Citizen Petition

Ernest C. Chisena and Jahangir Rastegar Date: February 25, 2020

The undersigned submits this petition under __ (relevant statutory sections, if known) of the __ (Federal Food, Drug, and Cosmetic Act or the Public Health Service Act or any other statutory provision for which authority has been delegated to the Commissioner of Food and Drugs) to request the Commissioner of Food and Drugs to__ (issue, amend, or revoke a regulation or order or take or refrain from taking any other form of administrative action).

A. Action Requested

As requested in my letter to the FDA in 1997 (enclosed), the petition requests the Commissioner to force Exogen-Bioventus to prove that it is Ultrasound that is responsible for enhancing fracture healing, as claimed in their PMA. None of their studies have controlled the pressure being applied over the fracture including the 1994 JBJS article (ref #1). That study of tibia fractures treated with casting is the basis for PMA # P900009 Docket # 94M-0363. As explained in my letter, the soft tissue deformation or pressure produced by the mounting device, the ultrasound device and the circular felt plugs inserted into the fixture and the cap placed over it were not measured or matched between the active and placebo-treatment groups. Our contention is that if the pressure applied to the soft tissues over the fracture was the same in both the active and placebo groups, no difference in healing rate would have been observed.

B. Statement of Grounds

Because of new evidence described below, we think that the effectiveness of Exogen Ultrasound Bone Healing System (LIPUS) to enhance bone healing should be re-visited. It is important for the appropriate treatment of patients that consideration be given to the alternative explanation that increased soft tissue pressure over the fracture causes the enhancement.

In 1997 a letter(copy enclosed) was sent to the FDA questioning the supporting study(ref #1) which was the basis of Exogen receiving from the FDA, PMA P900009 S003 allowing them to claim that its device enhances bone healing. In that letter it was pointed out that the pressure produced in the soft tissues over the fractured tibia applied by the ultrasound device and the cotton plugs used to prevent tissue bulging was not measured or controlled in that study.

There is a plausible basic science explanation that may explain why increasing the pressure in the soft tissues over a fracture would enhance endochondral fracture healing. Blood flow in the soft tissues is diminished with an increase in tissue pressure. Reduced blood flow would produce a relative hypoxic state (reduced pO2 still compatible with tissue viability). Recently, it has become evident that hypoxia activates hypoxic inducing factor-1 alpha (HIF-1A), which increases the production of VEGF and signals angiogenesis. Angiogenesis, the growth of new blood vessels is present and needed for new bone formation.

In 2010, an animal study (ref #2) had been performed supporting increased soft tissue pressure as the important parameter effecting fracture healing. Constant local soft tissue compression produced statistically significant increase in bone mineral density.

The positive effect of increasing the soft tissue pressure at the fracture site has been seen treating many of my patients including veterans with appendicular fractures. A case report is to be published in NYU *Bulletin of the Hospital for Joint Diseases* – Volume 77, Number 4, 2019, which describes a veteran patient with a pathologic fracture of the radius which healed with the application of pressure using a specialized orthosis.

X-rays of more than fifty cases of appendicular fractures demonstrating the enhancing effect of increasing the soft tissue pressure over the fracture are available for review. No ultrasound was applied as opposed to the studies performed supporting LIPUS where both pressure and ultrasound were present.

Conversely, over the last several years, multiple papers have been published questioning the effectiveness of the LIPUS device (ref #3,4). In particular (ref #3) should be

reviewed: Re-evaluation of low intensity pulsed ultrasound in treatment of tibial fractures (TRUST): randomized clinical trial.
The conclusion of that study was that "postoperative use of LIPUS after tibia fracture fixation does not accelerate radiographic healing and fails to improve functional recovery". This contradicts the conclusion of the 1994 JBJS paper which supported LIPUS enhancing tibia fracture healing which was cited in my letter to the FDA in 1997.

This reversal, the recent negative result demonstrating no effect of LIPUS after tibia fracture fixation while positive results were claimed in the 1994 JBJS paper requires explanation. The fractures were internally fixed in the recent study whereas cast treatment was used in the 1994 study. In the recent study fracture angulation could not occur because of the internal fixation, making it likely that the pressure applied by the ultrasound apparatus was the same on the control and active sides, even though not controlled or measured. In the 1994 study the pressure applied, through a sleeve embedded in the cast, on the soft tissues by the ultrasound head and the cotton plugs would have been greater in the active group if the fracture had angulated toward the ultrasound unit more frequently in that group. If the X-rays of the patients were archived, this could be easily checked.

From a scientific perspective, it is important to identify by whatever means necessary the effective parameter (low intensity pulsed ultrasound or increased soft tissue pressure) that results in enhance fracture healing to be able to optimize treatment of patients with fractures and avoid further uncertainties.

Feel free to request clarification of any of the above. I do respectfully ask that you please keep this communication confidential.

C. Environmental Impact

"We claim categorical exclusion under 25.30, 25.31, 25.32, 25.33, or 25.34 of this chapter or an environmental assessment under 25.40 of this chapter."

D. Economic Impact

Please state that "economic impact information will be submitted upon request of the commissioner."

E. Certification

"The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petition which are unfavorable to the petition."

Respectfully,

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