

# **Proposed Reclassification of Non-Invasive Bone Growth Stimulators (BGSs)**

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Office of Product Evaluation and Quality

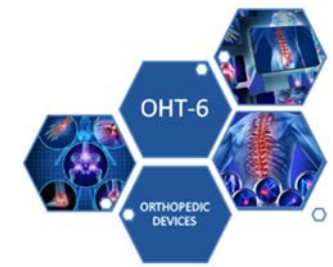
Center for Devices and Radiological Health

Food and Drug Administration

**Orthopaedic and Rehabilitation Devices**

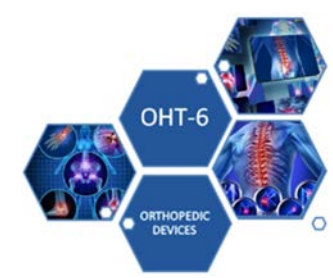
**Panel Meeting**

**September 8, 2020**



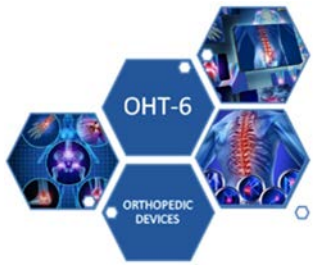
# Presentation Outline

- Purpose
- Device Description
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- Indications for Use
- Rationale for Proposed Re-classification
- Regulatory History
- Postmarket Data
- Analysis of PMA SSEDs
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- FDA Comments
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# Purpose

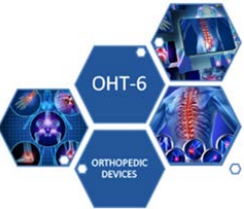
- Non-invasive bone growth stimulators (BGSs) are currently regulated as Class III devices subject to Premarket Approval (PMA) Applications
- FDA is proposing to reclassify these devices under the product code LOF and LPQ from Class III to Class II
  - LOF (Stimulator, Bone Growth, Non-Invasive)
  - LPQ (Stimulator, Ultrasound and Muscle, For Use Other Than Applying Therapeutic Deep)
- Implantable BGSs under the product code LOE are **not** within the scope. These devices have added risks compared to non-invasive BGSs
  - LOE (Stimulator, Invasive Bone Growth)



# Device Description

- BGSs typically utilize a generator and transducer to non-invasively deliver either an electrical, magnetic or mechanical (ultrasonic) waveform to the fracture site to augment bone healing.
- There are internal features to monitor the output of the waveform and delivery of treatment, and to provide a visual and/or audible alarm to alert the user of improper device function.
- These devices can incorporate patient-contacting components such as transducers, lead wires, and the device outer casing.





# Device Description- 4 Modalities



1

Capacitive Coupling (CC), in which a pair of electrodes are placed on the skin such that a current can be driven across that target site

2

Pulsed Electromagnetic Field (PEMF), in which a modulated electromagnetic field is generated near the treatment site through an external coil

3

Combined Magnetic Fields (CMF), in which a coil generates a combination of a static and pulsed magnetic fields near the treatment site

4

Low Intensity Pulsed Ultrasound (LIPUS), in which pulsed ultrasonic signals are generated using ultrasonic transducers



1 Biomet, OrthoPak

3 DJO, LLC, OL1000 BGS



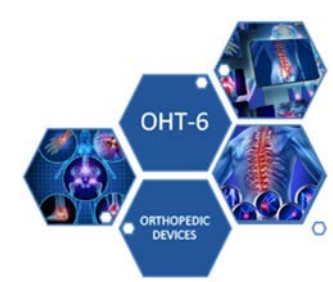
Successful fracture healing outcomes

4 Bioventus, LLC Exogen



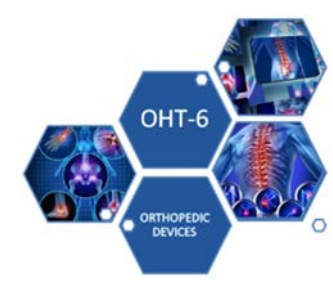
2 Orthofix, Inc. SpinalStim

High treatment Proven clinical



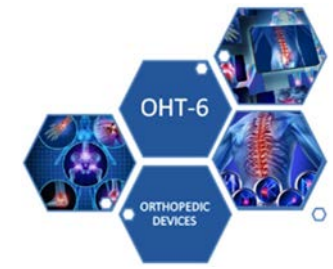
# Intended Use

- Promote osteogenesis as an adjunct to primary treatments for fracture fixation and spinal fusion or as a treatment for established nonunions or failed fusions



# Indications for Use

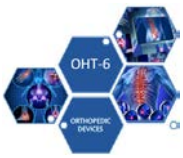
- Non-invasive BGSs have been approved under the following general category of indications:
  - Treatment of an established non-union secondary to trauma
  - Adjunctive treatment of certain fresh fractures
  - Treatment of congenital pseudarthrosis
  - As an adjunct to cervical fusion surgery in patients at high risk for non-fusion
  - As an adjunct to lumbar spinal fusion surgery at 1 or 2 levels



# Rationale for Proposed Reclassification

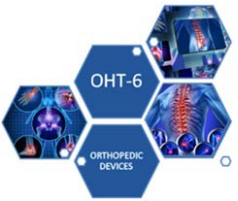
- CDRH 2014-2015 strategic priority “Strike the Right Balance Between Premarket and Postmarket Data Collection”
  - All active PMAs prior to 2010 were retrospectively reviewed to determine if certain devices would qualify for reclassification based on our current understanding of the technology.
  - On April 29, 2015, FDA published a document in the Federal Register identifying LOF and LPQ product codes as candidates for re-classification (80 FR 23798).
- FDA’s understanding of the safety and effectiveness of the approved devices, and the knowledge gained from the FDA 2006 Panel Meeting have all been factored into this recommendation.
- Proposed reclassification order was issued on August 17, 2020, and is available at <https://www.federalregister.gov/documents/2020/08/17/2020-17543/physical-medicine-devices-reclassification-of-non-invasive-bone-growth-stimulators>. Comments on the proposed order can be submitted through October 16, 2020.





# Background: FDA June 2, 2006 Panel Meeting

- On February 9, 2005, FDA received a citizen's petition from RS Medical Corporation to reclassify certain non-invasive BGS devices. Ultrasound based devices and certain indications were outside of the scope of this request.
- FDA June 2, 2006 Panel Meeting
  - Reviewed information provided by the petitioner
  - Identified the following risks to health: electrical shock, burn, skin irritation, and/or allergic reaction, adverse interaction with electrical implants and internal/external fixation devices, and biological risks
  - Determined there was insufficient understanding of waveform characteristics and clinical response to treatment



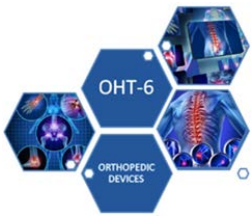
# Background: FDA June 2, 2006 Panel Meeting (Cont'd)

- 2006 Panel Recommendation
  - Clinical data and/or special controls needed to control for risk of inconsistent or ineffective treatment
  - As adequate special controls addressing the need for clinical evidence were not devised by the petitioner, the Panel recommended retaining the Class III classification
  - FDA concurred with the recommendation, and had concerns with the petitioner's proposed special controls to control the risks of inconsistent or ineffective treatment



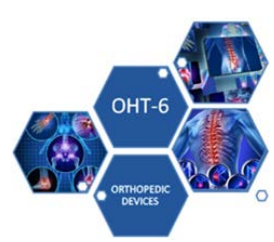
# Rationale for Proposed Reclassification

- Analysis of available clinical data, including the SSEDs of the approved PMA devices available for consideration of the data to support reclassification under section 520(h)(4) of the FD&C Act, and postmarket recall and MDR data suggest
  - There are probable health benefits from the use of these devices
  - Risk profile is well established and overall risk appears to be low
  - Risks identified with ultrasound based devices, along with their benefit are comparable to those of non-invasive bone growth stimulator incorporating other modalities



## Rationale for Proposed Reclassification Cont..

- Based on the totality of the evidence available since 2006 panel, FDA is proposing that sufficient information exists to establish special controls, that together with general controls, can provide a reasonable assurance of the safety and effectiveness of non-invasive BGS devices.
- FDA proposes the risks of inconsistent or ineffective treatment raised in the 2006 panel can be addressed through clinical data.



# Regulatory History of Non-Invasive BGSs



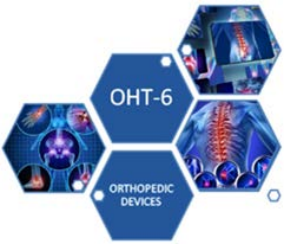
Trade Name	Current Holder	PMA # / Date	Device Type	Anatomic Location
Cervical Stim	Orthofix, Inc.	P030034 12/23/04	PEMF	Cervical Spine
Orthologic 1000, SpinaLogic	DJ Orthopedics, LLC	P910066 03/04/94	CMF	Non Spine/Flat Bones, Lumbar Spine
Exogen Ultrasound Bone Healing System	Bioventus LLC	P900009 03/25/90	LIPUS	Appendicular System
OrthoPak, SpinalPak	Zimmer Biomet	P850022 02/18/86	CC	Non Spine/Flat Bones, Lumber Spine
Physio-Stim, SpinalStim	Orthofix, Inc.	P850007 02/21/86	PEMF	Non-Spine/Flat Bones, Lumbar Spine
EBI Bone Healing System	Zimmer Biomet	P790002 11/06/79	PEMF	Appendicular System



# Summary of Safety and Effectiveness Document (SSED) Information

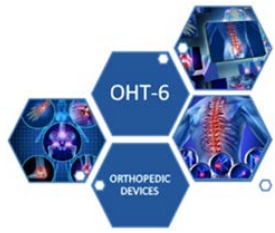


- Under 520(h)(4) of the FD&C Act, FDA has been granted authority to use clinical information from a PMA application that was approved more than six (6) years ago in the classification or reclassification of another device or in the development of special controls.
  - Only devices approved after November 28, 1990, are eligible
- Three PMA Devices have SSEDs that include clinical data that can be utilized under this rule
  - Orthofix's CervicalStim (P030034)
  - Zimmer Biomet's SpinalPak (P850022/S009)
  - DJO's SpinaLogic (P910066/S011)



# SSED Information – P030034 (Cervical-Stim)

- Same PEMF technology as PhysioStim (P850007)
- Clinical Study Design
  - 323 subject controlled randomized study
  - High risk patients undergoing cervical fusion
  - Control group of standard treatment (n=160) and treatment group (n=163)
  - 12 months of follow-up
- Effectiveness Results
  - 83.6% Fusion Rate (Treatment) vs. 68.6% (Control) at 6 months
  - 92.8% Fusion Rate vs. 86.7% at 12 months



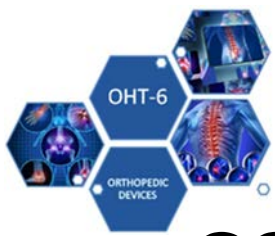
# SSED Information – P030034



- Safety Results

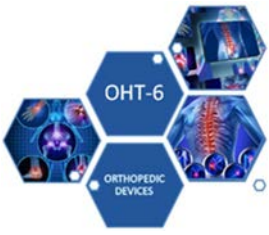
Adverse Event	Control Group # (%) of subjects	Treatment Group # (%) of subjects
Increased Neck Pain	9 (5.6)	15 (9.2)
Shoulder/Arm Pain	9 (5.6)	16 (9.8)
Re-Injury to Cervical Spine	8 (5.0)	9 (5.5)
Adjacent Level Pathology	3 (1.9)	8 (4.9)
Surgical Complications	2 (1.3)	5 (3.1)
LBP/Lumbar Pathology	8 (5.0)	5 (3.1)
Trauma/Injury (non-cervical)	2 (1.3)	4 (2.5)
Numbness/Tingling	6 (3.8)	4 (2.5)
Headache/Migraine	2 (1.3)	4 (2.5)





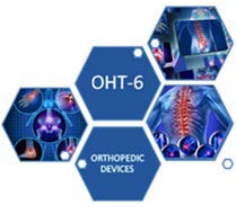
# SSED Information – 850022/S009 (SpinalPak)

- Same Capacitive Coupling (CC) technology as OrthoPak
- Clinical Study Design
  - 349 subject controlled randomized double-blinded study
  - Patients undergoing lumbar fusion procedures
  - Control group (n=177) and placebo group (n=172)
  - 12 months of follow-up
- Effectiveness Results
  - 79% Fusion Rate (Treatment) vs. 61% (Placebo)



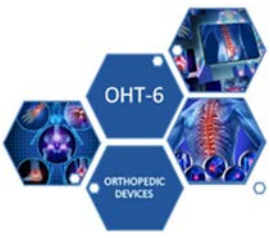
# SSED Information – 850022/S009

- Safety Results
  - Most common event was skin irritation (5 in placebo group, 4 in treatment group)
  - All other reported events were single events (7 in placebo group, 4 in treatment group)



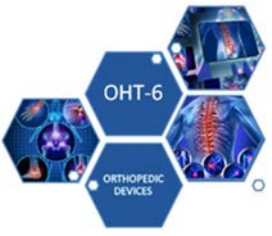
# SSED Information – P910066/S011 (SpinaLogic)

- Same Combined Magnetic Fields (CMF) technology as OrthoLogic
- Clinical Study Design
  - 243 subject controlled randomized double-blinded study
  - Patients undergoing lumbar fusion procedures
  - Control group (n=125) and placebo group (n=118)
  - 9 months of follow-up
- Effectiveness Results
  - 64% Fusion Rate (Treatment) vs. 42% (Placebo)



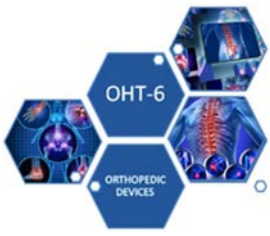
# SSED Information – 910066/S011

- Safety Results:
  - No device-related adverse events reported in SSED



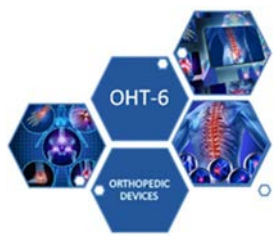
# Prior PMA Device Summary

- Based on the clinical data available in the three PMA SSEDs
  - BGSs demonstrate clinical benefit
  - The adverse event rates for the devices are low and similar to those of the control groups



# Literature Review: Pre-2006 Panel

- Early studies in the 1950's demonstrated the potential for electrical stimulation in accelerating bone healing (Yasuda)
- Clinical studies in the 1970's identified clinical effect in spinal fusion (Dwyer, Becker)
- Clinical studies in the 1990's showed a wide range of efficacy, with fusion rates ranging from 60% (Scott) to 80% (Garland)

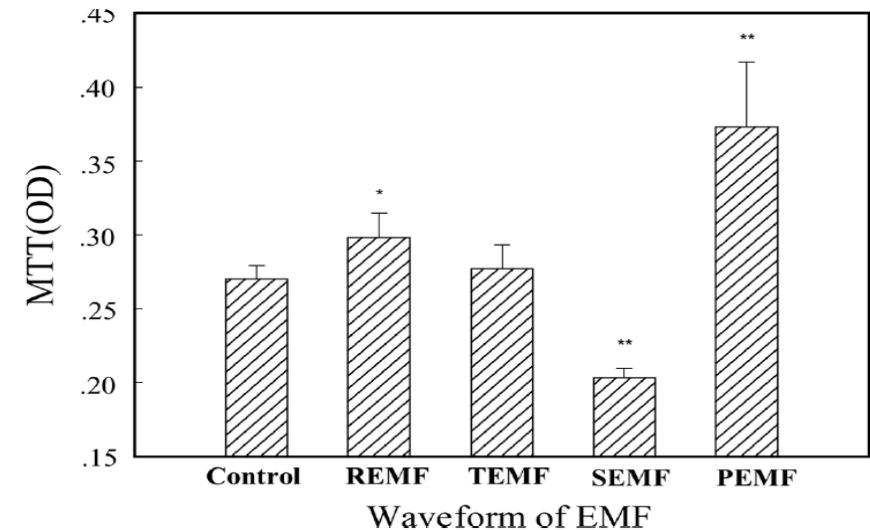


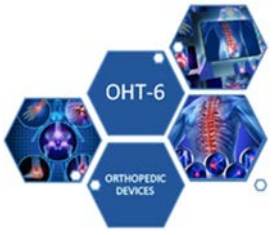
# Literature Review: Pre-Clinical

- Pre-clinical testing showed that changes in treatment waveform can affect therapeutic efficacy
  - Veronesi (2013) found that differences in primary frequency of PEMF treatment can mitigate the effect in treatment of osteoarthritis in an animal model
  - Zhang (2007) demonstrated that different EMF waveforms can either reduce or increase osteoblastic differentiation
  - Galli (2018) in a review article, shows various effects of SEMF frequency, duration, and magnitude differences on treatment efficacy

**Table 1.** Cartilage Histological Score (Mankin Modified by Carlson) Results of Sham-Treated and PEMF-Treated at 37 and 75 Hz Groups at Four Measurement Sites (Mean  $\pm$  SD,  $n = 10$ )

	Sham-Treated	PEMF-Treated at 37 Hz	PEMF-Treated at 75 Hz
Medial tibial plateau	9.8 $\pm$ 1.1	9.7 $\pm$ 0.8 <sup>a</sup>	5.0 $\pm$ 1.9 <sup>c</sup>
Medial femoral condyle	9.0 $\pm$ 1.4	6.8 $\pm$ 0.9	5.3 $\pm$ 2.2 <sup>d</sup>
Lateral tibial plateau	7.8 $\pm$ 1.0	5.5 $\pm$ 0.9	5.6 $\pm$ 1.0
Lateral femoral condyle	8.5 $\pm$ 0.9	5.6 $\pm$ 0.6 <sup>b</sup>	6.5 $\pm$ 1.0

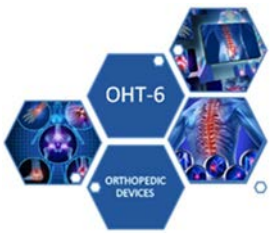




# Literature Review: New Evidence

- 14 clinical studies of various treatments
  - PEMF (5), LIPUS (7), CMF (2)
- >10,000 subjects total
- Treatment efficacy ranged from 32.8% (Bilgalri) to 97.4% (Nolte)
  - Various anatomic locations and patient subpopulations
- Two controlled studies showed improved healing
  - 83.6% vs. 68.6% fusion rate in the cervical spine (Foley)
  - 8.9 week vs. 14.7 week total time to fusion in 5<sup>th</sup> metatarsal (Streit)
- Only one adverse event reported

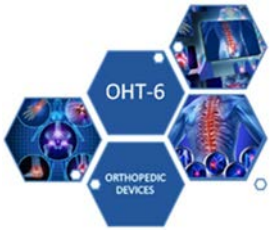




# Medical Device Reporting

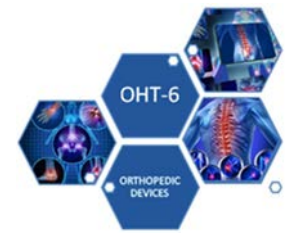
- Review of the MDR database identified 270 MDR reports since 1984
- No serious safety signals identified

Adverse event	Count
Skin reaction/issue	187
Pain	59
Device functional issue	21
Systemic issue	15
Swelling	14
Cardiac issues	12
Infection	12
Mass/tumor	11
Excessive bone growth	9
Hospitalization/ER visit	8
Shock sensation	8
Burning sensation	7
Gastrointestinal issue	7
Numbness	6



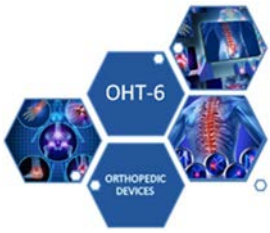
# Recall History

- A review of the FDA database found only two recalls for the PMAs approved under the LOF and LPQ product codes
  - Two class II recalls for the Exogen device (P900009) posted on August 4, 2009 and terminated November 18, 2010
  - Related to problems with the transducer component



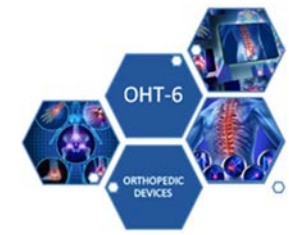
# Risks to Health & Mitigation

Identified Risk to Health	Mitigation Method
Failure or delay of osteogenesis	Clinical performance testing Non-clinical performance testing Software verification, validation, and hazard analysis Labeling
Burn	Non-clinical performance testing Electrical safety testing; Labeling
Electrical shock	Electrical safety testing; Labeling
Electromagnetic interference	Electromagnetic compatibility (EMC) testing Labeling
Adverse tissue reaction	Biocompatibility testing; Labeling
Adverse interaction with internal/external fixation devices	Labeling
Adverse biological effects	Non-clinical performance testing Software verification, validation, and hazard analysis



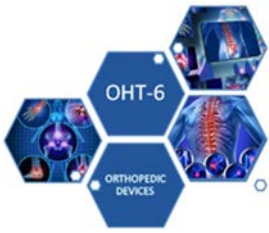
# Proposed Special Controls

- **Clinical Performance Testing**
  - Clinical data will be needed to demonstrate that any difference in the therapeutic signal does not affect the clinical effectiveness of the treatment



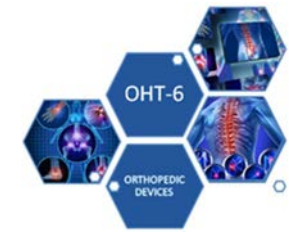
# Proposed Special Controls

- **Non-Clinical Performance Testing**
  - Intended to demonstrate the device performs as intended under the anticipated conditions for use
    - Verification and Validation of critical performance characteristics of the device, including characterization of the designed outputs of the device as well as the outputs that are delivered to the patient
    - Thermal safety and thermal reliability testing
    - Validation that the signal characteristics are within safe physiologic limits
    - Reliability testing consistent with the expected use-life of the device



# Proposed Special Controls

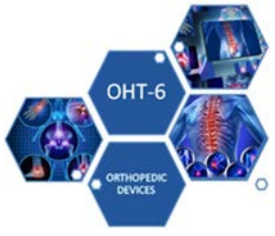
- **Additional Non-Clinical Performance Testing**
  - Biocompatibility evaluation of patient contacting components
  - Performance data must demonstrate the electrical safety and electromagnetic compatibility of the device
  - Appropriate software verification, validation, and hazard analysis



# Proposed Special Controls

- **Labeling**

- Warning against use on compromised skin or when there are known sensitivities;
- Appropriate warnings for patients with implanted medical devices;
- A detailed summary of the clinical testing, which includes the clinical outcomes associated with the use of the device, and a summary of adverse events and complications that occurred with the device;
- A clear description of the device;
- Instructions on appropriate usage, duration, and frequency of use;
- Instructions for maintenance and safe disposal;
- Instructions for appropriate cleaning of any reusable components;
- Specific warnings regarding user burns, electrical shock, and skin irritation; and
- The risks and benefits associated with use of the device.



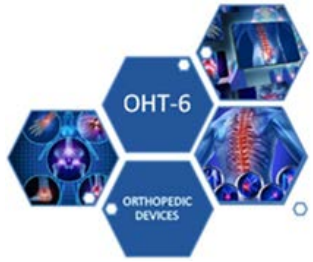
# FDA Comments

- A reasonable assurance of safety and effectiveness has been established for the FDA approved BGS devices
- The scientific literature indicates that small changes made to the general device type can cause the treatment to be ineffective
- The issue raised by the proposed reclassification is whether sufficient scientific knowledge exists to adequately define the risks to health associated with the proposed generic device type and if the proposed special controls are sufficient to control these risks to health

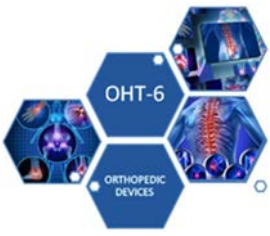


# Thank You!





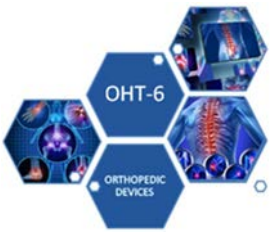
# Questions for the Panel



# Question 1 for the Panel

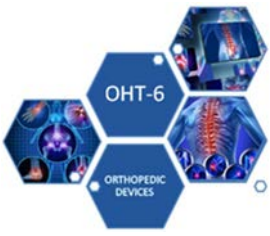
FDA has identified the following risks to health of non-invasive bone growth stimulators based on available information for these devices:

- Failure or delay of osteogenesis
  - Burn
  - Electrical Shock
  - Electromagnetic Interference (EMI)
  - Adverse Tissue Reaction
  - Adverse Interaction with Internal/External Fixation Devices
  - Adverse Biologic Effects
- a. Please comment on whether this list completely and accurately identifies the risks to health presented by non-invasive bone growth stimulators.
- b. Please comment on whether you disagree with inclusion of any of these risks, or whether you believe that any other risks should be included in the overall risk assessment when considering all indications for this device type.



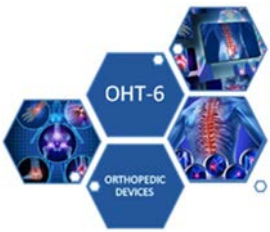
## Question 2 for the Panel

- a. FDA believes that general controls alone are not sufficient to provide a reasonable assurance of safety and effectiveness for non-invasive bone growth stimulators. If you disagree, please discuss how general controls alone are sufficient to provide a reasonable assurance of safety and effectiveness for this device type. General controls may include:
  - i. Prohibition against adulterated or misbranded devices,
  - ii. Good Manufacturing Practices (GMP),
  - iii. Registration of manufacturing facilities,
  - iv. Listing of device types,
  - v. Record keeping, etc.
- b. FDA does not believe that non-invasive bone growth stimulators are “life-supporting or life-sustaining, or of substantial importance in preventing impairment of human health.” Do you agree with this assessment? If not, please explain why.



## Question 2 for the Panel (Cont'd)

- c. FDA does not believe that non-invasive bone growth stimulators present a “potential unreasonable risk of illness or injury” Do you agree with this assessment? If not, please explain why.
- d. FDA believes sufficient information exists to establish special controls for non-invasive bone growth stimulators. Based on the information presented today, please discuss whether you believe that sufficient information exists to establish special controls that can provide a reasonable assurance of safety and effectiveness for this device type.



# Question 3 for the Panel

FDA proposes the following special controls for non-invasive bone growth stimulators to provide reasonable assurance of their safety and effectiveness.

- 1) Clinical performance data must support the intended use of the product.
- 2) Non-clinical performance testing must demonstrate that the device performs as intended under anticipated conditions of use.
- 3) Patient-contacting components of the device must be demonstrated to be biocompatible.
- 4) Performance data must demonstrate the electrical safety and electromagnetic compatibility of the device.
- 5) Appropriate software verification, validation, and hazard analysis must be performed.
- 6) Labeling for the device must include (i) Warning against use on compromised skin or when there are known sensitivities; (ii) Appropriate warnings for patients with implanted medical devices; (iii) A detailed summary of the clinical testing, which includes the clinical outcomes associated with the use of the device, and a summary of adverse events and complications that occurred with the device; (iv) A clear description of the device; (v) Instructions on appropriate usage, duration, and frequency of use; (vi) Instructions for maintenance and safe disposal; (vii) Instructions for appropriate cleaning of any reusable components; (viii) Specific warnings regarding user burns, electrical shock, and skin irritation; and (ix) The risks and benefits associated with use of the device.

Please discuss whether these special controls appropriately mitigate the identified risks to health of this device type, and whether you recommend additional or different special controls.