

FDA's Proposed Rule on Requirement for Premarket Approval for Cranial Electrotherapy Stimulation

Fact Sheet

History: Cranial electrotherapy stimulation (CES) devices have been on the market since the 1960s and in 1976 the Food and Drug Administration (FDA) was given control of medical devices (prior to 1976, medical devices were not federally regulated). The clearance from 1976 to today has been based on the 510(k) process (so named for the section of the Food, Drug and Cosmetic Act that governs this process) that requires the device registrant to establish that its device is substantially similar to a device which was on the market prior to 1976. The registrants must show that their device will produce “essentially equivalent” safe and effective results as a prior device had claimed. All CES devices on the market since 1976 have been cleared in this manner. Many devices cleared in this manner are considered Class III medical devices until such time as FDA completes its review of the device. FDA may down-classify (as outlined in section 515(i) of the Food, Drug and Cosmetic Act) the device to Class I or II or require the device go through the Pre-Market Approval (PMA) application process.

FDA was charged with completing the classification process for all device categories in the 1976 Food, Drug & Cosmetic Act. In 2009, the General Accounting Office (GAO) noted that FDA had *still* not fulfilled its statutory requirement (some 33 years after given the mandate) by not addressing the classification of 27 different categories of medical devices (including CES). This slap on the wrist from the GAO prodded FDA into action, and in the April 9, 2009 Federal Register (74 FR 16214), FDA required all of the manufacturers of devices in those 27 categories to submit information, consisting of all known research and safety data for their devices. As always, EPI complied with this request by providing FDA in August, 2009, 275 pages of research and clinical outcome data showing the safety and efficacy of Alpha-Stim® technology. FDA was to take all the information provided and determine if these “pre-amendment devices” (devices on the market before 1976) should be reclassified as Class II or Class I devices, or if they should go through the more strict, and more expensive, PMA process. The PMA process was put into place as a method of obtaining FDA approval for new devices, so the idea of going through a PMA process for a device that has legally been on the market for over 30 years is a bit unusual, to say the least. Yet on August 8, 2011, (76 FR 152) FDA published its proposed rule related to CES and actually recommended that all CES devices go through the PMA application process.

Proposed Rule: There are several areas of concern in the proposed rule requiring each CES manufacturer obtain a PMA for its device. While EPI would prefer down-classification without the need for a PMA, it understands that a PMA is not entirely a bad idea for the CES field. However, *how* FDA reached its conclusion, and EPI's previous experiences with FDA over the past 30 years, gives EPI great concern. The arbitrary and capricious manner in which FDA reached its conclusion leads one to be concerned about the biased, arbitrary and capricious evaluation CES will receive from FDA in the PMA process. There are three main areas of concern in the Proposed Rule: 1. FDA's review of the science; 2. FDA's review of safety data; and 3. FDA's evaluation of the economic impact of this ruling. Below is a brief explanation of all three.

1. **Scientific review.** In EPI's 2009 submission, it provided FDA with 44 studies conducted on Alpha-Stim®. EPI also provided FDA with 100 additional studies conducted on other CES devices, for a total of 144 CES Studies. Of the 144 studies, 53 have been completed since 1993. FDA brushed aside all but 8 of the studies since 1993 in an off-handed manner: "Many studies were excluded from further review because they were conducted on very specific populations (e.g., alcoholics or other types of substance abuse), and therefore were not representative of the general population suffering from insomnia, anxiety, or depression. **Six** studies were identified for further review (Refs. 1 through 6). FDA also identified **two** relevant meta-analyses (Refs. 7 and 8)." 76 Fed. Reg. 152, p. 48064 (*emphasis added*). Of the 53 studies completed on CES since 1993, FDA dismissed all but 8 of the studies because "they were conducted on very specific populations". EPI believes it is arbitrary and capricious for FDA to dismiss all but 8 of the studies conducted since 1993 because they were on specific populations. Later in the proposed rule FDA provides its definition of "valid scientific evidence" which is:

"...evidence from well-controlled investigations, partially controlled studies, studies and objective trials without matched controls, well-documented case histories conducted by qualified experts, and reports of significant human experience with a marketed device, from which it can fairly and responsibly be concluded by qualified experts that there is reasonable assurance of the safety and effectiveness of a device under its conditions of use." 21 CFR 860.7(c)(2).

FDA's own definition of "valid scientific evidence" does not discount studies simply because they were conducted on a "specific population", therefore the other 45 studies should have undergone review by FDA. Anxiety, insomnia and depression are ubiquitous in all populations and each study has inclusion criteria and various methods of evaluating outcomes in accordance with the scientific method. Such a dismissal, which is contrary to the statute, of these 45 completed research studies is of great concern to EPI. The Proposed Rule then discards the eight studies FDA felt were worthy of individual attention. FDA discredited each of the eight studies for various reasons, without addressing a single positive finding in any of the eight. None of the studies were discredited in a manner that would meet the criteria imposed in FDA's own definition of "valid scientific evidence." Additionally, EPI provided FDA with a meta-analysis of all the CES studies (conducted on over 10,500 subjects). The meta-analysis showed that studies in anxiety, insomnia and depression all had a high "r Effect Size" in each of the three categories, showing consistent, robust and significant effects as averaged across the studies on various populations. Every single fact concerning positive outcome data was completely ignored in the proposed rule. Also conspicuously missing was any mention of the significant human experience with Alpha-Stim®, a legally marketed device, or any other legally marketed device.

2. **Risks to Health.** FDA outlined six potential risks to health due to CES:

Worsening of the condition being treated—if the device is not effective and the patient is not treated in a conventional manner, the patient's psychological condition may worsen.

Skin irritation—the electrodes or the conductive cream used with the electrodes may cause skin irritation.

Headaches—reported cases of adverse effects of CES devices include headaches following treatment with electrical stimulation.

Potential risk of seizure—electrical stimulation of the brain may result in seizures, particularly in patients with a history of seizure.

Blurred vision—placement of electrodes over the eyes may cause blurred vision.

Potential adverse effects from electrical stimulation of the brain— The physiological effects associated with electrical stimulation of the brain by these devices have not been studied systematically; therefore, adverse effects which may be caused by these electrical stimuli remain unknown. 76 Fed. Reg. 152, p. 48065.

No data showing the likelihood of any of the potential risks was provided, nor were any references provided showing how the six potential risks were reached. Since the noted “risks to health” have been specified by FDA in every CES rule making since 1976 it can only be presumed that they are from outdated sources. FDA has never attempted to amend its 33 year old data by reviewing its records of risk incidents collected from EPI at each of its bi-annual inspections of its operations since 1981 nor from any of EPI’s submissions pending at FDA. At least half of the outlined “risks to health” from this notice have never been reported by any actual Alpha-Stim® user in thirty years of business.

In fact, EPI provided FDA with detailed and true data of all potential health risks. All were minor and self-limiting (*e.g.*, headaches, skin irritation, vertigo/nausea, anger, heavy feeling, and tinnitus were all reported in 0.10% (1 in 1,000) or less of patients). This data was completely ignored in the Proposed Rule. The risks to health outlined by FDA were not commented on or discussed in the Proposed Rule. Alpha-Stim® has been on the market for over thirty years and has been the subject of many research studies that examined potential side effects, so FDA’s concern that it poses a significant risk to health is not well conceived or based on fact.

3. **Economic Data.** The Proposed Rule concludes with a confusing display of economic data that suggests the CES market is small and meaningless, and requiring a PMA for all CES device manufacturers would not provide a significant impact on society. FDA then goes on to estimate that the cost of preparing a PMA is \$1 Million for each CES company. FDA also estimates that it will spend \$8.4 Million to review the initial PMAs and then \$1 Million per year thereafter to review additional PMAs, and then concludes that this is a good use of taxpayer money. While EPI prides itself on being a small business willing to take on the big companies and governments of the world, we do not feel that our existence is inconsequential. We hope you feel the same way. If FDA were allowed to stop EPI from marketing Alpha-Stim® based on an arbitrary and capricious review, it would put hundreds of Americans out of work in manufacturing, sales, customer service and administrative positions. More importantly, thousands of practitioners, and all of their patients, would be deprived of an effective and safe treatment for anxiety, insomnia and depression. EPI’s largest customer is currently the United States government, and preventing the marketing of Alpha-Stim® would deprive our Soldiers and Veterans of an effective tool in their battle against insomnia, anxiety, depression and PTSD. Ironically, while one branch of government (FDA) is attempting to justify spending millions of dollars to prevent the marketing of CES, other branches (the DOD and VA) are spending millions of dollars purchasing Alpha-Stim® CES and on research to study the effects of Alpha-Stim® CES on our Soldiers and Veterans.

Conclusion: FDA's Proposed Rule on CES is full of holes and vagueness, and shows that FDA was either unwilling or unable to review the scientific evidence and safety data provided by EPI. It is clear that the Proposed Rule has not been well thought-out, and as such it is placing an arbitrary and capricious standard on CES. All in the medical community should be concerned about such rulings from the government body that was given the power to regulate medical devices and pharmaceuticals.

EPI has, unfortunately, been down this road before with FDA, as the Proposed Rule will represent the seventh time in the last 30 years that EPI has had to defend its technology with FDA. We are prepared to enlighten FDA once again. We would like your help and support.

Call for Action: If you find Alpha-Stim® to be an effective and safe tool for your practice or for yourself, we invite you to share that information with FDA. EPI showing FDA that CES works is good, practitioners and patients telling FDA that CES works is great!

If you would like to respond to FDA, you must click on the link below and look at the "Submit a Comment" box in green at the upper right corner.

You must add all this information to your comments (the Docket Number must be in your filing):
The Federal Register, Vol. 76, No. 152, pgs. 48062-48070. Proposed Rule: "Effective Date of Requirement for Premarket Approval for Cranial Electrotherapy Stimulator." [Docket No. FDA-2011-N-0504].

All comments should be addressed to the signatory on the Proposed Rule:
Nancy K. Stade
Deputy Director for Policy, Center for Devices and Radiological Health.

Here is the link to upload your letter and please also fax it to FDA at 301-827-6870 so they can't say they never received the upload. Please also send EPI a final copy of your letter to scott@epii.com or 940.328.0888 (facsimile).

<http://www.federalregister.gov/articles/2011/08/08/2011-19957/effective-date-of-requirement-for-premarket-approval-for-cranial-electrotherapy-stimulator>

EPI is asking that you simply tell FDA the truth about how safe and effective CES is for you and/or your patients. EPI will deal directly with the issues in the Proposed Rule.

Thank you for your time and attention on this important matter. If you have any questions or concerns please do not hesitate to contact: Scott Elder, Vice President (scott@epii.com or 817-458-3279).