-618.
[33] Cook JJ et al. Healing in the New Millennium: Bone Stimulators. An Overview of Where We've Been and Where We May be Heading. Clin Podiatr Med Surg. Vol. 32(1), 2015: 45-59. Doi: 10.1016/j.cpm 2014.09.003.

pulse trains, pulse shapes, pulse repetition frequency, and magnetic field strength. LIPUS device transducers are coupled to the skin using ultrasound coupling gel; the transducer provides LIPUS waves, with a particular repletion rate and pulse trains, in response to an electrical drive signal.

Along with differences in signals, the designs of PEMF devices also differ by intended use. For spinal fusion, a PEMF device may use a Helmholtz coil design that surrounds the area and focuses a low-level magnetic field to the spinal fusion site. For long bone non-union, a PEMF device may use a custom-designed transducer unique to the particular anatomy for treatment, i.e., a triangular shape for the proximal humerus and a rectangular shape for the clavicle.

The dissimilarities among BGS Devices present different risks that cannot be addressed using the same set of special controls. FDA has historically required device-specific testing for each modality precisely for the purpose of "address[ing] the safety issues related to the specific modality involved" in a BGS Device.[34] FDA has also long recognized that "similarity in health risks is fundamental to the concept of classification by generic type of device."[35] Accordingly, in the Agency's words, where, as here, "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."[36]

Fundamentally, the differing BGS Device modalities, and slight variations within these modalities, affect bone growth and cellular processes in different ways, not all of which are fully understood. Experts reviewing the literature on various BGS Device modalities have recently commented that "the precise biological mechanisms underlying the phenomenon of electrically induced osteogenesis have not yet been fully elucidated[.]"[37] These experts have also remarked that "the literature is [still] inconclusive regarding biological risks (teratogenicity, mutagenicity) and the interaction of [BGS Devices] with simultaneous electrical implants…or metallic fixation devices."[38]

Other research has shown that CC, CMF, and PEMF modalities exhibit different biochemical pathways and produce different responses in bone-forming cells *in vitro*.[39] For example, CC signals appear to activate voltage-gated calcium channels leading to an increase in cytosolic calcium. By contrast, CMF and PEMF signals affect intracellular

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[34] FDA, Draft Guidance Document for Industry and CDRH Staff for the Preparation of Investigational Device Exemptions and Premarket Approval Applications for Bone Growth Stimulator Devices (April 28, 1998) (since withdrawn for other reasons).
[35] FDA, Final Rule on Medical Device Classification Procedures, 43 Fed. Reg. 32987, 32992 (July 28, 1978).
[36] Ibid.
[37] Khalifeh JM et al., Electrical Stimulation and Bone Health: A Review of Current Technology and Clinical Applications. IEEE Reviews in Biomedical Engineering Vol. 11, 2018: 217, 221-222.
[38] Ibid., p. 220.
[39] Brighton CT et al., Signal Transduction in Electrically Simulated Bone Cells, J Bone Joint Surg Am. 2001: 1514-23.

calcium release. Furthermore, each signal produces cell proliferation at different times and for different durations, and exposed cell cultures suggest that these electrical signals affect cellular pathways differently.[40] The pressure wave caused by LIPUS has been demonstrated to induce the formation of focal adhesions of integrins, initiating the production of cyclo-oxygenase-2 (COX-2), which is the rate-limiting enzyme in the production of prostaglandin E2 (PGE-2). The PGE-2 leaves the cell and therein triggers the production of other important bone biology factors, such as alkaline phosphatase, bone morphogenetic proteins (BMPs), and angiogenic factors such as vascular endothelial growth factor (VEGF) in the cells in the local environment.[41]

These points provide examples of the diversity among BGS Devices and highlight that varying or unknown risk implications of device differences prevent identification of a unitary set of special controls adequate to assure safe and effective performance for all products across or within the divergent modalities. Moreover, any attempt to specify a single set of special controls a priori, such as those in the proposed order, may not be sufficient to address new risks that can potentially be introduced by new BGS Devices with novel or altered signals. As FDA has stated, devices are good candidates for down-classification where "risks are now well understood…[and] technology uncertainties have been alleviated…." The distinctions among BGS devices and related implications show that these criteria are not met.

Waveform parameters critical to BGS Device safety and effectiveness are also complex and modality- and device-specific. These parameters vary as well by intended use. Relatedly, appropriate waveform tolerances are also product-specific.

FDA previously signaled the importance, for purposes of supporting a request for BGS Device down-classification, of identifying "a complete set of technical [waveform] parameters which would be sufficient to assure the reproducibility of clinically effective treatment."[42] In this vein, recent down-classifications of other waveform devices have included special controls for technical parameters that are "fully characterized and verified."[43] However, as discussed at the 2006 Panel Meeting, "what characteristics of [a] BGS signal are predominant in causing the biologic response" are not fully known;[44] nor is there knowledge by which to specify a common set of waveform parameters by which different BGS Devices within a purported "generic type" could be assessed for

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[40] Ibid.
[41] A Harrison, S Lin, N Pounder, Y Mikuni-Takagaki, Mode & mechanism of low intensity pulsed ultrasound (LIPUS) in fracture repair. Ultrasonics, 70 (2016); 45-52. http://dx.doi.org/10.1016/j.ultras.2016.03.016.
[42] Letter from Donna Bea-Tillman, Ph.D., FDA, to William Carroll, RS Medical re: RS Medical's reclassification petition for Non-invasive Bone Growth Stimulators (August 12, 2005), at 2.
[43] See 21 CFR § 882.5800(b)(v) (cranial electrotherapy stimulator, reclassified to Class II for certain uses via final order at 84 Fed. Reg. 70003 (December 20, 2019)) and 21 CFR § 882.5940(b)(i)-(ii) (electroconvulsive therapy device, reclassified to Class II for certain uses via final order at 83 Fed. Reg. 66103 (December 26, 2018)).
[44] 2006 Panel Transcript at 275-276 (comments of Dr. Ron Midura, Associate Professor, Department of Molecular Medicine, Cleveland Clinical Warner College of Medicine).

determining "substantial equivalence" under a Class II classification.[45] Rather, the waveform parameters and associated manufacturing tolerances permissible for any new BGS Device must be determined and substantiated through product-specific testing, including clinical testing.

The inability to ensure equivalent BGS Device performance through identity of waveform specifications is illustrated in the image below:

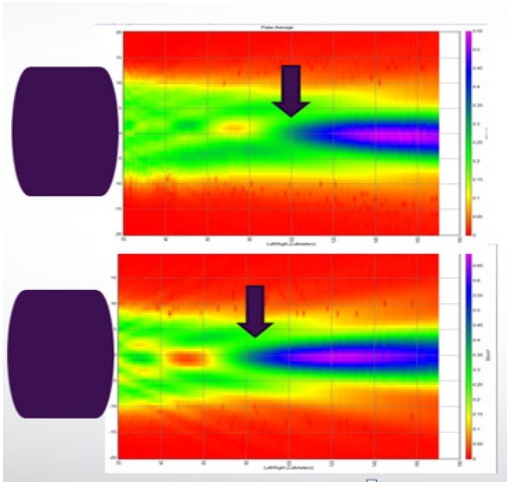

Figure: Acoustic Intensity Outputs of Two BGS Devices with Same Intensity Specification – Top (Unapproved BGS Device (LIPUS)), Bottom (FDA-approved LIPUS BGS Device)

The top image depicts a LIPUS-based device sold abroad that has not been approved by FDA; the bottom image depicts an FDA-approved LIPUS BGS Device. The average intensity over area for the unapproved device (top image) is quoted as 30 mW/cm^2, which is the same as that of the approved device (bottom image). Despite this identical specification, the maximum intensity of the ultrasound signal (denoted with the arrows) is further into the far field with the unapproved device as compared to the approved device; the near field shape is also different. Thus, the signal delivered to the fracture site is different between these two devices and may differentially impact efficacy. This highlights that new devices cannot be presumed to be safe and effective based on the appearance of equivalence to any approved BGS Device but, instead, must be proven through the same clinically rigorous standards met by currently approved devices.

Similarly, two other factors essential to device safety and effectiveness, dose and treatment time, are also specific to and vary across each BGS Device and indication.

[45] 2006 Panel Transcript at 234 (comments of Dr. Bruce Simon (member of BGS Stimulator Opposition Group (precursor to BGS Coalition)).

These, too, cannot be commonly defined to support a generic class of BGS Devices. For example, treatment times for approved BGS Devices range from 20 minutes a day to 24 hours a day.

Even within the same modality, different intended uses may require different treatment times. For instance, certain PEMF devices for use with non-unions are indicated for 3 and 10 hours of daily treatment, while other approved PEMF devices for lumbar and cervical spinal fusions are indicated for 2 and 4 hours daily, respectively. Duration of use and healing times can also vary by the anatomical site being treated (e.g., short versus long bone non-unions) and the patient's underlying comorbidities. As these variations reflect, treatment times and appropriate dosimetry must be established for any particular BGS Device through pre-clinical and clinical studies specific to the device and cannot be defined class-wide by a single set of design specifications or parameters.

As well, different BGS Devices have been approved for different uses/indications: acute fractures, non-unions, adjunct to lumbar spinal fusion, adjunct to cervical spinal fusion, number of vertebral levels, and non-operative treatment for pseudarthrosis. There are risks specific to particular indications (e.g., risks associated with the central nervous system for cervical spine use), and FDA has historically required different clinical testing across indications to address particularized safety concerns.[46] No two BGS Devices share the exact same technology, waveforms, indications, or treatment guidelines.

The variations among approved BGS Devices make clear not only that these devices are not controllable by a uniform set of special controls, but also that it is not presently possible to reasonably assure the safety and effectiveness of any BGS Device solely via special and general controls under a Class II classification. As the Panel and FDA concluded following the 2006 review of these devices, available special and general controls are insufficient to address the variables necessary to ensure that all BGS Devices provide consistent and effective treatment. Instead, Class III controls are required to avoid the substantial harms that result when these devices are ineffective.

B. Device-Specific Waveform Parameters Not Only Vary Across Devices, but Also Constitute Trade Secret Information Prohibited From Use in Supporting Reclassification

As discussed above, waveform parameters are particularized to individual devices and cannot be standardized across even a single BGS modality type, much less a "generic class" of BGS Devices comprised of multiple modalities. This is an important reality

[46] For example, citing the unique risks associated with cervical 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."

about waveform parameters that directs against reclassification, but not the only one.

Because the full listing of each approved BGS Device's specific parameters is maintained by the manufacturers as trade secret information, these parameters cannot be relied on to support reclassification of a "generic type" of BGS Device. This is disqualifying because, as FDA has stated, special controls to support reclassification of BGS Devices would need to include "a complete set" of waveform parameters that would be "necessary to ensure a clinically effective treatment signal/dose."[47]

C. Level 1 and 2 Clinical Data and Other Controls Associated with Class III are Necessary to Provide Reasonable Assurance of BGS Safety and Effectiveness

1. Clinical Data

The BGS Coalition respectfully submits that BGS Devices can only be shown to be safe and effective based on data that includes high-level clinical testing. Indeed, FDA has required all approved BGS Devices to be supported by Level 1 or Level 2 clinical data, and there is no basis to depart from this requirement. An important outcome of the 2006 Panel Meeting was the recognized "lack of knowledge about how waveform characteristics (e.g., pulse duration, amplitude, power, frequency) affect the clinical response to [BGS Device] treatment."[48] FDA agreed that relevant new preclinical test methods would be needed before Class III status could be lifted for these devices.[49]

FDA's proposed order affirms the need for new BGS Devices to be substantiated by clinical data but suggests allowing "flexibility in study design and the level of clinical evidence needed[.]"[50] We believe Level 1 and 2 clinical data continue to be necessary – and, thus, should continue to be required – to show appropriate performance of new BGS Devices. To date, no new knowledge or preclinical test methods adequate to determine clinical response to BGS have been developed; accordingly, well-controlled clinical studies remain essential to demonstrate the safety and effectiveness of these devices.

Though useful, current models for animal fracture repair have significant limitations that preclude their ability to fully represent the human clinical situation and predict human results, including with respect to approved BGS Device indications. The gaps in correlation of animal study results to results in humans is well-documented.[51] Just

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[47] Letter from Donna Bea-Tillman, Ph.D., FDA, to William Carroll, RS Medical re: RS Medical's reclassification petition for Non-invasive Bone Growth Stimulators (August 12, 2005), at 2-3.
[48] FDA, Orthopedic Devices; Reclassification of Non-invasive Bone Growth Stimulator; Notice of Panel Recommendation, 72 Fed. Reg. 1951, 1953 (Jan. 17, 2007) (published following June 2, 2006 Panel Meeting).
[49] Ibid.
[50] Proposed order, 85 Fed. Reg. 49986, 49990 (Aug. 17, 2020).
[51] See, e.g., Fredericks DC et al., Effects of Pulsed Electromagnetic Fields on Bone Healing in a Rabbit Tibial Osteotomy Model. 14 J. Orthop Trauma 2000; 93-100.

this year, researchers observed that animal studies are "foundational in bridging the gap from bench top to human subjects"[52]; in other words, they continue to be a prerequisite to – but not a replacement for – clinical studies.

One reason that animal studies cannot be a substitute for clinical studies is that well-known differences exist between animals and humans with respect to bone based cells (e.g., osteoblasts, osteoclasts). For example, rats and mice possess a primitive bone structure without Haversian systems compared to humans.[53] Rats and mice also have a greater healing capacity as animals of a lower phylogenetic scale compared to humans.[54] 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, and sheep to non-human primates used to evaluate bone morphogenetic proteins.[55] 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. These include:

- Acute Fracture Model Limitations

  There is no known standardized acute 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. Additionally, animal fracture models typically induce the 'fracture' by artificial means. For smaller animals this typically involves 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

[52] Gunderson ZJ et al. A comprehensive review of mouse diaphyseal femur fracture models. Injury, https://doi.org/10.1016/j.injury.2020.04.011.
[53] Nunamaker DM. Experimental Models of Fracture Repair. Clin Orthop Relat Res. October 1998; S56-65.
[54] Histing T, et al. Small animal bone healing models: standards, tips, and pitfalls results of a consensus meeting. Bone. 2011;49(4):591-9.
[55] Martin CJ et al. Posterolateral lntertransverse Process Spinal Arthrodesis with rhBMP-2 in a Nonhuman Primate: Important lessons learned Regarding Dose, Carrier, and Safety. J Spinal Disord. June 1999; 179-186.

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.[56,57]

Additionally, rodent definitions of a delayed or non-union are lacking.[58] 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. As previously discussed, 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.

Another limitation of significance is that animal studies evaluate radiographic healing only and cannot measure more clinically meaningful outcomes such as pain or functional improvement. Researchers have identified a need for future studies to assess these kinds of quality of life parameters.[59]

Lastly, there have been several instances where success in a preclinical model did not result in success in a clinical trial, underscoring the necessity of high-quality (Levels 1 and 2) human clinical trials prior to approval of a new BGS for commercialization. Examples include high rates of fusion in rat,[60] rabbit,[61] and canine[62] models for LIPUS, but a failure to demonstrate effectiveness for spinal fusion in a multicenter, prospective, double-blind, randomized, placebo-controlled pivotal clinical trial ("RCT")[63]; and successful acceleration of fibular and tibial

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[56] Manigrasso MB et al. Characterization of a closed femur fracture model in mice. J Orthop Trauma. 2004 18: 687-695.
[57] Lu C et al. Effect of age on vascularization during fracture repair. J Orthop Res 2008 26: 1384-1389
[58] Garcia P et al. Rodent animal models of delayed bone healing and non-union formation: a comprehensive review. Eur Cell Mater. 2013 16;26:1-12.
[59] See, e.g., Akhter S et al. Efficacy of Electrical Stimulation for Spinal Fusion: A Systematic Review and Meta-Analysis of Randomized-Controlled Trials. Sci. Rep. 10:4568; doi: 10.1038/s41598-020-61266 (2020); Griffin XL et al. Ultrasound and shockwave therapy for acute fractures in adults. *Cochrane Database of Systematic Reviews* 2012, Issue 2. Art. No.: CD008579. DOI: 10.1002/14651858.CD008579.pub2.
[60] Xu X et al. LIPUS promotes spinal fusion coupling proliferation of type H microvessels in bone. Sci. Rep 6, 20116; doi: 10.1038/srep20116 (2016).
[61] Glazer PA et al. Use of Ultrasound in Spinal Arthrodesis: A Rabbit Model. Spine 23 (10) 1142-1148 (1998).
[62] Cook SD et al. Low Intensity Pulsed Ultrasound Improves Spinal Fusion. The Spine Journal 1 (2001) 246-254.
[63] Park DK et al. Lumbar Spine Fusion Rates With Local Bone in Posterolateral and Combined Posterolateral and Interbody Approaches. Journal of the American Academy of Orthopaedic Surgeons Vol 3, No 11 (November 2019).

fracture healing in rats,[64] rabbits,[65] and canines[66] for a PEMF device, but no difference in reoperation rates in tibial fractures in a multicenter, double-blind RCT.[67]

In summary, as reported in recent literature regarding ultrasound BGS Devices, "[i]n-vitro studies are not appropriate to identify the full complexity of [human] biological effects…"[68] As such, only human trials can appropriately translate the complex character of a BGS Device's originating signal to the actual clinical performance of the device.

In addition to limitations in the ability of pre-clinical studies to determine clinical response, as noted above and remarked on by several Panel members and other experts at the 2006 Panel Meeting, clinical studies are vital for BGS Devices in light of certain other considerations as well. These include the need for effective dosing, which is specific to particular devices even within the same modality, to be determined through clinical trials (similar to drug dose-ranging studies),[69] as well as the biological effects of BGS Devices. Regarding the latter, as an independent expert at the 2006 Panel Meeting observed:

> The use of substantial equivalence to existing approved devices is particularly applicable for devices that are biologically-passive, such as total joint implants, but this approach presents a potential risk when the devices exert their intended influence directly through biological effects, such as the case with the spectrum of physical forces applied to humans for the purpose of enhancing fracture repair, including the use of electrical stimulation, application of electromagnetic fields, and exposure to ultrasound, all of which under specific circumstances influence bone biology for better or worse. …The manner in which target cells are activated by physical forces is only partially understood for this group of devices and for any individual bone growth stimulating device. As such, effectiveness should be demonstrated and similarity ascribed through dependable outcome analysis rather than rest on the argument of substantial equivalence in waveform generation to previously-approved devices. An approvable device should act safe and effective, not just look

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[64] Androjna C et al. Pulsed Electromagnetic Field Treatment Enhances Callus Biomechanical Properties in an Animal Model of Osteoporotic Fracture. Bioelectromagnetics 35:396-405 (2014); Midura RJ et al. Pulsed electromagnetic field treatments enhance the healing of fibular osteotomies. Journal of Orthopaedic Research 23 (2005) 1035-1046.

[65] Fredericks DC et al. Effects of Pulsed Electromagnetic Fields on Bone Healing in a Rabbit Tibial Osteotomy Model. Journal of Orthopaedic Trauma Vol. 14(2), February 2000, pp. 93-100.

[66] Inoue N et al. Effect of pulsed electromagnetic fields (PEMF) on late-phase osteotomy gap healing in a canine tibial model. Journal of Orthopaedic Research 20 (2002) 1106-1114.

[67] Adie S et al., Pulsed Electromagnetic Field Stimulation for Acute Tibial Shaft Fractures; A Multicenter, Double-Blind, Randomized Trial. J Bone Joint Surg Am. 2011;93:1569-76 http://dx.doi.org/10.2106/JBJSJ.00869.

[68] Padilla F et al., Stimulation of bone repair with ultrasound: A review of the possible mechanic effects. Ultrasonics 54 (2014) 1125-1145.

[69] See, e.g., 2006 Panel Transcript at 43 (remarks of Jim Ryaby, Ph.D., on behalf of the BGS Stimulator Opposition Group (precursor to BGS Coalition)) ("Most importantly, we have no predictive equations today that can define a priori what an effective signal is or what an effective dosage is without testing this in well-designed clinical trials").

the role.[70]

Well-controlled clinical trials are a fundamental control for Class III devices. By contrast, clinical data of any sort, much less Level 1 or Level 2 clinical data, are not standard for Class II devices. As FDA states, "Clinical data is not typically included in 510(k)s to demonstrate SE [substantial equivalence]."[71] Further, even in the rare instances where clinical data is sought for Class II devices, it need not be Level 1 or 2 data and often is not.[72] As FDA has noted, "In many cases, the clinical data necessary to support a 510(k) involve a relatively small number of patients and may involve a simpler study design than is necessary to support a premarket approval application [PMA]."[73] This is reflected in the down-classification of some devices with a special control of clinical data. For example, semi-rigid thoracolumbosacral pedicle screw systems were so reclassified, and recent 510(k) clearances for these devices have been supported by non-Level 1 or 2 clinical data.[74]

The Class II/510(k) pathway is distinct from the Class III/PMA pathway in important ways that make Class III best suited for devices for which high-level clinical evidence is necessary. For example, the standard for marketing authorization in Class II is "substantial equivalence" ("SE") to a predicate device (in terms of intended use and technological characteristics), which means that clinical data can be required only insofar as it is needed to show SE.[75] This is a different standard than the standard for Class III/PMA approval, which is an independent showing of the proposed device's safety and effectiveness.[76] For the reasons set forth in this letter, the latter showing is necessary to establish appropriate performance of BGS Devices. Moreover, FDA's review time for Class II/510(k) devices is 90 days, which is merely half the time allowed for Class III/PMA devices (180 days).[77] The extended review time afforded in Class III best accommodates and ensures a robust review of essential, substantial clinical data.

Consistent with the above, while FDA has, in a limited number of cases, required clinical studies as a special control in down-classifying certain devices, since its 2006 consideration of BGS Devices, this Panel has not recommended down-classifying, and FDA has not down-classified, any orthopedic device that, like BGS Devices, (i) requires

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[70] 2006 Panel Transcript at 28-29 and 31 (remarks of Gary Friedlaender, M.D., Professor and Chair of Orthopaedics and Rehabilitation, Yale University School of Medicine).
[71] FDA, Benefit-Risk Factors to Consider When Determining Substantial Equivalence in Premarket Notifications (510(k)) with Different Technological Characteristics (Sept. 25, 2018), at 7.
[72] Ibid. (besides randomized controlled trials, clinical data in 510(k)s can include data from "partially controlled studies, studies and objective trials without matched controls, well-documented case histories…, certain reports of significant human experience, and testing on clinically derived human specimens…").
[73] FDA, The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications [510(k)]; Draft Guidance (Dec. 27, 2011) (guidance later revised and finalized).
[74] See, e.g., K182928 (cleared based on clinical data from a retrospective study and clinical literature).
[75] See FDCA § 513(f) (21 U.S.C. § 360c(f)) and 21 CFR § 807.100.
[76] See FDCA § 515(d)(2)(A) and (B) (21 U.S.C. § 360e(d)(2)(A) and (B)).
[77] See 21 CFR § 807.81(a) and 21 CFR § 814.44(c).

determination of safety and effectiveness by Level 1 or 2 clinical data, and (ii) is considered to be of substantial importance to preventing impairment of human health. Also, in 2015, FDA advised that "factors to indicate a device is a good candidate for…reclassification" include, in relevant part, if "technology uncertainties have been alleviated, performance standards or non-clinical tests have been developed that could be surrogates for some clinical testing, [or] the need for a controlled study could be eliminated due to defined objective performance criteria[.]"[78] As discussed above, BGS Devices do not meet these criteria.

2. Class III Post-Approval Change Control and Pre-Approval Inspection and Manufacturing Review

FDA has emphasized that certain regulatory controls "are appropriately reserved to class III devices subject to [PMA] approval."[79] These include controls crucial to providing RASE for BGS Devices.

One such control is close FDA review of post-approval device modifications. As previously discussed, each BGS Device has a unique design; BGS manufacturing processes are also device-specific. FDA has explained that:

> [W]hen approval of a premarket submission for any change to a device that affects safety or effectiveness is necessary to provide RASE, general and special controls are insufficient…, and classification in class III is necessary. Section 515(d)(6) of the [FDCA] provides explicit authority to require premarket approval of a supplemental [PMA] application for any change to an approved device that affects safety or effectiveness (with the exception of changes to certain manufacturing methods or procedures, for which a notice to FDA must be submitted 30 days prior to implementation). FDA considers this to be a regulatory control reserved for class III devices. For higher risk devices with unique design characteristics or manufacturing processes, it is essential for FDA to assess any change that affects safety or effectiveness premarket to ensure that RASE is maintained, for example because of the cumulative impact that multiple changes may have on the safety or effectiveness of the device over time.[80]

[78] FDA, Retrospective Review of Premarket Approval Application Devices; Striking the Balance Between Premarket and Postmarket Data Collection, 80 Fed. Reg. 23798, 23800 (April 29, 2015).
[79] FDA, Medical Device Classification Procedures; Proposed Rule, 79 Fed. Reg. 16252, 16256 (March 15, 2014).
[80] Ibid. (emphases added).

While all device modifications must be reported to FDA under the Class III/PMA framework, in Class II/510(k), only those modifications that could "significantly" affect device safety or effectiveness - as determined by the device manufacturer - must be reported.[81] This is a substantial difference from the Class III standard and diminishes FDA's visibility into post-market modifications, both in terms of individual modifications as well as the cumulative effect of multiple modifications made over time. The difference in these reporting standards can be of high practical consequence. For example, in certain cases, FDA has up-regulated devices from 510(k) regulation to Class III precisely because the greater degree of oversight of device modifications in Class III could prevent harms associated with modifications made under 510(k).[82]

Moreover, at the 2006 Panel Meeting, the Panel expressed significant concern over the serious risks of inconsistent or ineffective treatment as implicated by post-market modifications to BGS Devices, including changes to waveform characteristics. As the Panel observed, "It is not known how a change to the device output due to device modifications may impact the clinical response to treatment."[83]

It remains the case that seemingly minor changes to the waveform parameters of a BGS signal can (individually and/or cumulatively) have significant impact on device effectiveness, the nature and extent of which cannot be accurately or reliably predicted. Research in the years since the 2006 Panel Meeting shows that even advanced, state-of-the-art pre-clinical methods do not permit determination of "how a change to the device output…may impact the clinical response to treatment."[84] For example, studies sponsored by a Coalition company and reported in 2017 to investigate the effects of a PEMF BGS Device in rat models (rotator cuff tears and osteoporosis) and guinea pig models (osteoporosis) revealed results "contrary to [study] hypotheses" that were developed using current knowledge and pre-clinical methods.[85]

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[81] 21 CFR § 807.81(a)(3)(i).
[82] See FDA, Effective Date of Requirement for Premarket Approval of Automated External Defibrillator Systems; Final order, 80 Fed. Reg. 4783, 4785 (Jan. 29, 2015) ("[M]any of the design and manufacturing changes that have led to [device] recalls were not required to be reported to FDA under the 510(k) process. If these changes had been reported prior to implementation, as would be required in the PMA regime, these recalls may have been avoided.").
[83] FDA, Orthopedic Devices; Reclassification of Non-invasive Bone Growth Stimulator; Notice of Panel Recommendation, 72 Fed. Reg. 1951, 1953 (Jan. 17, 2007)
[84] Ibid.
[85] Huegel J et al. Effects of pulsed electromagnetic field therapy at different frequencies and durations on rotator cuff tendon-to-bone healing in a rat model. J Shoulder Elbow Surg 2017; see also Androjna C et al. Optimizing Pulsed Electromagnetic Field (PEMF) Signals to Reduce Bone Loss Associated with Osteoporosis. Poster category: Bone – Osteoporosis, Metabolic Bone Disease, Biomarkers (PS2-110), Poster #: 1670, March 19-22, 2017, ORS (Orthopaedic Research Society), San Diego, California.

In its proposed order, FDA continues to recognize that ineffective BGS treatment is "clinically significant" and "may lead to clinical symptoms (e.g., pain) and the need for surgical interventions."[86] In light of of the severe risks to human health when BGS Devices are not effective in promoting osteogenesis, FDA review and approval of all device modifications remains essential to assure the continued safety and effectiveness of BGS Devices post-marketing. Modifications to BGS Devices are not uncommon and often occur because of supply chain disruptions or essential components experiencing end-of-life. These events can necessitate design or production process modifications, the review of which by FDA is crucial to ensure continuing conformance to critical product and manufacturing specifications.

Another control specific to Class III that is essential to provide RASE for BGS Devices is FDA's authority to conduct pre-market inspections and review of comprehensive design and manufacturing information. Because FDA lacks authority for Class II devices to routinely conduct premarket inspections of, or condition 510(k) clearance on, manufacturing/quality system compliance, the Agency has advised that:

> [W]hen a review of a full description of the methods used in, and the facilities and controls used for, the manufacture [and] processing…of a device is necessary to provide RASE 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.[87]

FDA has also stated that premarket inspections are vital to help the Agency ensure that important "clinical or nonclinical data were collected in a manner that ensures the data accurately represents the risks and benefits of the device."[88]

The design and manufacturing processes for all BGS Devices are critical to enable correct and consistent production of products that conform to waveform parameters and manufacturing tolerances that are precise, unique, and necessary to ensure device safety and effectiveness. Further, manufacturers rely on customized tools to develop and ensure alignment with key device specifications. Proprietary measuring equipment and techniques are used to inspect each device's therapeutic output and accommodate local ambient conditions. Manufacturing controls and specifications are not uniform across all BGS Devices or within BGS Device modalities, and standardized manufacturing criteria and test methods to which conformity can be declared do not exist. FDA's ability to

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[86] Proposed order, 85 Fed. Reg. 49986, 49992 and 49990.
[87] FDA, Medical Device Classification Procedures; Proposed Rule, 79 Fed. Reg. 16252, 16256 (March 15, 2014
[88] FDA, Medical Device De Novo Classification Process; Proposed Rule, 83 Fed. Reg. 63127, 63136 (December 7, 2018).

review manufacturing tools and techniques prior to authorizing the launch of a new device is thus an essential means of providing RASE for BGS Devices. Moreover, the Agency's ability to assess and ensure the quality and accuracy of data submitted in support, and as critical representations, of the safety and effectiveness of these devices, is also essential for these complex and highly important products.

In short, multiple controls specific to or primarily associated with Class III are necessary to reasonably assure the safety and effectiveness of BGS Devices. As such, these devices must be retained in Class III.

IV. Additional Harms Would Result from Reclassifying BGS Devices

Beyond the definitions and standards specific to Class II and Class III devices, any proposed down-classification of BGS Devices would also implicate broader considerations with relevance to patient health. One important consideration is the potential impact of a down-classification decision on innovation in this space. Many experts have stressed the need for "further technological improvements in available [BGS] device systems"[89] and "further research through high-quality randomized trials…to establish the efficacy of [these devices] on pain and functional outcomes."[90] Down-classification would substantially lessen opportunities and incentives to pursue such efforts.

The BGS Coalition companies are, and have consistently been, actively engaged in clinical research and technological improvements. Their efforts include both optimizing device use for current indications as well as addressing new indications to meet patient needs. Indeed, FDA is aware of and involved in the efforts of one Coalition member to develop important clinical data regarding prevalent, real-world off-label uses of ultrasound BGS Devices. As another example, FDA is also aware of ongoing IDE studies by another Coalition member to evaluate PEMF BGS Devices as an adjunct to surgical repair of rotator cuff tears, a common injury marked by high rates of re-tear and revision surgery that may be mitigated if BGS treatment is effective.

To a large extent, the BGS Coalition's research and innovation efforts are spurred by the Class III framework. Each Coalition member understands that all other members are held to the strict standards of PMA approval, which require and reward the conduct of clinical studies and continued evolution of device technologies.

Depending on the scope of any change in BGS Device classification, such a change could mitigate or remove structural incentives that, over the decades, have proven to promote device innovation (e.g., the "gold standard" PMA threshold to gain market entry, the six-year rule precluding competitor reliance on an approved PMA). Insofar as such a change would allow and

[89] Khalifeh JM et al., Electrical Stimulation and Bone Health: A Review of Current Technology and Clinical Applications. IEEE Reviews in Biomedical Engineering Vol. 11, 2018: 217-232.
[90] Akhter S et al., Efficacy of Electrical Stimulation for Spinal Fusion: A Systematic Review and Meta-Analysis of Randomized-Controlled Trials. Sci. Rep. 10:4568; doi: 10.1038/s41598-020-61266 (2020).

encourage market entry by entities with interests limited to producing follow-on products, rather than pursuing research or significant device innovation, reclassification of BGS Devices would quell Coalition members' ability and impetus to continue pursuing device research and improvements that could further patient health.

This is not a generic or theoretical concern but, rather, one grounded in actual experience. In the ultrasound BGS Device space, one BGS Device manufacturer is aware of a company that markets a non-FDA-approved ultrasound BGS Device in international markets. That company's practice is to promote its device with express comparison, reference to, and reliance on the BGS Device manufacturer's approved ultrasound BGS Device and related published studies. In the US, the approved ultrasound BGS Device is used in certain off-label indications, which have arisen without the approved manufacturer's promotion, but with respect to which (with FDA's knowledge) the approved manufacturer has initiated a clinical study to support future approval. Based on observed marketing practices, it is foreseeable that the unapproved competitor, if it were to gain entry to the US market following a Class II reclassification, could obtain widespread use of its device in these additional indications, even if it does not (i) seek or obtain marketing authorization for the indications, or (ii) prove its device to be safe or effective for the same. The prospect of this scenario serves as a disincentive to future research investments by the approved BGS Device manufacturer.

Further, as recognized by the Panel at the 2006 Panel Meeting and reiterated by FDA in its recent proposed order, ineffective BGS devices pose a substantial risk to patient health. The potential for regulatory action to facilitate the availability of ineffective devices, whether in on-label and/or medically recognized off-label indications, is an important harm that can and should be considered when evaluating the consequences of device reclassification and whether such action is warranted. For example, FDA's decision on reclassification of cranial electrotherapy stimulator (CES) devices was guided in part by concerns regarding reports of improper marketing of CES devices for certain unsubstantiated indications.[91] The potential risks of furthering wide-scale availability of purported, but unproven, "me-too" devices are best avoided by maintaining BGS Devices in Class III. Moreover, as detailed above, not only is this desirable, it also necessary because, for the reasons recognized by FDA and the Panel following the 2006 Panel Meeting, the legal and regulatory standards necessary for reclassification remain unmet.

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As FDA acknowledged following the last Panel review of BGS Devices, these devices are appropriately regulated in Class III and do not meet the statutory criteria for Class II reclassification.

[91] See FDA, Neurological Devices; Reclassification of Cranial Electrotherapy Stimulator Devices Intended to Treat Anxiety and/or Insomnia; Effective Date of Requirement for Premarket Approval for Cranial Electrotherapy Stimulator Devices Intended to Treat Depression; Final Amendment, Final Order, 84 Fed. Reg. 70003, 70009 (December 20, 2019).

In 2015, FDA stated that Class III devices would be favorable for down-classification if, among other things, their "risks are now well understood…, technology uncertainties have been alleviated, performance standards or non-clinical tests have been developed that could be surrogates for some clinical testing, [or] the need for a controlled study could be eliminated due to defined objective performance criteria….."[92] As detailed above, BGS Devices do not satisfy any of these factors.

Instead, the scientific realities that precluded reclassification of BGS Devices following the 2006 Panel Meeting still persist today. As the Panel and FDA recognized then, and as remains the case at present, seemingly minor differences between BGS Devices can produce differences in the devices' safety or effectiveness; moreover, adequate pre-clinical methods do not exist to avert the need for controlled clinical studies to evaluate each device. As well, there continue to be numerous performance-related distinctions among the divergent spectrum of BGS Devices. As such, they cannot be grouped together for reclassification, and information is not available to enable the development of special controls that, together with general controls, would be adequate to ensure the safety and effectiveness of these devices class-wide. Also, the importance of precise manufacturing tolerances and the potentially significant impact of device modifications necessitate FDA pre-approval review of design and manufacturing processes as well as FDA review of all post-market modifications. These controls are available only under a Class III classification.

For all the reasons above, BGS Devices must be retained in Class III.

Thank you for your consideration of these comments. Please contact Elaine Tseng (etseng@kslaw.com; (415) 318-1240) with any questions.

Respectfully submitted,

King & Spalding / Elaine Tseng

King & Spalding
Counsel to the BGS Coalition

Attachment (slide presentation for September 8, 2020 Panel Meeting)

[92] FDA, Retrospective Review of Premarket Approval Application Devices; Striking the Balance Between Premarket and Postmarket Data Collection, 80 Fed. Reg. 2378, 23800 (April 29, 2015).

Opposition to the Reclassification of External Bone Growth Stimulators

September 8, 2020

Food and Drug Administration
Medical Devices Advisory Committee
Orthopaedic and Rehabilitation Devices Panel

PRESENTED BY:

The BGS Coalition

bioventus® Active Healing Through Orthobiologics

DJO®

ORTHOFIX®

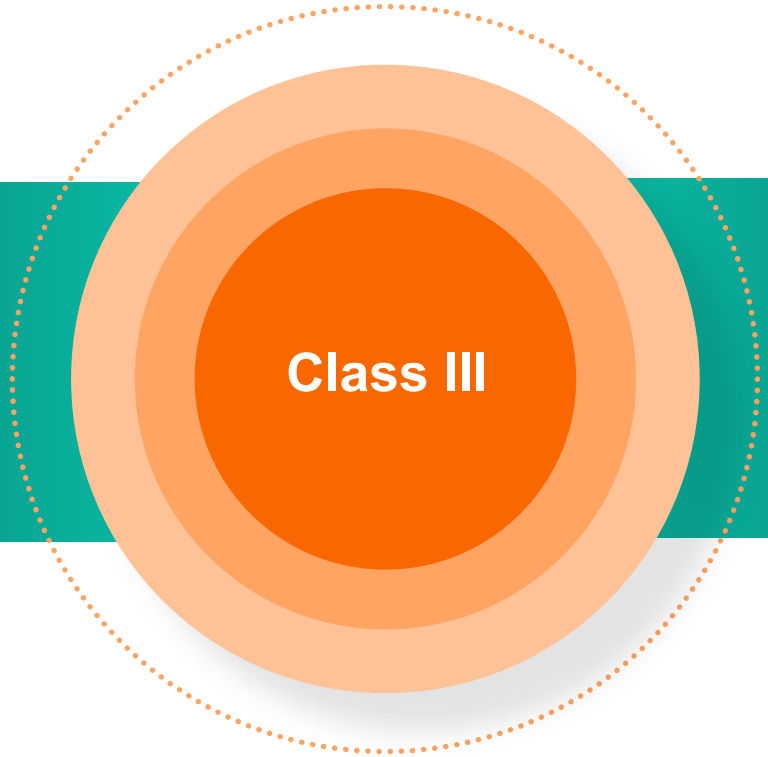
ZIMMER BIOMET

BGS Coalition

The BGS Coalition is an informal group of all the manufacturers of FDA-approved external bone growth stimulators (BGS): Bioventus LLC, DJO Global, Inc., Orthofix Medical Inc., and Zimmer Biomet. They are the leaders in the development of BGS technology.

The BGS Coalition supports maintenance of BGS devices in Class III.

Reclassification would permit potentially ineffective devices to enter the market.



BGS devices require control by Class III controls. An ineffective device poses serious harms to vulnerable patients.

BGS Coalition Presenters

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- Dr. Bhandari is Professor and Academic Head of the Division of Orthopaedic Surgery at McMaster University. He is the Associate Chair of Research in the Department of Surgery and holds a Canada Research Chair in Evidence-Based Orthopaedics - the only chair of its kind in Canada.
- Dr. Bhandari is recognized as a global leader in evidence-based trauma surgery and orthopaedic research. He has published 1000+ papers and major research textbooks.

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- Dr. Lim is a practicing orthopaedic spine surgeon with extensive experience treating patients with external bone growth stimulators. He is certified by the American Board of Orthopaedic Surgery and is a member of the American Academy of Orthopaedic Surgery, Lumbar Spine Research Society, North American Spine Society, and South Carolina Orthopaedic Society.
- Dr. Lim also conducts research, lectures, and consults to industry in the orthopaedic space.

James T. Ryaby, Ph.D.

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Orthofix Medical

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- Dr. Ryaby serves as Orthofix Medical's lead scientific advisor. He is a renowned authority on electrical bone growth stimulator technology and is widely published in this space.
- Dr. Ryaby has held memberships in the American Academy of Orthopaedic Surgery, North American Spine Society, International Cartilage Repair Society, The American Society for Bone & Mineral Research, and Orthopaedic Research Society, and has served as Professor of Bioengineering at Arizona State University.

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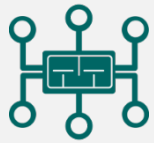
Clinical Experience with BGS Devices in Spine Applications		03
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Regulatory Considerations That Preclude BGS Reclassification

James T. Ryaby, PhD

Key Regulatory Requirements for Reclassification

- Devices to be reclassified must constitute a "generic type of device" that "do not differ significantly… in any…feature related to safety and effectiveness"
- Must be able to establish special controls, based on non-proprietary valid scientific information, to reasonably assure safety and effectiveness

Class III

Following the 2006 Panel review, FDA and the Panel agreed that BGS do not meet reclassification requirements, and *no new evidence changes this fact*. Safety and effectiveness remain reasonably assured only in Class III.

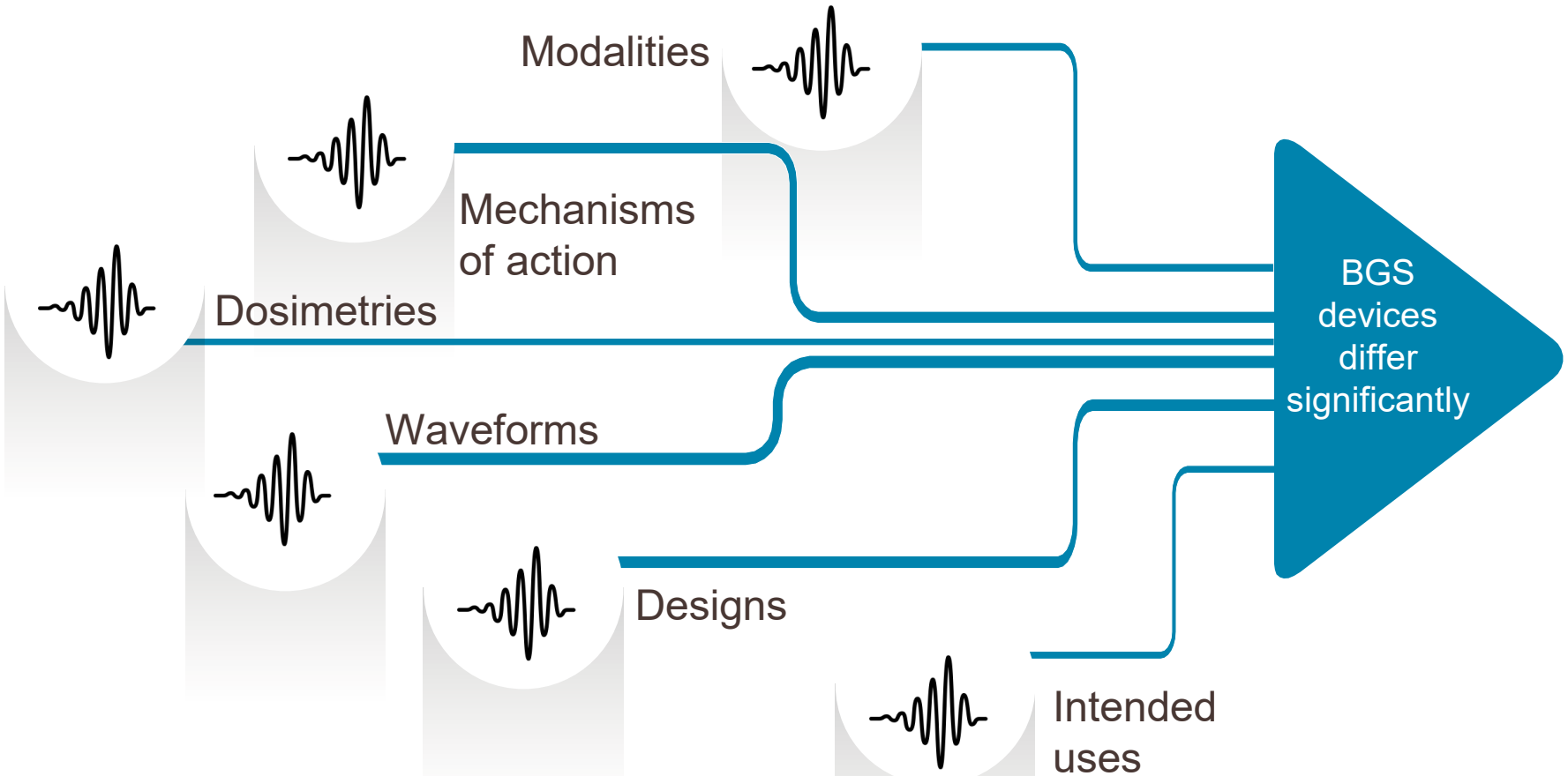
Overview: Class III is Appropriate - Findings from Last Panel Review Have Not Changed

- We appreciate FDA's re-review of BGS classification.
- Panel and FDA declined reclassification after 2006 Panel review citing:
  - **Lack of evidence to establish special controls** to mitigate risk of inconsistent or ineffective treatment
  - **Lack of knowledge about how waveform characteristics** affect clinical response to treatment
  - **Lack of knowledge about impact of device modifications** on clinical response to treatment
  - **Lack of adequate preclinical test methods** to mitigate risk of inconsistent or ineffective treatment

  "FDA concurs with the Panel's recommendation to retain [BGS] as a class III device."

  72 Fed. Reg. 1951, 1953 (Jan. 17, 2007)
- These findings are still applicable today. Class III remains the right classification.

BGS Devices Are Varied and Not a "Generic Type"

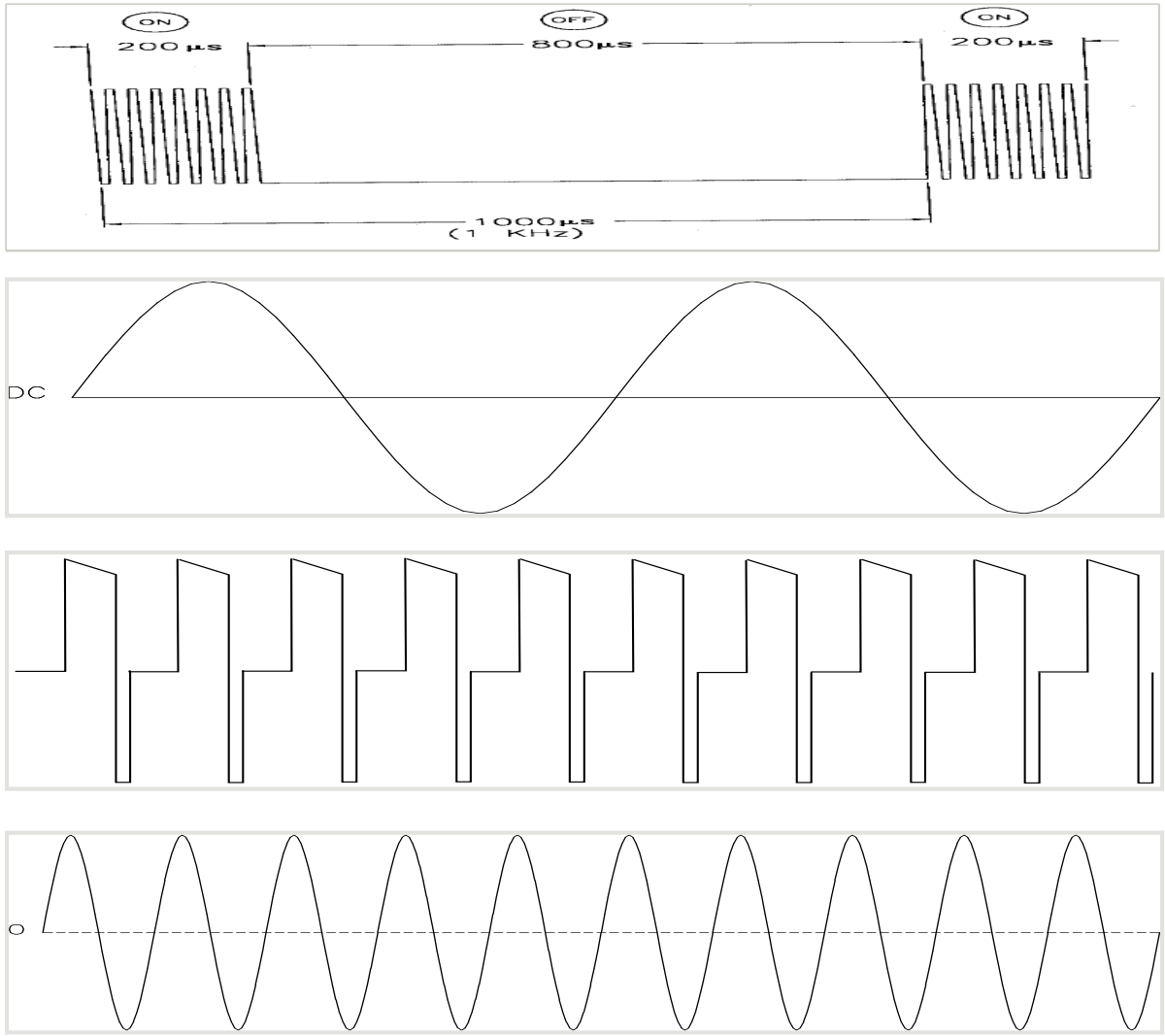


All are features that directly impact safety and effectiveness. The various types of BGS thus do not comprise a "generic type of device."

BGS Devices: Not a “Generic Type”

	bioventus	DJO	ORTHOFIX	ZIMMER BIOMET
DEVICES				
MARKET	SPINE | TRAUMA	SPINE | TRAUMA	SPINE | TRAUMA	SPINE | TRAUMA
	√	√ √	√ √	√ √
WEAR TIME	20 minutes / day	30 minutes / day	2 - 4 hours / day	3 – 10 hours / day
SIGNAL	Ultrasound	CMF	PEMF	CC

Distinctly Different Waveforms



Ultrasound (LIPUS)

- Sound waves are longitudinal waves consisting of areas of compression and rarefaction.
- Particles, when exposed to a sound wave will oscillate about a fixed point rather than move with the wave itself.

Combined Magnetic Field (CMF)

- 0.4 gauss AC
- 0.2 gauss DC @ 76Hz
- Combination of direct & alternating current to produce static & alternating fields

Pulsed Electromagnetic Field (PEMF)

- 20 gauss p-p
- Pulse Burst 200µsec up to 10kHz
- Rectangular Waveform

Capacitive Coupling Sinusoidal Electromagnetic Field (CC)

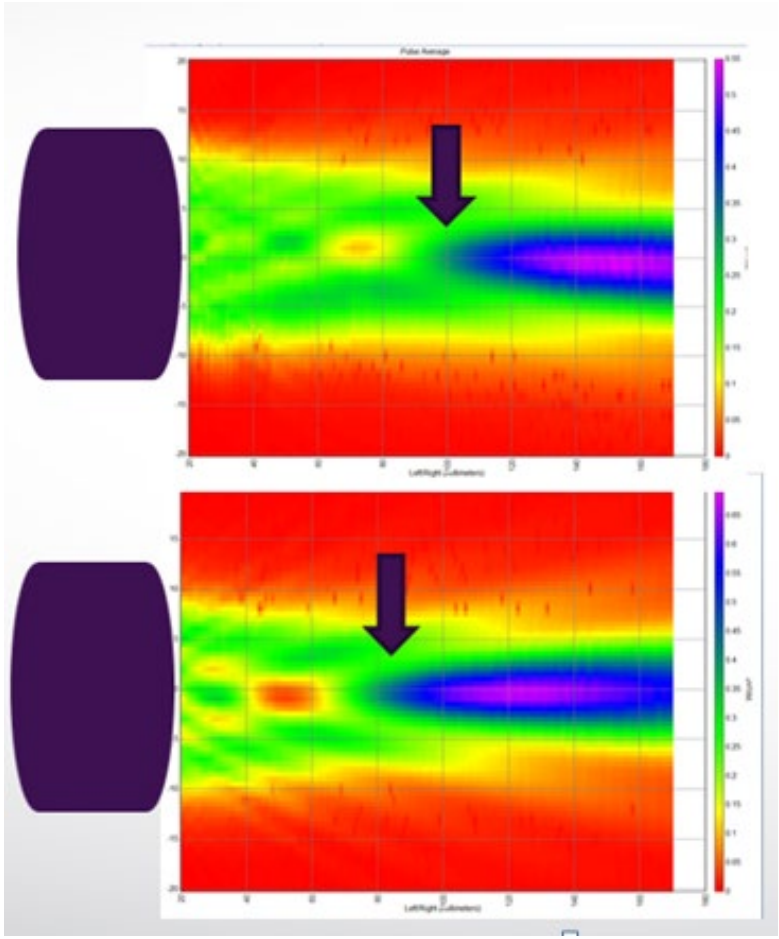
- 7µA/cm^2 @ 60kHz
- Constant Amplitude & Frequency

Product Class Differences

- Modalities/Designs:
  - Capacitive Coupling Electric Field (CCEF); Combined Electromagnetic Field (CMF); Low Intensity Pulsed Ultrasound (LIPUS); Pulsed Electromagnetic Field (PEMF)
  - Lumbar/cervical models (excluding LIPUS), along with long bone designs
- Dosimetries:
  - Vary from 20-30 minutes/day (LIPUS, CMF) to 24 hours/day (CCEF)
  - Even within same modality, different intended uses may require different treatment times
    - Certain BGS devices for treatment of non-unions require 3 hours of treatment per day; for lumbar spinal fusion applications, require 2-10 hours of use
- Indications:
  - All BGS devices share indications in treatment of non-union fractures
  - LIPUS only device with acute fracture indications; CCEF/CMF/PEMF devices possess indications in lumbar and cervical spine

Waveforms: Differing and Complex

- Each group of BGS devices operates using *distinctly different* waveforms that are *complex*.
- It is not known which of the numerous parameters best characterize these waveforms.
- Even with select identical parameters, output (and therefore delivered treatment) can differ.



Acoustic Intensity Outputs-Top (OUS LIPUS device), Bottom (US PMA approved device); maximum intensity marked by arrows

Unknown Allowable Tolerances

- Waveforms are sensitive to circuitry/component changes; allowable tolerances outside those PMA-approved will be difficult to establish without an understanding of impact on performance and/or safety for each group of products.
- For example, changes to any of the following will alter ultrasound output signal (i.e., will change average ultrasound output power, ultrasound intensity over area, and ultrasound field intensity):
  - Frequency of drive signal
  - Pulse modulation rate
  - Transducer size and shape
  - Transducer acoustic matching layer material
  - Transducer piezoelectric material
- **The same issues exist for the CCEF, CMF, and PEMF technologies.**

Information Does Not Exist to Establish Special Controls

- Modifications to waveforms, even if seemingly minor, may adversely impact device safety and effectiveness.
- FDA has thus long recognized the need to review all proposed changes (Class III control).
- 2006 Panel review concluded the "lack of knowledge about how waveform characteristics…affect the clinical response to [BGS] treatment." FDA agreed that "[a]dditional evidence…including preclinical test methods" would be "required to establish special controls" to address this under a Class II classification. (72 Fed. Reg. 1951, 1953 (Jan. 17, 2007))
- **No new knowledge or preclinical methods exist today to enable reclassification. Instead, newer studies highlight continuing applicability of the Panel's and FDA's prior conclusions.**

Incongruent Pre-Clinical vs. Clinical Data

Positive results of preclinical testing of BGS signals/waveforms have not always been predictive of human clinical performance. As examples:

Technology	Pre-Clinical Findings	Clinical Findings
PEMF	Accelerated tibia fracture healing in rabbits	No difference in reoperation rates in tibial fractures
	Reversed osteoarthritis in guinea pig model	No benefit as measured by WOMAC in IDE feasibility study on knee osteoarthritis
LIPUS	High rates of fusion in rat and canine models	Failed spine fusion IDE pivotal study
	Prevention of osteoporotic bone loss in ovariectomized mice	No effect on bone mineral density in osteoporotic patients
	Repair of mid portion tendon injuries in rats and healing at bone/tendon interface in partial patellectomies in rabbits	No improvement of pain or function in conditions involving tendinopathies (e.g., lateral epicondylitis) over placebo

Class III Maintains the IDE-PMA Pathway

- The BGS Coalition strongly supports the IDE-PMA Pathway for all new devices and market entrants.
- Member companies since 2007 have made major investments in preclinical and clinical research.
  - Preclinical research has been presented and published in peer-reviewed journals.
  - Many IDE clinical trials have and are currently being conducted.
- Class III ensures this essential research will continue.

Continued Need for Class III Controls

- In total, the information presented today demonstrates that Class III controls remain necessary for BGS devices.
- Based on this information, multiple regulatory controls are needed to provide reasonable assurance of safety and effectiveness (RASE) for BGS, including:
  - Substantiation of each new device by Level 1 or 2 clinical data
  - FDA review of all post-approval device modifications
  - Comprehensive review of BGS manufacturing, including pre-approval inspection and post-approval review of all changes.
- This set of controls is available only in Class III.

Level 1 and 2 Clinical Data Remain Essential for BGS

- Panel and FDA previously recognized need for clinical data for BGS and lack of adequate preclinical models.
- Knowledge gaps persist about how device parameters affect performance.
- BGS mechanisms of action continue to vary across the devices and are still not fully understood.
- There are still no scientifically validated preclinical tests that can fully predict BGS safety and effectiveness. Level 1 and 2 clinical data thus remains essential to support each new BGS device.
  - FDA acknowledges devices are not good candidates for reclassification absent development of "performance standards or non-clinical tests…that could be surrogates for some clinical testing…." (80 Fed. Reg. 23798, 23800 (April 29, 2015))

Class III Best Ensures Level 1 and 2 Clinical Data

- Current FDA reclassification proposal concurs that risk of ineffective BGS is "clinically significant" and proposes clinical data as class II special control with "flexibility in study design and the level of clinical evidence needed" (85 Fed. Reg. 49986, 49990 (Aug. 17, 2020)).

- Level 1 and 2 clinical evidence are required to date for new BGS approval, and need for substantiation by these high-quality data continues.

- Level 1 and 2 clinical evidence is standard in Class III but not for Class II devices.

  - Class III requires proof that device is safe and effective.
  - By contrast, Class II devices are authorized based on "substantial equivalence" (SE) of intended use and technological characteristics to a predicate device – no independent showing of safety and effectiveness is required. Clinical data may thus be sought only to extent needed to help show SE.

Class III Best Ensures Level 1 and 2 Clinical Data (Cont'd)

- Even in rare instances where clinical data are required, Class II does not necessitate Level 1 or Level 2 clinical evidence.
  - *"Clinical data is not typically included in 510(k)s to demonstrate SE. However, when appropriate," clinical data in 510(k)s can include data other than RCTs, such as "partially controlled studies, studies and objective trials without matched controls, well-documented case histories…, certain reports of significant human experience, and testing on clinically derived human specimens…."*[1]
  - *"In many cases, the clinical data necessary to support a 510(k) involve a relatively small number of patients and may involve a simpler study design than is necessary to support a premarket approval application."*[2]
  - *Clinical data in 510(k)s is "usually confirmatory" only.*[3]

- Class II clinical data special control thus may not ensure generation of PMA-type clinical data.
  - Example: thoracolumbosacral pedicle screw systems (semi-rigid systems) reclassified with clinical data special control (21 CFR 888.3070(b)(3)(i); 81 Fed. Reg. 96366 (Dec.30, 2016))
  - Recently cleared system relied on clinical data from retrospective study and clinical literature (K182928).

[1] FDA, Benefit-Risk Factors to Consider When Determining Substantial Equivalence in Premarket Notifications (510(k)) with Different Technological Characteristics (Sept. 25, 2018), at 7
[2] FDA, The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications [510(k)]; Draft Guidance (Dec. 27, 2011), at 21 (guidance later revised and finalized)
[3] Owen Faris, Ph.D., FDA, Clinical trials for medical devices: FDA and the IDE process (slide presentation), at 4

Class III Controls Are Necessary for BGS Manufacturing

- Full PMA review of manufacturing process and changes is crucial to ensure consistent production of BGS devices with appropriate waveform parameters.
  - For example, each manufacturer relies on custom equipment in BGS design and manufacture to precisely measure its proprietary waveforms and form the specifications unique to each BGS device.
- Pre-market inspection of these processes continues to be essential to provide RASE.
- Comprehensive review of manufacturing information and routine pre-approval inspections are reserved for Class III devices.

Class III Controls Are Necessary for Post-Approval BGS Changes

Prior Panel review concluded Class III is necessary for BGS because, "It is not known how a change to the device output due to device modifications may impact the clinical response to treatment."
(72 Fed. Reg. 1951, 1953 (Jan. 17, 2007))

This remains true today. As discussed:

- Waveform parameters are unique and proprietary to each device. Seemingly minor changes can *significantly impact device performance.*
- Nature and *extent* of impact not predictable, with some signal parameters completely ineffective to activate bone growth.
- BGS performance remains *highly sensitive* to device-specific manufacturing tolerances and processes.

Class III Controls Are Necessary for Post-Approval BGS Changes (Cont'd)

Per FDA:

- It is "essential for FDA to assess any change that affects safety or effectiveness" for devices with "unique design characteristics or manufacturing processes." Such review is "reserved for class III devices."[1]
- "FDA's oversight of postmarket changes to devices is very different in the 510(k) context as compared to the PMA context. …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…FDA requires PMA supplements… for any change to a PMA-approved device that affects safety or effectiveness."[2]
- Difference between class II and III controls is significant. In up-regulating certain devices from 510(k) to PMA, FDA noted that "many of the design and manufacturing changes that have led to [device] recalls were not required to be reported to FDA under the 510(k) process. If these changes had been reported prior to implementation, as would be required in the PMA regime, these recalls may have been avoided."[2]

BGS have performed safely under Class III controls for 40 years and these controls remain important.

[1] 79 Fed. Reg. 16252, 16256 (March 25, 2014)
[2] 80 Fed. Reg. 4783, 4785 (Jan. 29, 2015) (automated external defibrillators)

Class III is Also Essential Because BGS are "of Substantial Importance in Preventing Impairment of Human Health"

- BGS meet another criterion for Class III status: they are "of substantial importance in preventing impairment of human health." (21 USC 360c(a)(1)(C)(ii)(I))
- Panel previously recognized this, and more recent data affirms it remains true today.
  - The harms of ineffective BGS include severe adversities to patients' physical health and quality of life, as to be discussed.
  - These harms amplify the importance of Class III controls to ensure safety and effectiveness of BGS devices.

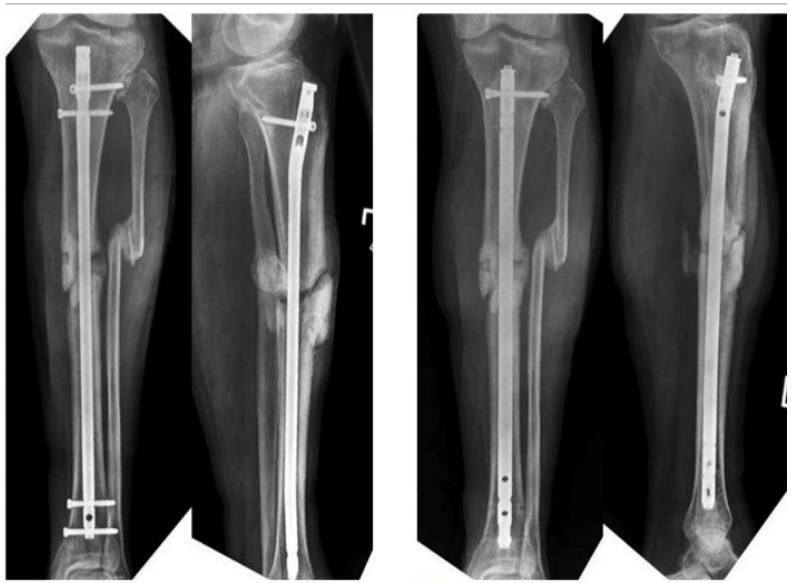


Fig. 2-B Fig. 2-C

Fig. 2-B Anteroposterior and lateral radiographs made five months postoperatively demonstrate a delayed union of the tibia. **Fig. 2-C** Anteroposterior and lateral radiographs made two months after exchange reamed intramedullary nailing demonstrate fracture union.

Goulet J (2006) JBJS 88A:206-16

Evidence-Based Medicine: A Call for Continued High Quality Clinical Trials for Regulation of BGS Devices and Trauma Applications

Mohit Bhandari, MD, PhD

The FDA Position is Consistent With EBM Principles

- Pre-clinical Studies are **hypothesis-generating** and do not confirm the ‘effectiveness’ of a new BGS device
- Clinical studies require a number of **bias-reducing measures** to assure valid, scientific results
- Introduction of BGS without assurance of high quality clinical trials **risks harm** to patients

A Rush to Under-Tested Treatments Places Patients at Risk

"The adequately powered, comparative, and robust clinical research that is needed for optimal evidence-informed decision-making remains absent in COVID-19."

— Alexander et al 2020; Journal of Clinical Epidemiology; 123: 120-126. DOI: 10.1016/j.jclinepi.2020.04.016

"You need to be skeptical about [COVID-19] treatments…if you really want to know, wait for the randomized trials."

— Guyatt, 2020; www.myorthoevidence.com

Evidence Based Medicine

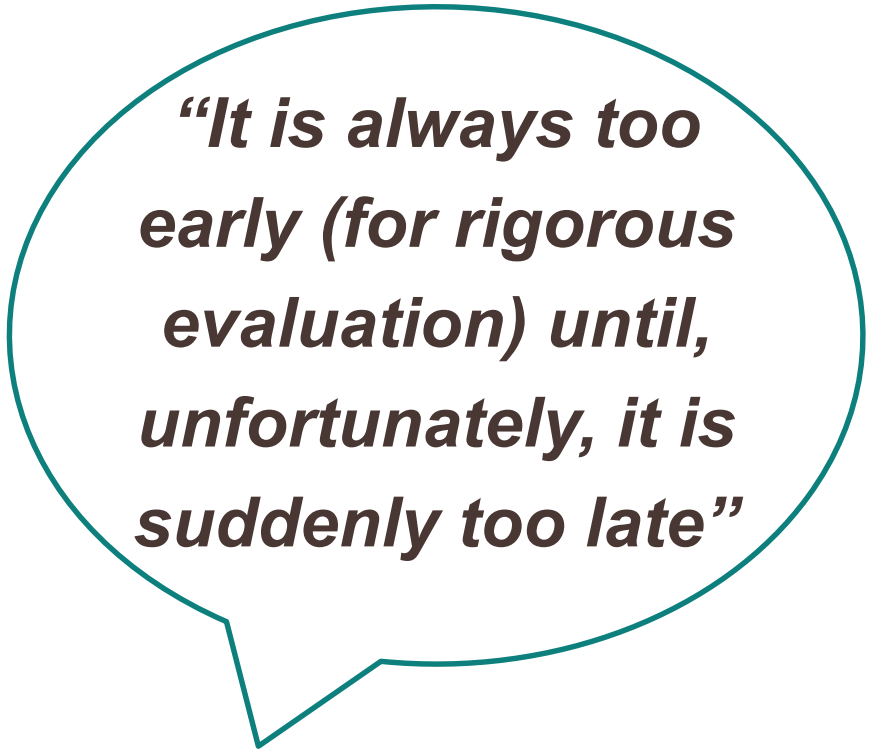
- The term EBM first appeared in the published literature in 1991
- 5 years later, the most-cited EBM landmark article described EBM as the conscientious, explicit and judicious use of the **current best evidence in making decisions about the care of individual patients**

Guyatt GH. Evidence-based medicine. ACP J Club. 1991 114:A16

Sackett DL et al: Evidence based medicine: What it is and what it isn't. Br Med J. 1996;312:71–2

Buxton's Law

In an effort to accelerate access to new BGS, we risk serious mis-steps and potential for harm



1 in 4

devices are pulled from the market within 5 years

Bhattacharyya, CORR 2006

Clinical Trials Are Critical

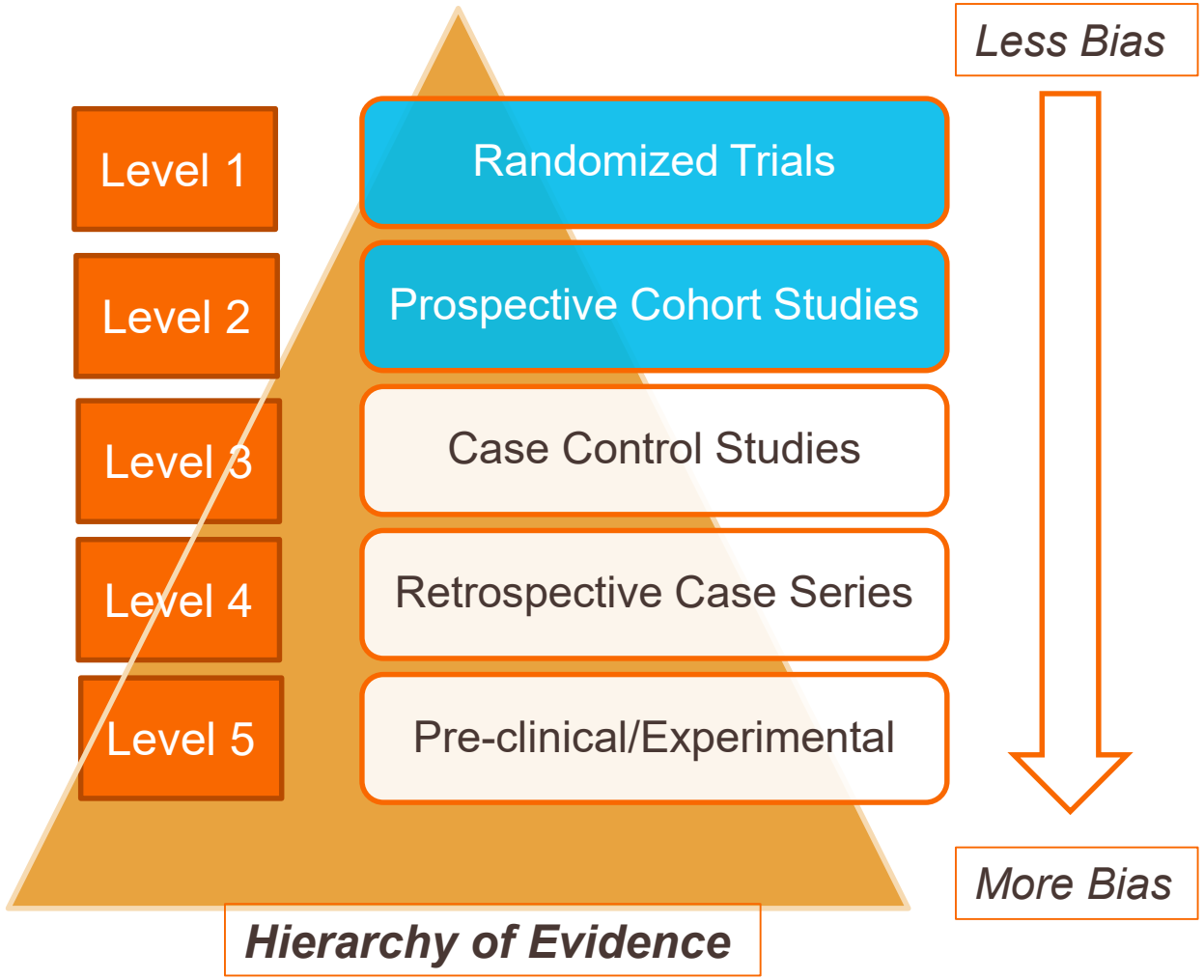
Finding "Signal" in Research

- **Randomize Patients**
- **Prospective Designs (Levels 1, 2)**

- "Conceal" randomization
- Blinded/Independent Outcomes
- Objective (patient important) outcomes
- Complete follow up
- Sufficient Patient Numbers

Per FDA (21 CFR 860.7):

"[P]rinciples have been developed…and are recognized by the scientific community as the essentials of a well-controlled clinical investigation. They provide the basis for the Commissioner's determination whether there is reasonable assurance that a device is effective based upon well-controlled investigations."



Clinical Orthopaedics and Related Research: 2003:413, p.19-24

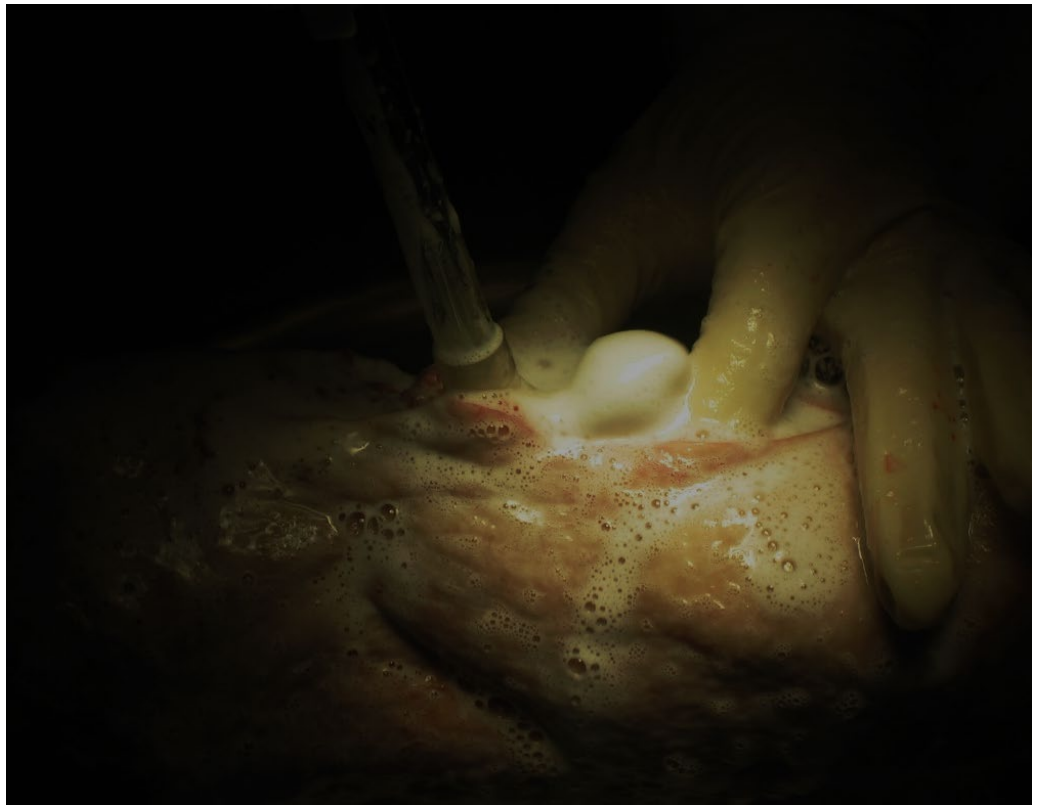
Pre-Clinical Studies Do Not Replace A Well Designed Clinical Trial

- "[B]ridging the gap from bench top to human subjects."
  — Injury, https://doi.org/10.1016/j.injury.2020.04.011

- Well-known differences exist between animals and humans with respect to bone based cells
  — Bone. 2011;49(4):591-9

- Fracture healing and spine fusion models remain inadequate (fresh fractures and especially nonunions)
  — Eur Cell Mater. 2013 16;26:1-12

- Animal models do not adequately assess patient-important outcomes (function, pain, and HRQL)
  — Sci. Rep. 10:4568; doi



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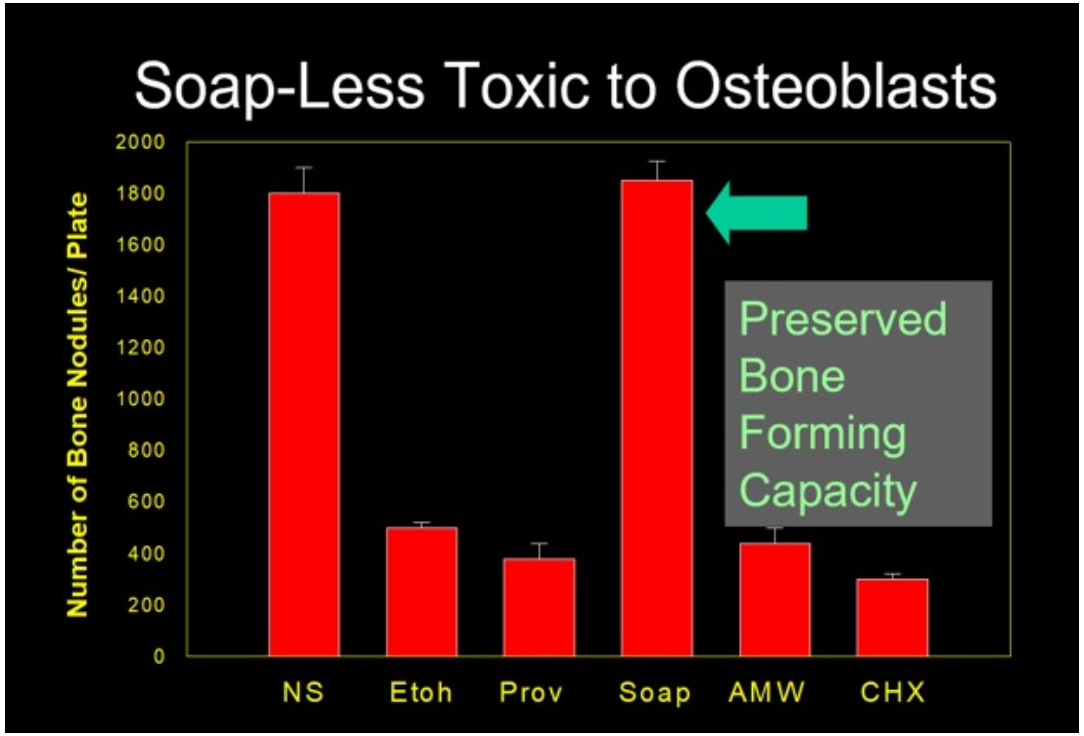
1745 NOTICES

1747 CONTINUING MEDICAL EDUCATION

Irrigation with soap versus saline solution significantly increased reoperations

N Engl J Med. 2015 Dec 31;373(27):2629-41

Misled By Pre-Clinical Data



Soap irrigation solution least toxic to Osteoblasts — **JBJS. 2001 Mar;83(3):412-9**

Soap solution irrigation was better than alternatives

The Harm of "False Positives"

Type I Error (Alpha)

- Falsely Concluding Benefit of BGS
- Risks increase with:
  - Fewer methodological safeguards
  - Lesser designs (no controls, no randomization, pre-clinical designs)

Clinical Impact

"The impact of…fracture nonunion on physical health was comparable with the reported impact of end-stage hip arthrosis and worse than that of congestive heart failure.

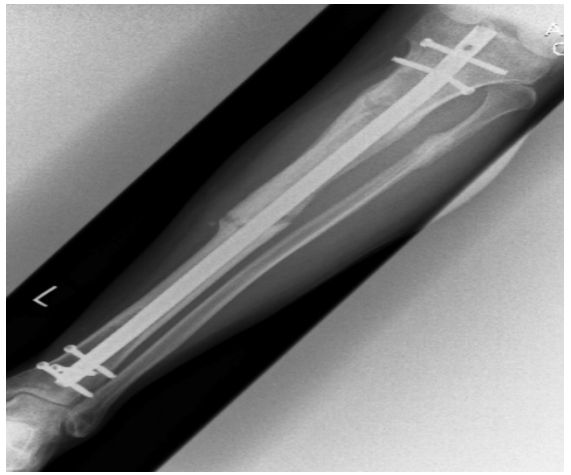
…fracture nonunion is a devastating chronic medical condition that negatively affects both physical and mental health and quality of life."

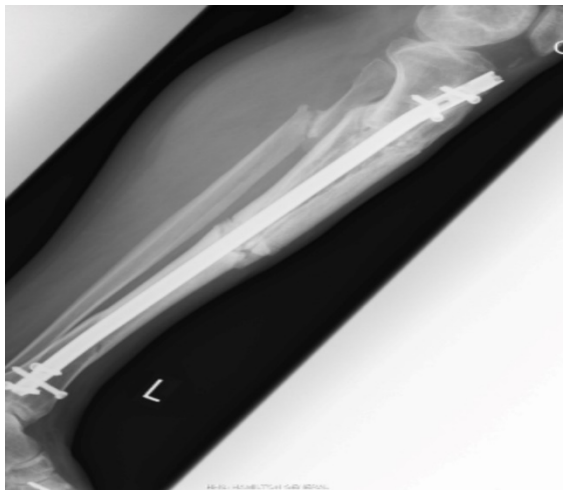
The Journal of Bone & Joint Surgery: 2013: 95: 24- p 2170-2176

Tibial Nonunions Are Worse Than A Myocardial Infarction

Effective Treatment is Critical

- Given the profound deficits in quality of life experienced by individuals with tibial nonunion, attempts should be focused on **effective treatment**.
- One year after successful treatment of tibial nonunion, Short Form (SF)-36 physical and social function scores improve significantly from the values before treatment.





The Journal of Bone & Joint Surgery: 2013; 95:24,p e199

J Trauma. 2005 Feb;58(2):312-7

The Harm of "False Positives"

Type I Error (Alpha)

- Falsely Concluding Benefit of BGS
- Risks increase with:
  - Fewer methodological safeguards
  - Lesser designs (no controls, no randomization, pre-clinical designs)

Clinical Impact

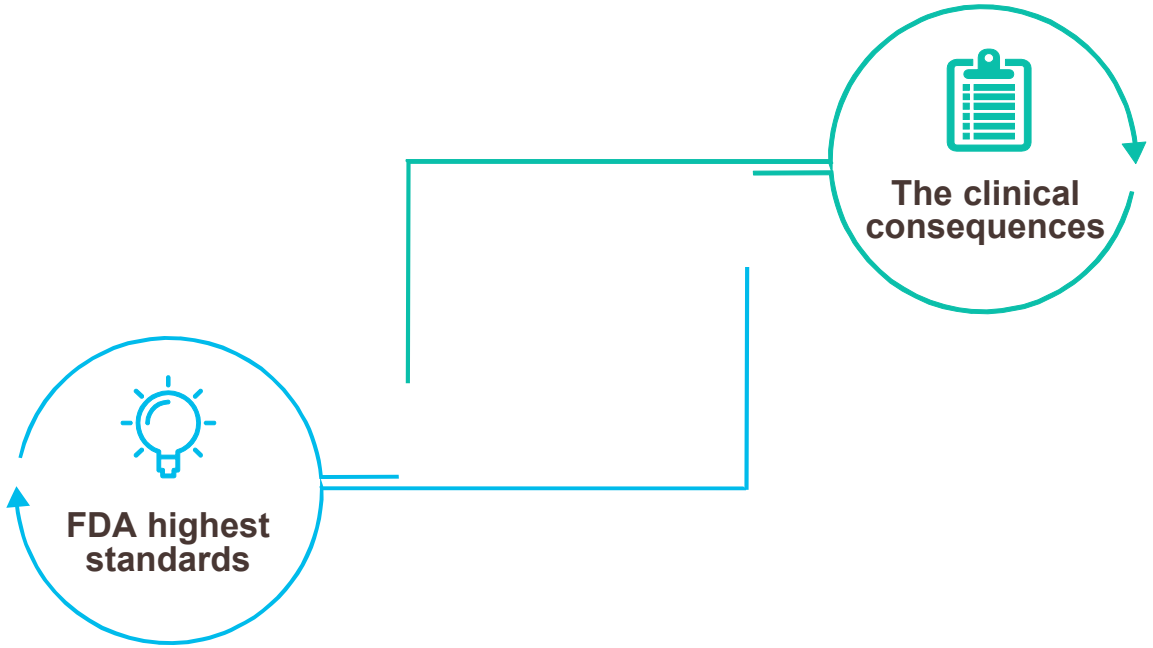
"Patients with Failed Back Syndrome and neuropathic pain experience higher levels of pain and a poorer quality of life and physical function compared with those with osteoarthritis, rheumatoid arthritis, complex regional pain syndrome, and fibromyalgia."

Asian Spine J. 2018;12(2):372-379

Clinical Experience with BGS Devices in Spine Applications

Chi Lim, MD

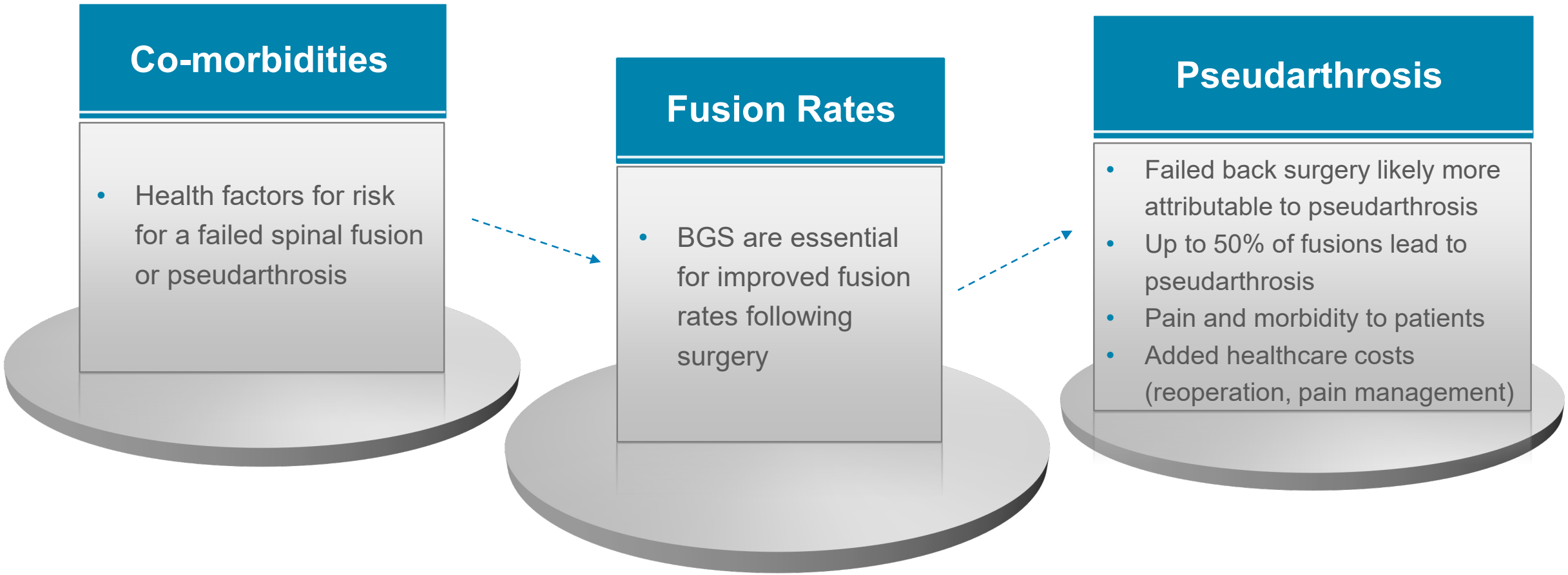
Overview



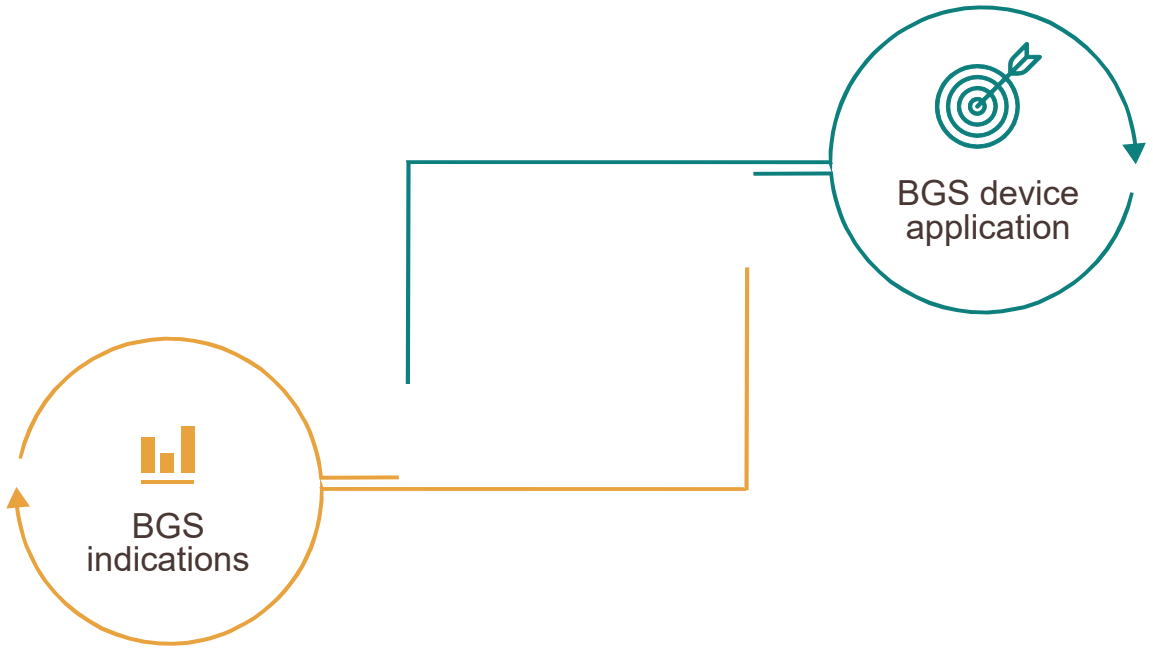
- Ineffective devices have poor clinical outcomes
- Unsafe BGS devices have potential for injury

- Ensure patient safety and well-being

BGS Spine Patients



Patient Selection



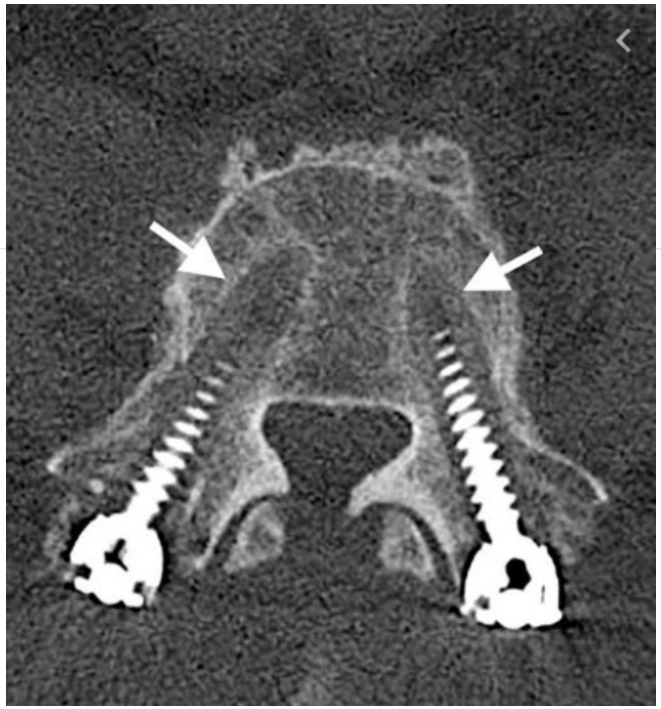
- As an adjunct to fusion
- Treatment of a failed spine fusion
- Treatment of fractures – fresh, delayed unions, and nonunions

- Co-morbidities dictate whether a patient is prescribed a BGS device
  - These include smoking, osteoporosis, diabetes, peripheral, or systemic vascular disease

Surgical Approach, Anatomy and Injury Affect Healing

Pseudarthrosis of the spine

- Surgical approach
  - Anterior vs. Posterior
- Bone graft quality
  - Autograft vs allograft

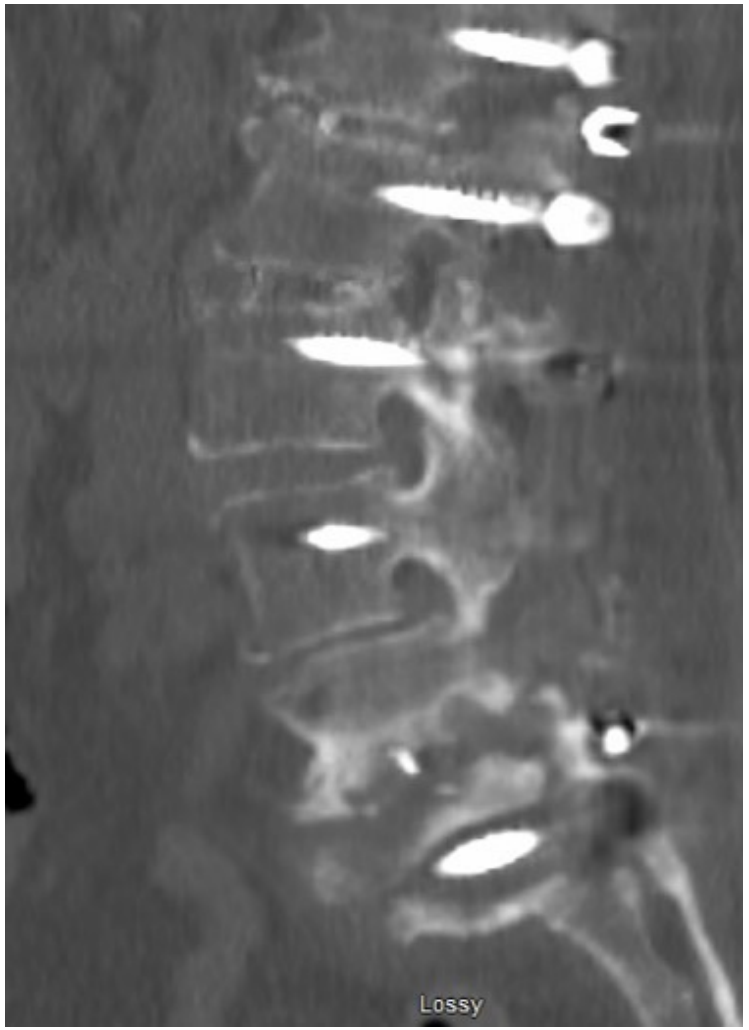


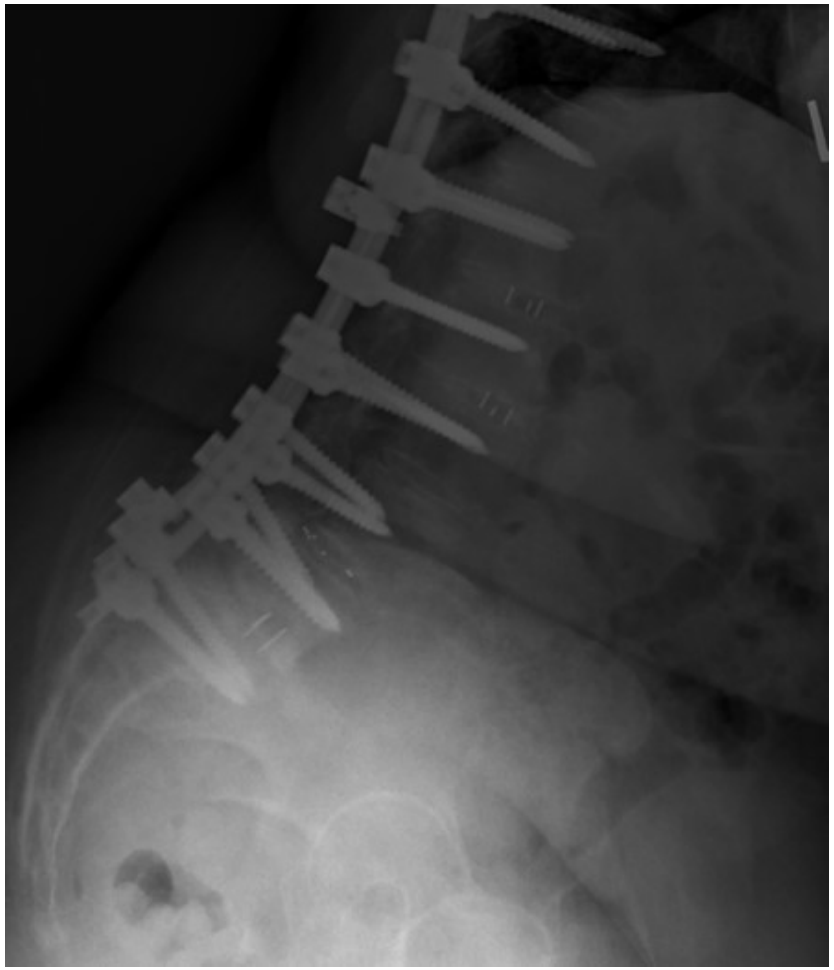
Clinical Example – JT

68 yo F with prior multilevel fusion presents with pseudarthrosis with kyphotic deformity and hardware failure

- Comorbidity
  - DM II
  - Obesity
  - Osteopenia

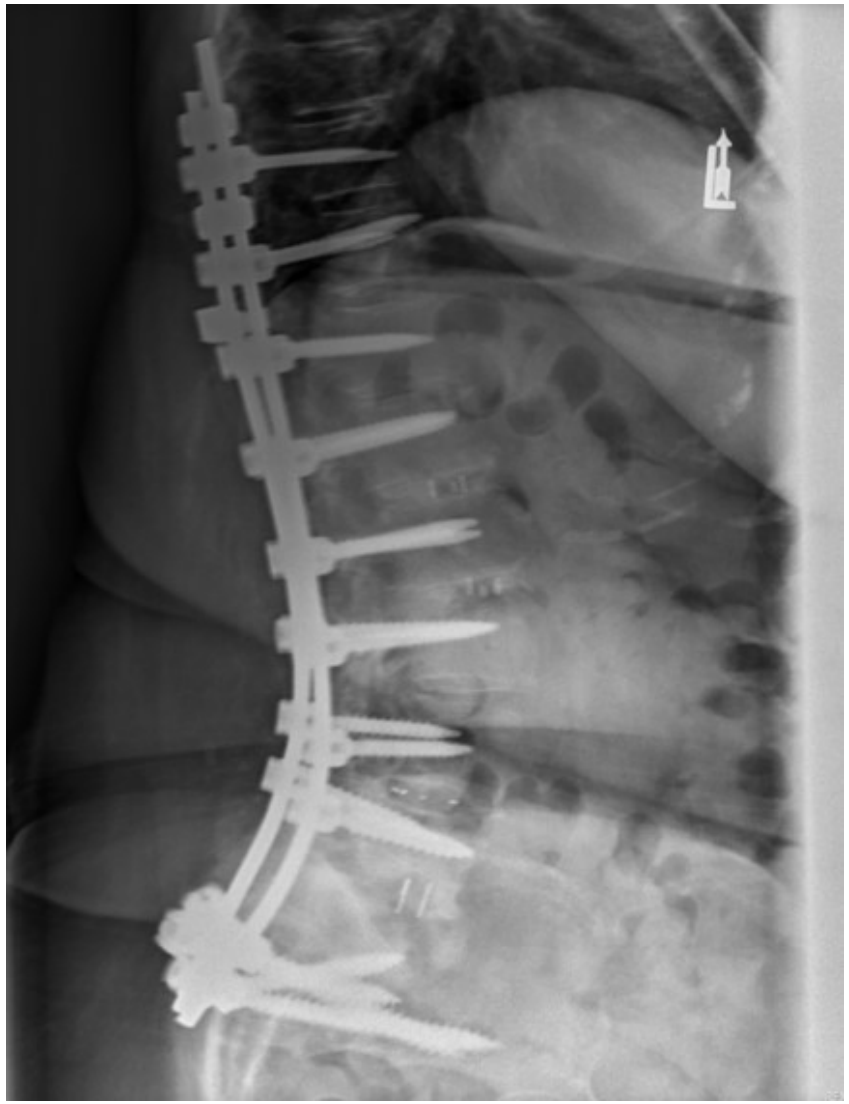
JT - Preop





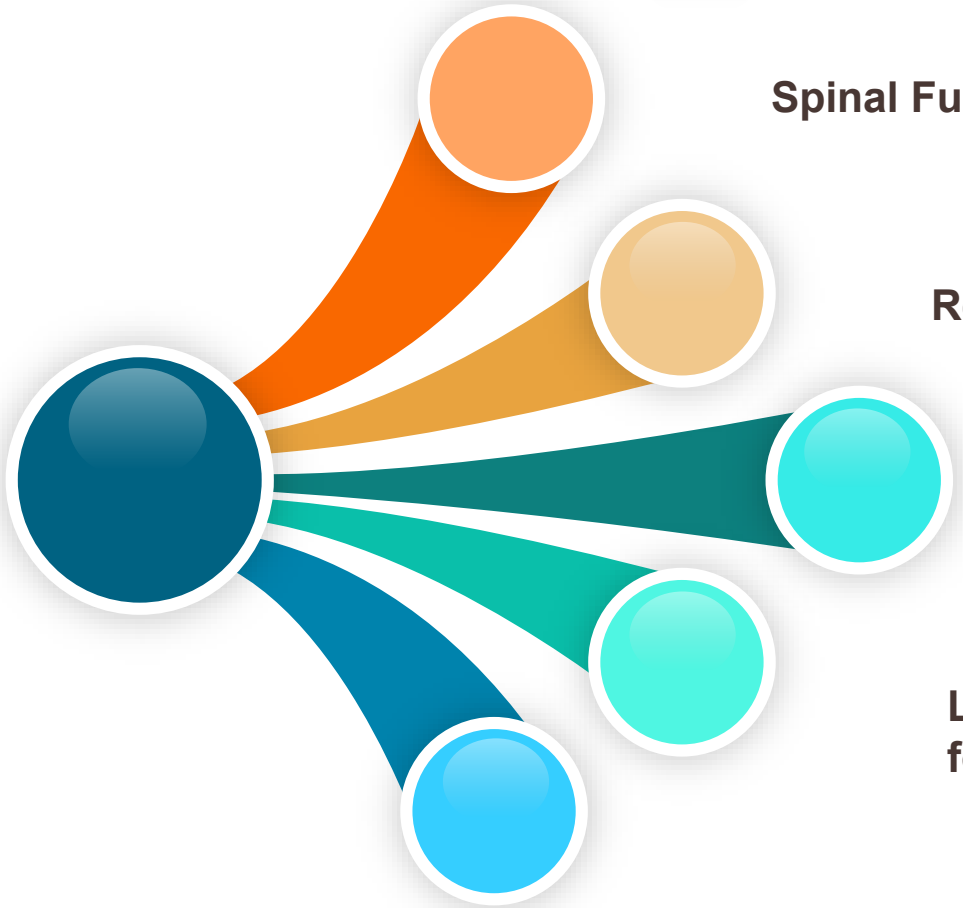
Standing

JT – Postop



Surgical Approach, Anatomy and Injury Affect Healing

NASS Coverage Policy Recommendations – BGS for Spine Fusion (Aug. 2016)



Spinal Fusion of 2 or more levels

Revision Spinal Fusion

Current Smokers

Lumbar Fusion exhibiting the following comorbidities

- Diabetes
- Inflammatory arthritis
- Systemic Vascular disease
- Osteopenia/Osteoporosis

NASS Recommendations Depend on High Quality Clinical Data

- Bassett CA, Becker RO. Generation of electric potentials by bone in response to mechanical stress. *Science*. 1962;137(3535):1063-1064. doi:10.1126/science.137.3535.1063
- Brighton CT, Wang W, Seldes R, Zhang G, Pollack SR. Signal transduction in electrically stimulated bone cells. *J Bone Joint Surg Am*. 2001;83(10):1514-1523. doi:10.2106/00004623-200110000-00009
- Simmons JW Jr, Mooney V, Thacker I. Pseudarthrosis after lumbar spine fusion: nonoperative salvage with pulsed electromagnetic fields. *Am J Orthop (Belle Mead NJ)*. 2004;33(1):27-30

Future High Quality Clinical Trials Are Essential

- Not all BGS are created equal
- Structured, high quality clinical trials are necessary to ensure effectiveness and safety
  - High-risk patients push the boundaries of fusion healing and BGS devices mitigate increased rates of pseudarthrosis
- Deregulation and elimination of PMA will lead to ineffective devices
  - Ineffective devices will create harm and increase burden to healthcare costs

Clinical Experiences Summary

- BGS for high risk patients are vital to high success of spine fusions
- Ineffective BGS devices lead to catastrophic failures
  - Reoperations with high morbidity
  - Continued pain - possible lifetime pain management and opioid use
  - Increased burden on healthcare
  - May lead to patient injury
- High quality data needed to support clinical decisions
  - Demonstrate safety and effectiveness for BGS devices

Summary

James T. Ryaby, PhD

Summary

- Class III status for BGS is consistent with FDA's mission to protect and promote patient health.
- In 2007 FDA concurred with Panel findings that fundamental knowledge gaps preclude reclassification. These gaps persist today.
- Level 1 or 2 clinical studies are still necessary to demonstrate efficacy of new BGS. Class III best ensures this level of evidence.
- BGS are not a "generic type of device." Instead, approved devices represent wide-ranging, varied technologies that are not fully understood. For 40 years, the totality of Class III controls has ensured that approved BGS are safe and effective, as reflected by marketing history.

Summary (Cont'd)

- No evidence exists to show that BGS safety and effectiveness can be assured without Class III controls; in fact, information discussed today shows otherwise.
- Risk of inconsistent or ineffective treatment continues to present unacceptable risks to a large and vulnerable patient population.
- There continues to be no substitute for substantiation of BGS safety and effectiveness by rigorous clinical data and FDA pre- and post-market review of BGS manufacturing and all modifications — Class III controls.

Reasonable assurance of safety and effectiveness for BGS devices is provided only in Class III.

Questions?

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