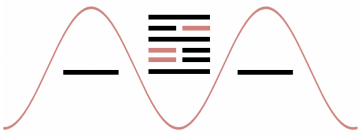

Acoustic Sciences Associates

To: Mr. Patricio Garcia
From: Acoustic Sciences Associates LLC (ASA)
Re: Docket No. FDA-2020-N-0008
Date: August 26, 2020

Mr. Garcia,

Please see below for ASA's revised written input on the reclassification of noninvasive bone growth stimulators as Class II medical devices, as input to the Orthopaedic and Rehabilitation Devices Panel of the Medical Devices Advisory Committee.

Summary

ASA supports the proposed reclassification of LIPUS noninvasive bone growth stimulators as Class II medical devices, and proposes a specific set of special safety and efficacy controls for 510(k) equivalence validation.

About ASA

Acoustic Sciences Associates (ASA) conducts cutting edge research and development in medical ultrasound. Our experience includes a technical background in the military sonar anti-submarine warfare space, with significant experience in both biomechanics and fluid mechanics. Founded by leaders in the ultrasound community, ASA's unique capabilities make us extremely well-suited to address and solve extremely complex problems in medical ultrasound. Key principals of ASA include:

- Dr. Robert Muratore, a well-published and patent-holding biophysicist with 20 years ultrasonics experience. Dr. Muratore's specialties are in integrating ultrasonic imaging and therapy. He has served as President of the Ultrasonic Industry Association and is a Fellow of the American Institute of Ultrasound in Medicine.

- Alan Winder, a well-known and published expert in ultrasound and sonar, with 11 patents in the areas of ultrasound and bone fracture healing. Mr. Winder's areas of specialty include acoustical signal processing and acoustic transducer/array design.

Introduction

ASA's response to the potential reclassification of bone growth stimulation (BGS) devices is limited to low intensity pulsed ultrasound (LIPUS) devices in this space. Our opinions on this subject are based on our understanding of the science that forms the efficacy and safety of this technology. In 1990, building on original research published by Duarte, the team of Pilla and coworkers established the efficacy of ultrasonic stimulation for enhanced bone fracture healing

[1][2]. Since then, ongoing research has shown that utilization of a LIPUS signal enhances soft callus mineralization (endochondral ossification) and further increases fracture hard callus strength in the remineralization and remodeling stages.

Animal connective tissues, including bone, consist largely of a collagenous extracellular matrix (ECM). Mechanical stimulus of the ECM is transferred across the plasma membrane to the cytoskeleton via integrin molecular protein linkages, as shown by Lefkowitz and others. Therefore, the integrin molecular protein response is a key to generating cellular functions. Ultrasonic waves trigger an integrin response, which in turn, initiates a cascade of intracellular events, including a release of cytoplasm growth factors and subsequent genetic transcription and protein synthesis.

Published research studies on molecular mechanisms since 2005 have shown that LIPUS insonification enhances the mechano-biochemical conversion efficiency and the production of cyclo-oxygenese 2 (COX-2) in the nucleus of the bone cell. COX-2 plays an enzymatic role in the production of prostaglandin E_2 (PGE2) which in turn stimulates and promotes fracture repair [6].

The medical community now has a greater understanding of the utility of LIPUS for the treatment of fresh fractures at risk, and delayed and non-union fractures in patients. It is now clear that LIPUS up-regulates integrin expression and differentiation of osteoprogenitor cells to osteoblasts, thereby promoting the bone formation process.

In summary, a study of the science clearly establishes that LIPUS stimulation triggers a cascade of cellular bone healing processes: (1) starting with releasing vascular endothelial and platelet-derived growth factors (VEGF, PDGF) that play a key role in increasing vascularity in the inflammatory and early soft callus repair phases, leading to (2) COX-2 upregulation being extremely effective for accelerating soft to hard callus remodeling phases from cartilage and woven bone into lamellar (cortical) bone in the final stage of the repair process. After more than 26 years of clinical use, it can be confidently stated that the correct application of a LIPUS signal for bone growth stimulation therapy (as labeled) poses little or no risk of danger to humans.

Device Safety

A LIPUS signal is defined by its spatial-average temporal average (SATA) acoustic rms power, and properties such as the transmit carrier frequency, modulation envelope, period, duty cycle, effective radiation area of the acoustic transducer, and the control of the acoustic propagation modes. The selection of these parameters will be informed by the linear and nonlinear characteristics of the propagating medium. The dynamics of living tissue are generally nonlinear, and to facilitate the understanding and visualization of physical phenomena we tend to linearize the response to various stimuli, both naturally-occurring in nature and man-made.

This linearization process is particularly accurate at non-thermal low intensities, which produce biological effects through mechanical stimulation.

Non-thermal nonlinear effects include cavitation and the associated acoustic streaming, and acoustic caustics. Acoustic cavitation is the formation and activity of small (micron sized) gas bubbles that oscillate and collapse in response to the amplitude and frequency of the ultrasound pressure wave. Cavitation bubbles can form in response to high amplitude and low frequency ultrasound pressure waves, and lead to localized streaming and severe pressure changes upon collapse. Acoustic caustics arise from "hot spots" in the sound field, which may result from the reinforcement of intersecting acoustic rays. Either of these non-thermal effects can cause physical damage to intervening tissue. Metrics are therefore required to assure that any acoustic pressure does not exceed thresholds for inducing these non-linear effects.

The accepted measures of non-thermal nonlinear ultrasound behavior in biological tissue are the **mechanical index (MI)** and the **beam nonuniformity ratio (BNR)**, required for diagnostic scanning and therapeutic operation, respectively.

- MI is a measure of the destructive behavior of ultrasound induced in biological tissue due to cavitation effects, and is intended for B-mode short-pulse, low duty cycle diagnostic imaging where high peak pressures are often obtained. An acceptable value for MI in the Output Display Standard (ODS) is less than 0.7 in the unscanned mode, below which cavitation (theoretically) will not occur [3]. Published test results to date indicate that the likelihood of adverse nonthermal biological effects is effectively zero if the MI is less than 0.5.

- BNR is defined as the [max I_{SPTA}/I_{SATA}], where [max I_{SPTA}] is at the acoustic axial distance of maximum pressure {for unfocused transducers, at a point approximately the (transducer diameter)^2/(4 x wavelength λ) along the maximum response axis, MRA}, and I_{SATA} is the total rms acoustic power divided by the Effective Radiation Area (ERA). The ERA is the width of the beam intensity profile function at the -13 dB point, at a distance of 5 mm along the transducer MRA axis and can be measured against IEC 62359 specifications. To avoid generating acoustic caustics or "hot spots" in biological tissue, the BNR for therapeutic devices must be less than 8.0 [5].

In order to demonstrate 510(k) equivalence vis-à-vis suitable device safety, ASA believes a potential vendor must therefore show that the I_{SATA} and rms acoustic power of a LIPUS signal will not produce deleterious biological effects in terms of measurable nonthermal biological nonlinearities. Specifically, ASA recommends the following additional special controls for safe clinical treatment with diagnostic and therapeutic ultrasound:

1. Mechanical Index (MI) < 0.5
2. Beam Nonuniformity Ratio (BNR) < 8.0

Device Efficacy

In order to demonstrate 510(k) equivalence vis-à-vis suitable device efficacy, ASA believes that a candidate device must have a certain set of signal parameters and related transducer design parameters, and must respect a well-defined set of contraindications.

Signal Parameters

A well-understood set of LIPUS signal parameters have been shown to be effective in promoting bone growth:

1. **Power level.** The rms power must be sufficient to overcome attenuation in the tissue pathway between the transducer located on the skin surface and the fracture site. Proper determination of the power level depends on the transducer design parameters, described below.
2. **Pulse rate.** The pulse repetition frequency must be in a biologically relevant range, on the order of a kilohertz.
3. **Frequency.** The wavelength of the acoustic carrier signal must be smaller than the fracture width. Therefore, the frequency must be on the order of a megahertz.

Transducer Design Parameters

An effective LIPUS signal depends on the details of the transducer design:

1. **Effective radiating area (ERA)**. If the matching layer of the transducer (with area A) has a uniform thickness, then measuring the acoustic field in the plane 3mm (IEC) or 5mm (AIUM) from the transducer along the MRA will produce symmetrical patterns with the ERA and A being essentially equal. If they are asymmetrical, then the ERA must be measured in accordance with IEC or AIUM specifications.
2. **Spatial average-temporal average intensity.** If the matching layer is nonuniform, then I_{SATA} is given by P (average acoustic power)/ERA, where P is measured with a radiometer or force balance. For a matching layer of uniform thickness, I_{SATA} is given by P/A.

Contraindications

Over the past 26 years, a wealth of literature has established the effectiveness of LIPUS within specific constraints:

1. **Fracture types.** LIPUS has not been proven effective for other than long bone (tibia, fibula, tibia/fibula, femur, ulna, and humerus) and small bone (scaphoid, ankle, and foot) fractures.
2. **Chronic NSAID use.** Numerous animal studies have demonstrated a consistent negative effect of NSAID treatment on endochondral ossification during fracture healing, likely caused by COX-2 inhibition. LIPUS has not been shown to be particularly effective in overcoming this mechanism [4].

Conclusion

ASA believes noninvasive bone growth stimulators based on LIPUS fit the definition of an FDA Class II device, in that the FDA General Controls for medical devices would by themselves be insufficient to provide reasonable assurance of safety and effectiveness. However, ASA equally believes that LIPUS bone growth stimulators should NOT be classified as Class III devices, for the following reasons:

1. These devices do not sustain or support life, in the same way as more advanced medical devices such as pacemakers or defibrillators.
2. These devices are not implanted inside the body, and are used externally.
3. These devices, which rely on ultrasound at diagnostic levels, do not present an unreasonable risk of illness injury.
4. These devices have been demonstrated safe by 26 years of clinical use.
5. These devices are designed for use on the bones in the limbs, and therefore the ultrasound signal does not traverse any organs.
6. Requiring pre-market approval (PMA) for these devices places an unreasonable cost and burden on innovation, and has had a dampening effect on technical advancement and competition in this space, to the detriment of the public.
7. A reasonable set of special controls as proposed above could entirely mitigate any additional risks that are not mitigated by the General Controls.

ASA therefore supports the proposed reclassification of LIPUS noninvasive bone growth stimulators as Class II medical devices, under the recommended 510(k) equivalence guidelines presented above.

References

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3. The AIUM Bioeffects Report, Section 7.1: Discussion of The Mechanical Index and Other Parameters, JUM, 19: 143-148, 2000.
4. Sue B, O'Connor JP, NSAID therapy effects on healing of bone, tendon, and the enthesis, J Appl Physiol, 115(6), 892–899, 2013.
5. IEC 61689 Edition 3.0 Ultrasonics – Physiotherapy systems – Field specifications and methods of measurement in the frequency range 0,5 MHz to 5 MHz (2013-02).
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Glossary

A	Transducer Area
ASA	Acoustic Sciences Associates
BGS	Bone Growth Stimulation
BNR	Beam Nonuniformity Ratio
COX-2	Cyclo-Oxygenese 2
ECM	Extracellular Matrix
ERA	Effective Radiation Area
I_{SATA}	Spatial-Average Temporal Average Intensity
I_{SPTA}	Spatial-Peak Temporal Average Intensity
LIPUS	Low Intensity Pulsed Ultrasound
MI	Mechanical Index
MRA	Maximum Response Axis
ODS	Output Display Standard
PGE2	Prostaglandin E_2
PMA	Pre-Market Approval