

# EPI Response



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Nancy K. Stade  
Deputy Director for Policy  
Center for Devices and Radiological Health  
Food and Drug Administration  
5630 Fisher Lane, Room 1061  
Rockville, Maryland 20852

**Re: 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].**

Dear Ms. Stade:

Electromedical Products International, Inc. (EPI) is submitting this response at the request of the Food and Drug Administration (FDA) in its Proposed Rule for Cranial Electrotherapy Stimulation (Proposed Rule) issued in the *Federal Register* on August 8, 2011 (76 F.R. 48062). EPI appreciates the opportunity to comment on the Proposed Rule and highlight the deficiencies it feels exist in the FDA’s review of cranial electrotherapy stimulation (CES).

What would you say if I told you that a United States governmental agency was seeking to require an industry get that agency’s approval, prior to marketing, for a device that has been legally cleared to market by that same agency for over 30 years? What if I told you that device has had no significant adverse effects reported by its customers during such 30 year period, has over 144 studies supporting the effectiveness of the device, and has clinical outcomes data showing that 99.9% of the device’s users found the device effective? Would you think that the government agency might be overstepping its discretionary functions and perhaps acting in an arbitrary and capricious manner?

On July 20, 2011, Representative Joe Barton, Chairman Emeritus and senior Republican on the Energy and Commerce Committee, submitted a statement to the Oversight and Investigations Subcommittee entitled “FDA Medical Device Regulation: Impact on American Patients, Innovation, and Jobs.” In his statement, Congressman Barton stated as follows:

“Unfortunately, the issues we are discussing today harm the sick, inhibit innovation and stifle domestic economic and job growth. The Medical Device Review Process at the Food and Drug Administration (FDA) has become overly burdensome, unpredictable and inconsistent under its current leadership...Small companies and entrepreneurs want to create businesses and design products that will help save lives and be profitable. For this to happen, we need a regulatory system that is predictable, consistent and open. These words do not describe the current regulatory environment at the FDA, especially at the Center for Devices and Radiological Health.”

EPI would like to echo Congressman Barton’s call for a “predictable, consistent and open” system for medical device reviews. Unfortunately, the Proposed Rule provides CES with anything but a predictable, consistent and open review. Much of what is written as fact in the Proposed Rule is not supported and, EPI believes, not supportable. During its thirty years in business, EPIs Alpha-Stim Technology has safely and effectively treated millions of patients for anxiety, insomnia and depression. The responses EPI has received from practitioners, patients and researchers over that time period have been tremendous, and the thirty year track record supports that EPI’s Alpha-Stim Technology is not only safe for the patient, but it is also highly effective. Notwithstanding the thirty years of clinical based evidence EPI has provided to FDA establishing the safety and effectiveness of the Alpha-Stim Technology, FDA has determined that CES is not safe or effective, and has reached such conclusions in a manner that is truly disconcerting to those who value a “predictable, consistent and open” review of medical devices applying “sound science.”

## **I. BACKGROUND ON PROPOSED RULE.**

Cranial electrotherapy stimulation (CES) devices have been on the market since the 1960s. In 1976 the FDA was given greater regulatory authority of medical devices (prior to 1976, medical devices were subject to limited federal regulation). As noted in the Proposed Rule, the availability of CES devices from 1976 to today has been based on the 510(k) process which 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” results as a prior devices had claimed.

FDA was charged with completing the classification process for all device categories available prior to 1976. As noted in the Proposed Rule, FDA has previously proposed a rule (or even adopted a final rule) requiring Premarket Approval (PMA) for CES devices on 5 different occasions: September 4, 1979 (44 FR 51770); January 6, 1989 (54 FR 550); August 31, 1993 (58 FR 45865); August 24, 1995 (60 FR 43967); and June 4, 1997 (62 FR 30600). In each instance, FDA has either elected not to proceed and make a final rule on the requirement, or, in the case of the August 24, 1995 ruling, FDA issued a final rule requiring a PMA for CES devices only to later recall its ruling (*see* 60 FR 43967, 62 FR 4023, and 62 FR 30456). CES has remained a Class III device requiring the showing of substantial equivalency to pre-1976 devices in order to market the technology.

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 failing to address the classification of 25 different categories of medical devices (including CES). On April 9, 2009, FDA required all of the manufacturers of devices in those 25 categories to submit information, consisting of all known research and safety data for their devices (74 FR 16214). The request for information by FDA required that the manufacturers of devices in the 25 different categories submit information within 120 days that either: supported a request for reclassification as either a Class I or Class II device or supported a request for Premarket Approval (PMA) of the device. EPI elected to request reclassification of CES as a class II device. For such a request, FDA required the manufacturer to provide the following information:

1. Identification. (A brief narrative identification of the device specific enough to distinguish a particular device from a generic type of device and, where appropriate, should include a listing of the materials, component parts, and a description of the intended use of the device);
2. Risks to health. (An identification of the risks to health summarizing all adverse safety and effectiveness information that has not been submitted under section 519 of the act, particularly the most significant information, describing the mechanisms or procedures that will control the risk and including a list of the general hazards associated with the device);
3. Recommendation. (A statement whether the manufacturer believes the device should be reclassified into class I or class II);
4. Summary of reasons for recommendation. (A summary of the reasons for requesting reclassification of its device and an explanation of why it believes the device meets the statutory criteria for reclassification into class I or class II. The manufacturer also needed to identify the special controls that it believes are sufficient to provide reasonable assurance of the safety and effectiveness of its device if it believes the device should be reclassified into class II); and
5. Summary of valid scientific evidence on which the recommendation is based. *Id.*

EPI complied with this request for information within the 120-day period by providing FDA 275 pages of research and clinical outcome data showing the safety and effectiveness of its Alpha-Stim Technology. FDA indicated it would 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. On August 8, 2011, almost 2 years to the date from the submission deadline for the 25 devices, FDA published its proposed rule related to CES, recommending that all CES devices go through the PMA application process.

## II. EPI'S BACKGROUND WITH FDA.

EPI believes it is important to understand the background of FDA's review of CES technology to fully understand EPI's concern over the Proposed Rule and the conclusions reached by FDA. Generally, EPI is somewhat troubled by the assertion that FDA believe EPI's Alpha-Stim CES devices should go through a "Premarket Approval" process when EPI has been legally cleared to market the Alpha-Stim Technology for over 30 years. In that time, EPI has accumulated an abundance of research and clinical outcome data supporting its position that its CES technology is both safe and effective. EPI has submitted all of its research and safety/effectiveness data to FDA on at least eight occasions, and yet EPI is still answering the basic questions as to the safety and effectiveness of the Alpha-Stim Technology.

Alpha-Stim Technology was first introduced to the market in 1981 and has been in continuous commercial distribution for 30 years. Over that time period EPI has provided FDA with five 510(k) applications, one mandatory Premarket Approval Application (PMA) submitted in 1995, and two mandatory reclassification petitions, which are governed by Section 515(i). There have been **no reports** of any significant adverse side effects in the 30 year history of the technology. The Alpha-Stim CS, a third generation product, was cleared for interstate marketing and export by FDA under Section 510(k) as a TENS for pain control without incident. Another 510(k) was then submitted for the same product as a cranial electrotherapy stimulator (CES) to expand the indications to include anxiety, depression, and insomnia. In 1993 and 1997 the technology was upgraded to the Alpha-Stim 100 and Alpha-Stim SCS respectively.

Attached hereto as Attachment "A" is a brief history of EPI's dealings with the FDA. EPI has attached the history to this response in an effort to allow the reader to fully understand the past dealings EPI has had in the regulation of its medical devices. FDA has reviewed this technology on many occasions and has placed many demands on CES manufacturers to provide documentation, research and consumer-product testimonials, all at a major cost to the manufacturers. Unfortunately, the Proposed Rule ignores all of the data that has been provided over the years with respect to the safety and effectiveness of the Alpha-Stim Technology. The Proposed Rule demonstrates a lack of understanding of the research provided, the safety of the device and its effectiveness. While EPI has fully complied with the latest FDA requirements for a 515(i) submission and is providing this requested response to the Proposed Rule, it is also justifiably concerned that FDA's review of CES to this point has clearly been superficial and not the product of "sound science."

Throughout the many years of regulation by the FDA, EPI has complied with the reporting and safety requirements imposed on device manufacturers by FDA, and has completed all audits imposed upon it by the FDA. The FDA serves a great purpose in protecting consumers from faulty medical technology, and EPI wishes to be a good corporate citizen and abide by the regulations in place. However, as the history of EPI with the FDA demonstrates, EPI is justifiably concerned about the review of CES devices by the FDA's Center for Devices and Radiological Health (CDRH), which is responsible for the regulation of companies that manufacture, repackage, re-label, and/or import medical devices sold in the United States.

In addition to FDA regulatory clearance for pain, anxiety, insomnia and depression, EPI currently holds the following certifications from around the world:

1. International Standards Organization (ISO) 13485 Certification;
2. Underwriters Laboratories (UL) Safety/EMC Test Certification;
3. European Union (EU) Medical Device Directive Approval;
4. Canadian Medical Device Quality Systems Approval;
5. Mexican Regulatory Approval;
6. South Korean Regulatory Approval;
7. Israeli Regulatory Approval;
8. South African Regulatory Approval;
9. Latvian Regulatory Approval;
10. Australian Regulatory Approval;
11. Chinese Regulatory Approval; and
12. Japanese Regulatory Approval.

It is interesting to note that *everywhere in the world other than the United States, CES is an over-the-counter device*, meaning that its safety and effectiveness has been established, and a lower threshold for marketing the device exists. EPI is a good corporate citizen who complies with regulations and certification requirements around the world. EPI is not seeking special treatment from the FDA, but does expect and demand that the “valid scientific evidence” provided to FDA for CES be reviewed thoroughly and fairly, so that FDA can accurately determine whether EPI has demonstrated that the valid scientific evidence provided establishes reasonable assurance of the safety and effectiveness of CES.

### III. PROPOSED RULE.

There are many areas of concern in the Proposed Rule, a proposal which would require each CES manufacturer obtain a PMA for its device. EPI recommends the down-classification of CES into Class II, with special controls, and without the need for a PMA. The primary concern of EPI with respect to the Proposed Rule is *how* FDA reached its conclusions, and EPI’s previous experiences with FDA give EPI cause for concern on how Alpha-Stim will be evaluated in a PMA.

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.

As the Proposed Rule could drastically alter the approval process for a technology that has been legally cleared to market for over thirty years, EPI and, in fact, all CES manufacturers have a fundamental right to expect that FDA will undertake a thorough and objective scientific review of all of the clinical and scientific evidence before a proposal or decision regarding the classification of CES Devices is made. The Proposed Rule places a high standard on CES device

manufacturers with regards to establishing the safety and effectiveness of their CES devices. Unfortunately, FDA did not adhere to its same high standards in the writing of the Proposed Rule, as many of the assertions and conclusions reached in the Proposed Rule lack support.

**A. Scientific review.**

“A central lesson of science is that to understand complex issues (or even simple ones), we must try to free our minds of dogma and to guarantee the freedom to publish, to contradict, and to experiment. Arguments from authority are unacceptable.” Carl Sagan, as quoted in the *Journal of Neurotherapy*, July-September 2011 at 191.

The effectiveness of Alpha-Stim is demonstrable, more often than not, in a single treatment. It does not take a large scale study for a statistician to tease out a small effect after a six week trial, as is often the case with drugs. As a noted psychiatrist told an FDA official at a recent meeting of the American Psychiatric Association “Alpha-Stim melts away anxiety.” To the credit of EPI, there are several double-blind studies showing good effects. All the studies might not be big enough to satisfy FDA, or published in the journals FDA likes, or use FDA’s favorite diagnostic criteria, but they reveal a redundancy of effectiveness, the primary hallmark of science, by independent, U.S. government or university based investigators. It has been proven effective in a double blind study of anxiety during dental procedures and in another double blind study of preoperative anxiety by neurosurgeons. These contribute to the evidence that there is a demonstrable effect. Adding the mechanistic EEG, LORETA and fMRI studies completed to date that prove there is a considerable central nervous system effect consistent with the letters being sent by Service Member physicians and psychologists as well as civilian Alpha-Stim users and prescribers, priests and chaplains, there can only be one conclusion reached: Alpha-Stim is effective for the indications it is legally marketed for now.

Doctor Forest Tennant, Editor in Chief of *Practical Pain Management*, recently noted that:

“There is an increasing trend toward claiming that the only evidence of effective treatment is that derived from a double-blind, randomized controlled study. While such studies have great merit, the danger arises when the value of individual patient response regarding the efficacy of a treatment is dismissed.” Forest Tennant, *Evidence-based Medicine: Losing the Patient’s Voice?* PRAC. PAIN MGMT., September 2011, at 8.

While EPI has provided FDA with “double-blinded, randomized controlled” studies, FDA dismissed every study provided on minor technicalities, failing to consider benefits achieved by the patients. 21 C.F.R. Section 860.7 provides the guidelines by which the FDA Commissioner is to make determinations concerning the safety and effectiveness of medical devices. The FDA Commissioner is to determine whether evidence submitted or otherwise available constitutes “valid scientific evidence” for the purposes of determining the safety and effectiveness of a medical device and “whether the available evidence, *when taken as a whole*, is adequate to

support a determination that there is reasonable assurance that the device is safe and effective.” 21 C.F.R. § 860.7(c)(1)(2008)(*emphasis added*). “Valid scientific evidence” is defined as:

“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 be fairly and reasonably be concluded by qualified experts that there is a reasonable assurance of the safety and effectiveness of a device under its conditions of use. The evidence required may vary according to the characteristics of the device, its conditions of use, the existence and adequacy of warnings and other restrictions, and the extent of experience with its use.” *Id.* at § 860.7(c)(2).

Section 860.7 goes on to further explain that “the valid scientific evidence used to determine the effectiveness of the device shall consist principally of well-controlled investigations....unless the Commissioner authorizes reliance upon other valid scientific evidence.” *Id.* at § 860.7(e)(2). “Well-controlled investigations” are then explained as those investigations which include:

1. A clear statement of the objectives of the study.
2. A method of selecting subjects that:
  - a. provides adequate assurance that the subjects are suitable for the study, provides diagnostic criteria of the condition treated, and provides confirmatory laboratory tests;
  - b. assigns subjects to the test groups, if used, to minimize potential bias;
  - c. assures comparability between test groups and any control groups of pertinent variables such as sex, severity or duration of the disease, and use of therapy other than the test device.
3. An explanation of the methods of observation and recording of results utilized, including the variables measured, quantitation, assessment of subject’s response, and steps taken to minimize any possible bias of the subjects and observers.
4. A comparison of the results of treatment or diagnosis with a control in such a fashion as to permit quantitative evaluation. Generally, four types of comparisons are recognized:
  - a. No treatments (comparing treated and untreated patients);
  - b. Placebo control (comparison of the results of use of a device with an ineffective device);
  - c. Active treatment control (comparing device to an effective regimen of therapy); and
  - d. Historical control (comparing the device with the prior effects of the disease in comparable patient populations).

5. A summary of the methods of analysis and an evaluation of the data derived from the study, including any appropriate statistical methods utilized. *Id.* at § 860.7(f).

In EPI's 2009 submission, it provided FDA with 44 studies conducted on EPI's Alpha-Stim Technology. 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. On August 19, 2011, EPI submitted to FDA Supplemental information for Reclassification (as requested in the Proposed Rule) which provided FDA with an additional 17 studies (either completed since the 2009 submission or currently on-going) which are all on EPI's Alpha-Stim Technology. In all, EPI has submitted 58 studies to FDA on Alpha-Stim Technology. Of those studies, 28 meet the FDA's definition of "well-controlled investigations" and therefore should all be considered when determining the effectiveness of the device. All the studies provided provide "valid scientific evidence" which should be considered when determining the safety and effectiveness of CES. EPI has provided FDA with:

- a. 25 studies showing the devices effectiveness in the treatment of anxiety;
- b. 5 studies showing its effectiveness in the treatment of insomnia; and
- c. 6 studies showing its effectiveness in the treatment of depression.

If the CDRH would retain qualified experts who would fairly consider all the studies provided by EPI, then it would reach the conclusion that the research, "when taken as a whole", provides adequate and reasonable assurance of the effectiveness of Alpha-Stim Technology.

Many of the studies completed on Alpha-Stim Technology are small studies, and all have been completed by independent researchers. EPI believes that many independent small studies, conducted in various institutions on various populations, is more compelling and more objective scientific evidence of effectiveness than one large study organized, funded, and conducted by the company seeking approval of the drug or medical device. EPI has never funded any of its studies except for loaning researchers Alpha-Stim devices, usually modified for double-blind studies, after the study is approved by a governmental or university IRB.

According to the Merriam Webster Dictionary, the definition of Scientific Method is: "principles and procedures for the systematic pursuit of knowledge involving the recognition and formulation of a problem, the collection of data through observation and experiment, and the formulation and testing of hypotheses." Some scientists add that there should be honest observations and it is a hallmark of science to duplicate the experiments because there are many factors that can alter the outcome of a single scientific investigation. EPI's research provided to the FDA meets this definition. Unfortunately, FDA's response in the Proposed Rule to the scientific evidence provided was cursory, inadequate and not supported.

**1. FDA Dismissal of pre-1993 Studies.** The Proposed Rule first indicates that any studies conducted prior to 1993 will not be considered as part of FDA's current evaluation process:

“In support of a subsequent proposed rule in 1993 for classification of CES into class III, FDA performed a literature review and identified additional studies that had been performed for CES. After a review of the scientific literature, FDA concluded that the effectiveness of CES had still not been established by adequate scientific evidence. FDA has performed a literature search for studies of CES published after the 1993 proposed rule [January 1, 1993 to present].” 76 Fed. Reg. 48064.

This statement by FDA suggests that in this review of CES FDA did not consider any research conducted prior to 1993. The Code of Federal Regulations (CFR) clearly provides that the FDA Commissioner shall take into consideration all “valid scientific evidence” in reaching a determination, and that the valid scientific evidence shall be considered “when taken as a whole.” See 21 C.F.R. at § 860.7(c)(1). Excluding all pre-1993 valid scientific evidence from FDA’s determination in this Proposed Rule is not in compliance with the CFR. As FDA noted, the 1993 determination was a “proposed rule” and FDA never reached a final ruling on the classification of CES (thus, we are addressing this issue now---again) so the exclusion of pre-1993 research and studies is not a reasonable approach. When the FDA is asked to consider the evidence “as a whole” it should not exclude all evidence available prior to an earlier proposed rule, a proposed rule that never resulted in a final rule.

The Proposed Rule fails to indicate which studies were reviewed in 1993 when the FDA issued an earlier proposed rule. The cursory review that FDA conducted of the post-1993 research (discussed below) leads EPI to question the quality of the review and qualifications of the CDRH personnel that conducted the 1993 review of CES. When considering all “valid scientific evidence” and taking all valid scientific evidence “as a whole”, FDA should not exclude studies conducted before it issued a prior proposed rule.

**2. FDA Dismissal of 45 studies from 1993 to Present.** After limiting its review to studies completed after the 1993 proposed rule, FDA then incorrectly brushed aside all but eight 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 at 48064 (*emphasis added*).

Of the 53 studies completed on CES from 1993 through August, 2009, FDA dismissed all but eight of the studies because “they were conducted on very specific populations.” FDA’s own definition of “valid scientific evidence” does not discount studies simply because they were conducted on a “specific population”, and 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 runs contrary to intent of the CFR, of these 45 completed research studies is of great concern to EPI.

The relevant portions of the CFR do not support a position that studies should be excluded from consideration because the studies were conducted on “specific populations.” Quite the contrary, the CFR quite clearly states that all valid scientific evidence should be considered, and the evidence should be “taken as a whole” in the FDA’s considerations. All CES studies should be considered by FDA in determining the classification of CES, and not just the eight FDA elected to highlight. The dismissal of all but eight of the studies appears to be arbitrary and capricious, and not in line with the pertinent sections of the CFR.

**3. FDA Dismissal of Eight Remaining Studies.** After discarding all but eight of the studies completed on CES, the Proposed Rule then tries to discredit the remaining studies FDA felt were worthy of individual attention. FDA elected to ignore the results of each of the eight remaining studies for various reasons and failed to discuss a single positive finding in any of the studies. Instead, FDA elected to find a fault in each of the eight studies and thereby discredit the entire study. None of the studies were discredited in a manner that would meet the criteria imposed in FDA’s own definition of “valid scientific evidence” or “sound science.” Below is a brief explanation addressing why each of the eight studies FDA highlighted to specifically discredit must be considered in FDA’s determination of the safety and effectiveness of the Alpha-Stim Technology. It is deeply concerning that CDRH went into this review process looking for ways to discredit every study rather than analyzing the scientific findings of the studies. FDA’s decision to, for example, discredit the scales used and the number of subjects in the study, rather than analyzing the validity of the scientific evidence provided is very troubling.

a. *Bystritsky study.* FDA eliminated a study done by one of the top anxiety experts in the world: Alexander Bystritsky, M.D., Ph.D., Professor of Psychiatry and Bio-behavioral Sciences and Director, Anxiety Disorder Program, The Semel Institute for Neuroscience and Human Behavior, Stewart and Lynda Resnick Neuropsychiatric Hospital, David Geffen School of Medicine, University of California, Los Angeles, because:

“The Bystritsky et al. study (Ref. 1) was conducted open-label, and on only 12 subjects. The study involved observational baseline versus post-treatment without a control and therefore provided insufficient evidence of safety and effectiveness.” 76 Fed. Reg. 48064-65.

EPI contends that the independent study by this renowned anxiety specialist and distinguished professor should, at the very least, be included as qualifying for the FDA definition of “valid scientific evidence” as the study clearly falls within the definition of “...studies and objective trials without matched controls, well documented case histories conducted by qualified experts...” 21 C.F.R at § 860.7(c)(1). The study was a pilot study but provides “valid scientific evidence” establishing that CES is a safe and effective treatment for chronic anxiety disorders.

b. *Heffernan study.* The Proposed Rule indicates that the Heffernan Study did not measure outcomes of anxiety, insomnia or depression, and that it should not be considered because it was “conducted on only 20 subjects.” 76 Fed. Reg. 48065. Like all research on CES devices, the Heffernan Study should be considered as valid scientific evidence and made part of the FDA’s determination, when all the safety and effectiveness research is “taken as a whole.” FDA’s review of the Heffernan Study is incorrect in that the study does look at aspects of anxiety. According to WebMD (<http://www.webmd.com/anxiety-panic/guide/mental-health-anxiety-disorders>) the general symptoms associated with anxiety include muscle tension, palpitations and cold hands. The study measured the physiological rather than psychological methods to measure anxiety including electromyogram readings, heart rates and finger temperatures. The fact that the N for the study was 20 is of no bearing on the validity of the science. The FDA’s own definition of “valid scientific evidence” makes no predications on the size of a research study.

c. *Overcash study.* Overcash’s anxiety study was discarded because FDA did not like the anxiety psychometric scale used: “The Overcash study [Ref. 3] was a retrospective study design and used an anxiety rating scale that was not validated.” 76 Fed. Reg. 48065. For Overcash’s study of 197 patients diagnosed with anxiety disorders referred by local physicians, Overcash used multiple measures to assess change from Alpha-Stim CES including electromyogram (EMG) to study the reduction of muscle tension in these anxiety patients. All of the different psycho-physiological measures of anxiety used in the Overcash study—cardiovascular response (temp), glandular response (EDR) and electromyography (EMG)—are accepted and validated approaches to measuring anxiety. The study used a Numerical Visual Analog Scale (NVAS) to obtain a subjective measure of anxiety from the subjects. Validity for the NVAS in the study of anxiety is well established in research literature. Dr. Overcash, as a licensed psychologist-researcher, as well as many other researchers whose research on CES FDA discarded, considered reductions in EMG a valid measure of progress in anxiety patients. The Overcash study should be considered by FDA as the study clearly establishes that CES effectively treats the psychological aspects of anxiety as well as the body’s physiological response to it.

d. *Voris study.* The Proposed Rule then discredits the Voris Study because the study analyzed only a subgroup of “psychiatric subjects” which “included many types of anxiety disorders as well as non-anxiety psychiatric disorders. The subgroup represents a diagnostically heterogeneous group.” *Id.* The study meets the FDA’s definition of “well-controlled investigation” and provides valid scientific evidence establishing the effectiveness of the Alpha-Stim Technology. CES is currently cleared for the treatment of “anxiety” without any specific designation as to the type of anxiety. FDA’s decision to limit the types of populations and types of anxiety is not in keeping with a basic understanding of anxiety. The Voris study should be considered by FDA when evaluating the “valid scientific evidence” for CES as the study clearly establishes effectiveness in treating chronic anxiety disorders.

Anxiety disorders are the most common mental illness affecting 27.4 million people in the U.S. According to *The Economic Burden of Anxiety Disorders*, a study commissioned by the Anxiety

Disorders Association of America, anxiety disorders incurred an economic burden of approximately \$63.1 billion a year in 1998 dollars, with 54% of that amount spent on non-psychiatric medical treatment costs. People with an anxiety disorder are three to five times more likely to seek medical attention and six times more likely to be hospitalized than non-sufferers. Post traumatic stress disorder (PTSD) and panic disorder are forms of anxiety that have the highest rates of medical care and PTSD has proven refractive to drug therapy in United States Service Members and Veterans who are currently the primary users of Alpha-Stim CES .

These disorders are a serious societal problem because of their potential interference with work, schooling, and family life. They have also been shown to contribute to alcohol and substance abuse and other major psychiatric disorders in the United States. Thus, it is unreasonable for FDA to exclude these, or any other patient populations from evaluating the science behind CES for anxiety when the co-morbidity is so high to be nearly universal in the populations FDA excluded. CES has been clearly proven in numerous studies across several patient populations to be a safe and effective option for the treatment of the entire spectrum of anxiety disorders. Certain anxiety disorders such as panic attacks which are incipient and not chronically severe may respond to CES as the least complex, least expensive, and most efficacious treatment modality. Attached as Attachment “B” is a more complete discussion of anxiety and how CES can be used in the control of this serious mental illness. Attachment “B” also includes a discussion of insomnia and depression, and how those categories should be considered in FDA’s evaluation of CES.

e. *Kim study.* FDA asserts in the Proposed Rule that a Likert Scale, as used in neurosurgeon Hyun Kim’s anxiety study and dentist Reid Winick’s preoperative study is not a standardized validated rating instrument thus, according to FDA, justifies the dismissal, without evaluation, of two of the eight studies FDA identified for further review. 76 Fed. Reg. 48065. EPI believes both studies are “well-controlled investigations” that provide “valid scientific evidence” of the effectiveness of the Alpha-Stim Technology. Many studies have validated the Likert Scale. For example, one such study is titled, “A comparison of Likert scale and traditional measures of self-efficacy.” By Todd J. Maurer and Heather R. Pierce, published in the *Journal of Applied Psychology*, Vol. 83, No. 2, April 1998, 324-329:

“This study addressed whether a Likert-type measurement format can be used as an alternative to the traditional format for measuring self-efficacy. Classical reliability, observed correlations with relevant criteria, and confirmatory factor analyses were used to assess the similarity of the two formats in a sample of 128 college students. The results indicated that Likert-type and traditional measures of self-efficacy have similar reliability–error variance, provide equivalent levels of prediction, and have similar factor structure and similar discriminability. Overall, considering both practicality and the apparent similarity of empirical results from the two methods, a Likert scale seems to offer an acceptable alternative method of measuring self-efficacy.”

The Kim study uses a reliable, predictable and accepted method to prove that CES is effective in treating preoperative anxiety which is a ubiquitous form of state anxiety.

f. *Winick study.* The Proposed Rule then discredits the Winick study by asserting that it “utilized a 7-point Likert scale” and “suffers from the same limitations as the Hyun (sic) study.” 76 Fed. Reg. 48065. As discussed above, the Likert scale is a validated measurement device. However, the Winick Study actually used a visual analog scale (VAS) to measure anxiety. VAS is the most commonly used scale in treatment outcome research and has established validity in the measurement of anxiety. The Likert Scale was used as a second measure of anxiety, and its findings were consistent with the findings of the VAS scale. So, while the Winick study provides support for acceptance of the Likert Scale, it does not use the Likert Scale, as the FDA suggests, as its basis of measurement of anxiety.

There is no medical test that can measure anxiety accurately so the only possible progress measurements in anxiety patients for research or clinical practice are psychometric (pencil and paper) tests that FDA discarded, physiological measures that FDA discarded and self reports such as Visual Analog Scales (VAS) and Likert Scales that FDA discarded. To discard all these measures leaves nothing left except physician and patient opinions, which FDA also discards.

The Winick study used a validated primary method and a reliable and predictable secondary method to prove that CES is effective in treating preoperative anxiety which is a ubiquitous form of state anxiety.

g. *O’Connor meta-analysis.* FDA also considered and discarded two independent, university based meta-analyses as invalid. The O’Conner Study was discarded because “the results of this analysis do not relate to the question of safety and effectiveness since the labeled indications for CES currently include insomnia, depression or anxiety, and not withdrawal symptoms of chemical dependence.” 76 Fed. Reg. 48065. The O’Connor meta-analysis actually measures symptoms associated with chemical withdrawal, which according to the National Institute of Health (NIH), include anxiety, insomnia and depression. See (<http://www.nlm.nih.gov/medlineplus/ency/article/000949.htm>). The O’Connor meta-analysis showed good effects supported by the studies cited.

h. *Klawansky meta-analysis.* The Proposed Rule actually concedes that the Klawansky meta-analyses performed at the Harvard School of Public Health showed “CES to be more effective than sham for anxiety,” 76 Fed. Reg. 48065, but decided to discard this study because there were various forms of anxiety studied in various patient populations. Diverse patient populations are absolutely representative of the American People. Anxiety, depression, and insomnia are ubiquitous in all facets of American populations regardless of co-morbidities, race, religion or gender. FDA does not exclude patient populations from other medical devices so why use this limitation only for CES? For example, all people may benefit from blood pressure monitoring. Are sphygmomanometers just approved for women between the ages of 14 and 32? Are cardiac pacemakers only approved for use in Caucasians? This list can go on for thousands of devices and the answer will always remain the same; patient populations are

insignificant in this context. The Klawansky meta-analysis clearly establishes that CES is significantly effective in treating anxiety. This is supported by the studies cited.

4. **1974 Panel.** Rather than conducting an actual review of the science on CES, FDA apparently elected to rely upon the prior findings of a panel, whose findings were published in 1974, and on the prior investigation of the FDA in preparation of its 1993 proposed rule, which, as was highlighted earlier, never became a final rule. Reliance on the prior investigation for a proposed rule that never became a final rule is a very arbitrary and capricious standard of review. Relying upon the findings of a panel that reported its findings prior to the enactment of the 1976 FDA amendments is even more so. The 1974 Panel did not have the benefit of reviewing over 30 years of valid scientific evidence that was provided to the FDA during the current submissions. EPI has provided FDA with mechanistic studies which establish via EEG, QEEG, LORETA and fMRI that CES does have a measureable and imageable effect on the brain and does what it is intended to do in treatment. EPI provided FDA with 144 studies in 2009 (and more in 2011) showing that CES is an effective tool for the treatment of anxiety, insomnia and depression. EPI has provided FDA with a patient survey showing that, of 1,745 Alpha-Stim users, 99.9% considered Alpha-Stim effective. None of this data was available to the 1974 Panel, and FDA’s reliance on 1974 Panel findings in its 2011 review of CES is troubling.

5. **Additional Data Provided to FDA.** In addition to the 144 CES studies EPI provided to FDA in 2009 (44 studies conducted on EPI’s Alpha-Stim Technology and 100 additional studies conducted on other CES devices) EPI provided FDA with 14 additional studies in its 2011 submission. Of those 14 studies, five have been completed and 9 are currently ongoing. Below is a brief summary of the new Alpha-Stim Research provided to FDA in EPI’s 2011 submission:

**NEW RESEARCH COMPLETED (2009-2011)**

	<b>Study Specifics</b>	<b>Location</b>
1.	Efficacy of cranial electrotherapy stimulation for neuropathic pain following spinal cord injury: a multi-site randomized controlled trial with a secondary 6-month open-label phase.	VAMC US government study
2.	Incorporating Complementary and Alternative Medicine (CAM) Therapies to Expand Psychological Services to Veterans Suffering From Chronic Pain.	VAMC US government study.
3.	Feasibility of Using Cranial Electrotherapy Stimulation for Pain in Persons with Parkinson’s disease.	VAMC US government study.
4.	New Techniques of Neuromodulation. fMRI mechanistic study.	University of California at Los Angeles
5.	The effects of cranial electrotherapy stimulation on attention: a double-blinded, placebo-controlled investigation. Doctoral dissertation.	Chicago School of Professional Psychology

## ONGOING ALPHA-STIM RESEARCH PROJECTS

### U.S. Government Funded Studies

	Study Specifics	Funding Entity
1.	CES to treat symptoms caused by chemotherapy (anxiety, insomnia, depression, pain and fatigue) in breast cancer patients.	National Cancer Institute
2.	CES for Soldiers with combat related symptoms.	US Department of Defense
3.	CES used to treat anxiety and cravings in alcohol relapse prevention.	National Institute of Health
4.	CES for the treatment of insomnia in military Service Members.	US Department of Defense
5.	CES to treat pain and psychological disorders seen in mild traumatic brain injury patients.	US Veterans Affairs Medical Center
6.	Integrative approach to pain management in patients with advanced cancer.	US Department of Defense

### University and Hospital Based Studies

	Study Specifics	Location
1.	Using cranial electrical stimulation to improve symptoms and functional status in individuals with fibromyalgia.	University of Virginia
2.	Alpha-Stim to reduce stress in patients undergoing In-Vitro fertilization.	Washington University School of Medicine
3.	CES to reduce anger in a troubled pediatric population.	Youth Villages--Inner Harbor

6. **Conclusion as to FDA’s Scientific Review of CES.** Following its 2009 request for information, FDA was provided a large amount of “well-controlled investigations” and other “valid scientific evidence” establishing the effectiveness of CES in the treatment of anxiety, insomnia and depression. FDA was additionally provided with a significant amount of “valid scientific evidence” in EPI’s 2011 515(i) Supplemental Information Petition for Reclassification. If FDA were to take all of the valid scientific evidence received, and review it “as a whole” there would be a “reasonable assurance” that CES is an effective treatment for anxiety, insomnia and depression. Unfortunately, FDA took a review approach of exclusion, rather than inclusion, and sought ways to avoid reviewing the valid scientific evidence provided. In addition to the numerous studies provided to FDA, 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.

It is important to note that *every single fact in the studies concerning positive outcome data was completely ignored by FDA 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. Each and every study was discarded by FDA and thus eliminated from further review for questionable reasons inconsistent with the scientific method and current diagnostic classifications within the practice of psychiatry and psychology. EPI asks that FDA reconsider and, with documentation, support its review of the valid scientific evidence provided before it determines that the effectiveness of CES has not been established by adequate scientific evidence. EPI feels that if all the valid scientific evidence were reviewed and considered by qualified experts, then when taken as a whole, the evidence would clearly establish a “reasonable assurance” as to the effectiveness of CES for the treatment of anxiety, insomnia and depression.

## **B. Risks to Health.**

**1. Health Risks Listed by FDA.** In the Proposed Rule, 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 by the FDA, nor were any references provided explaining how the six potential risks were reached. The Proposed Rule makes no comment one way or the other regarding the known, and CDRH confirmed, safety data compiled for CES devices. FDA's failure to provide accurate safety information on CES is misleading to the public.

Since the noted “risks to health” within the Proposed Rule have been specified by FDA in every CES rule making since 1976, it can only be presumed that they are from outdated sources. For example, “Blurred vision” was a listed side effect in the 1974 Panel’s findings, due to the use of orbital electrodes. Orbital Electrodes have not been used by CES manufacturers since the 1970’s, and yet blurred vision is still listed as a potential risk to health. The 1974 Panel, upon which FDA relied for a majority of its decisions in the Proposed Rule, reported side effects of CES as:

“limited to a tingling sensation that is generally not uncomfortable; a disagreeable sensation of light in the eyes when the electrodes over the orbits are used with particular current characteristics; mild blurring of vision, attributed to pressure, for some minutes after orbital electrodes were removed; and transient headache after prolonged sessions.” *An Evaluation of Electroanesthesia and Electrosleep*, National Research Council (Prepared for the Food and Drug Administration) (December 14, 1974), p. 37.

Interestingly, the 1974 Panel, upon which FDA has relied for a majority of its decisions in the Proposed Rule, reached the determination that “**significant side effects or complications attributable to the procedure are virtually nonexistent.**” *Id.* at p. 42 (*emphasis added*).

The inclusion of “worsening of the condition being treated” as Risk to Health is an interesting position for FDA to take. As indicated in the Code of Federal Regulations, while FDA reviews primarily “well-controlled investigations” for a determination of the effectiveness of a device, FDA is to review all “valid scientific evidence” in determining the safety of the device. *See* 21 C.F.R. § 860.7(d)(1), (e)(1), and (e)(2). So while the FDA may argue that there is not sufficient “well-controlled investigations” to support a finding of effectiveness, it is certainly wrong in applying the same standard to safety. All “valid scientific evidence” provided shall be considered when reviewing the safety of the device. A simple review of the Proposed Rule would lead one to question whether *any* of the current scientific evidence provided by EPI has been reviewed by FDA in reaching its “Risk to Health” conclusions. As FDA is aware, there is not drug or medical device that works 100% of the time on every patient, so well educated licensed practitioners rely on their training to determine what works for an individual patient.

The valid scientific evidence clearly demonstrates that CES is more effective than most other options available for the treatment of anxiety, insomnia and depression, and as such worsening of condition is not a valid risk. Moreover, the CES device, as a prescription device, provides licensed practitioners a safe, non-pharmacological, treatment option that must be available in the treatment of anxiety, insomnia and depression. By listing “worsening of condition” as a risk to health (without any apparent support), FDA is telling all licensed practitioners that they are not qualified to determine what is and what is not working for their patients.

**2. Health Data Provided by EPI to FDA.** EPI has provided FDA with all reports of adverse effects at each of its bi-annual inspections of its operations since 1981, and has provided FDA with adverse effect analysis with each of its 510(k), 515(i) and PMA submissions, yet FDA has not reviewed or altered its “risks to health” from those which were originally provided in a 1974 report. At least half of the outlined “risks to health” from the Proposed Rule **have not once been reported to EPI by any actual Alpha-Stim user in EPI’s thirty years of business.** In its 2009 submission, EPI provided FDA with detailed and true data of all potential health risks. **All reported health risks 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).**

In its 2011 submission, EPI provided FDA with additional valid scientific evidence on adverse effects reported from 2007 through 2011, further establishing the safety of CES devices. While EPI has sold over 50,000 devices since 2007, only 11 cases of adverse effects have been reported to EPI. It is important to note that there were many more than 50,000 Alpha-Stim devices out in the public at that time, as EPI has been in business since 1981. Since 2007, the most commonly reported adverse effect is skin irritation at the electrode site (seven reports). All seven patients reporting skin irritation healed and reported no long lasting effects. Tinnitus has been reported twice, although in one of the two cases the patient's physician later attributed the tinnitus to another cause. There has also been one reported case of a panic attack and one reported case of tongue discoloration, but the discoloration was later attributed to medication the patient was taking (Pepto Bismal). Every reported adverse effect was deemed minor and self-limiting. EPI is very confident in the safety and effectiveness of its devices, so much so that it provides a thirty-day money-back guarantee with every device purchase, and it also provides a 5 year warranty with each device.

EPI has provided FDA with 49 studies on Alpha-Stim in its 2009 and 2011 submissions, and in those studies far less than 1% of all patients receiving treatment from an active device reported an adverse effect. A review of more than one hundred phase I double-blind, placebo-controlled trials found an overall rate of spontaneously reported side-effects in those receiving placebo of 19%. *The Nocebo Effect*, Dr. Sundararajan Rajagopal, Consultant Psychiatrist, South London & Maudsley NHS Foundation Trust, Adamson Centre for Mental Health, St. Thomas' Hospital, London, England. September, 2007 (Priory Lodge Education Limited). Comparing the two results, one can infer that Alpha-Stim is at least 19 times less likely to have an adverse effect reported than a placebo.

**3. Conclusion as to Risks to Health.** EPI has provided FDA with a significant amount of valid scientific evidence supporting the safety of CES devices, and in particular the Alpha-Stim Technology. EPI asks that FDA review all of the safety data provided and revise the findings within the Proposed Rule. Relying upon the findings of a panel who reviewed CES in 1974 when EPI has provided FDA with safety data from the past 30 years is arbitrary and capricious. It is also disappointing that FDA neglected to echo the **1974 Panel's conclusion that the side effects were "virtually nonexistent."** The FDA's review and analysis of the Risks to Health clearly demonstrates that it is reviewing CES in a slanted manner, as it has found small issues and collected them for publishing, while ignoring the vast amount of information, research, data, studies, and even its own panel recommendations, all of which support the conclusion that CES is a very safe treatment option for anxiety, insomnia, and depression.

**C. Economic Data.** The Proposed Rule concludes with a confusing display of economic data that suggests the CES market is small and meaningless and that requiring a PMA for all CES device manufacturers would not impose a significant economic impact on society. FDA then estimates that the cost of preparing a PMA is \$1 Million for each CES company and that FDA will spend \$8.4 Million to review the initial PMAs and then \$1 Million per year thereafter to review additional PMAs, concluding that this is a good use of taxpayer money. FDA provides no

support for its conclusion that it is a good use of tax-payer monies to spend \$8.4 Million reviewing a Premarket Approval Application for a medical device that: i.) has been legally cleared by FDA to market for over 30 years; ii.) is sold over-the-counter throughout the rest of the world; iii.) has been the subject of at least 144 studies showing its effectiveness; and iv.) has had no reported significant adverse effects during its 30 year history.

Again showing the slanted view that FDA has taken in its approach to drafting this Proposed Rule, FDA referred to the Klawansky Study in support of its position that “CES studies in the literature are beset with weakness.” 76 Fed. Reg. 48066. The Klawansky Study was a study that the Proposed Rule earlier highlighted as insufficient in its support of CES. It is the essence of hypocrisy to discount a study which concludes that CES is significantly effective in treating anxiety and ignore its findings, yet then use a statement from the study to support a position that the FDA is reaching to achieve.

The Proposed Rule then provides an unsupported assertion that “More recent literature indicates that there is still much uncertainty about the safety and effectiveness of CES.” *Id.* EPI has conducted a literature search to determine what studies, if any, have recently questioned the safety and effectiveness of CES. None have been found. Quite the contrary, the weight of the research conducted over the past 30 years all points to the extreme safety and overall effectiveness of CES in the treatment of anxiety, insomnia and depression. Unsupported statements like this lead one to further question FDA’s objectivity in drafting this Proposed Rule.

The comments in the Proposed Rule highlighted above are provided in an apparent effort to support the assertion that more studies would benefit society and a PMA requirement would cause more research on CES, thereby serving an overall benefit to society. EPI completely agrees that research serves a great benefit to society, and that is why EPI is currently supporting (but not funding) twelve ongoing studies on CES, nine of which are being funded by the United States government, including the Department of Defense, U.S. Veteran’s Affairs Medical Centers, the National Institute of Health and the National Cancer Institute. Providing sufficient research to benefit the consumer and gain their confidence in CES has never been an issue with EPI, and EPI continues to seek additional research on CES and its applications. The overriding concern which all in the CES field face is whether these studies will be considered by FDA in a fair and equitable manner, or if they will be discounted like all the prior research was in this Proposed Rule. A failure to review most studies conducted since 1993 because the FDA felt they were conducted on “specific populations” is very concerning. Providing more research is not, and has never been, an issue for EPI, but getting FDA to review the research in a fair manner is a concern. This Proposed Rule show how legitimate that concern is.

Much of the economic analysis in the Proposed Rule was based on numbers from questionable sources (such as 25 year old studies on the cost of a 510(k) and PMA submissions, internet search engines for determining the market size of an industry, and data collected by FDA on a company’s size, when FDA does not have the authority to review a company’s financial information), and rather than discuss the inadequacies of each conclusion reached separately,

EPI feels that it should instead highlight the economic impacts it has on the United States economy, and leave the value determinations to others.

EPI has its principal offices in Mineral Wells, Texas, and currently has 21 employees at that location. Additionally, EPI has 14 independent representatives who reside around the country and sell EPI's products. EPI also has over 50 distributors throughout the United States who sell EPI's Alpha-Stim products. In 2011, EPI moved its manufacturing to Oklahoma, adding additional manufacturing jobs to the "Heartland of America". In 2010, EPI sales generated an estimated \$11,000,000 for the U.S. economy. EPI sells its products world-wide, exporting its products to Europe, Asia, Australia, the Middle East, Africa and South America, not to mention to our North American neighbors Canada and Mexico. Exporting products is of course a great benefit to the U.S. economy, and EPI is doing its part to grow internationally as well as in the United States. In fact, EPI's second largest market, after the U.S. Government, is China.

A PMA may not cause EPI or other CES device manufacturers to reduce their work force or manufacture fewer products, although it would place a large time and money burden on EPI and other small medical device manufacturers, distracting EPI from its mission of helping people, especially U.S. Service Members and Veterans. However, if the data provided to FDA in a PMA is reviewed in the same manner that FDA has reviewed the data for this Proposed Rule and in all of its prior reviews of CES, then one needs to question whether CES would be able to stay on the market in the United States, and that uncertainty would lead first to fewer distributors and representatives wanting to sell the products, which would eventually lead to fewer employees for EPI, and ultimately a need to move operations and manufacturing outside the United States. Obviously EPI has no desire to move outside the United States, but if the FDA continues to rule in an arbitrary and capricious method then EPI will need to move to a location with more even-handed, equitable and fair government oversight, places such as Europe or China. EPI sees the economic effect of the Proposed Rule in this manner, not in confusing charts or societal benefit analysis, but rather in jobs created or lost in the United States. As Congressman Barton correctly pointed out, "Small companies and entrepreneurs want to create businesses and design products that will help save lives and be profitable. For this to happen, we need a regulatory system that is predictable, consistent and open." FDA's review of economic data does not consider the possible effects its ruling will have on jobs here within the United States, nor does FDA seem to consider how inconsistent rulings push businesses, small and large, out of the United States.

#### **IV. FDA RULING ON rTMS.**

Of particular concern to EPI is the apparent uneven manner in which FDA is reviewing the Class III devices marketing through the 510(k) process, or the "pre-amendment devices" as FDA refers to them, which have not yet been classified. As earlier discussed, on April 9, 2009, FDA required all of the manufacturers of devices in the 25 categories of "pre-amendment devices" to submit information, consisting of all known research and safety data for their devices (74 FR 16214). This request for documentation certainly resulted in FDA's resources to be stretched thin, as it considered the appropriate classification for 25 different devices, with countless

numbers of manufacturers responding in each category. This deluge of information has apparently led to FDA issuing its rulings in an arbitrary and capricious manner, and certainly not in a consistent manner upon which the device industry or, more importantly, the public, can rely. One such example of this obvious inconsistency in the review of data provided was FDA's determination that Repetitive Transcranial Magnetic Stimulation (rTMS) should be down-classified to Class II while two weeks later proposing that CES face the burden of PMA approval.

On July 26, 2011, FDA published a final rule in which it classified rTMS as a Class II device, thereby avoiding the need for Premarket approval. 76 Fed. Reg. 44489. Interestingly, the Final Rule lists under "risks to health" for rTMS "ineffective treatment," which leads one to believe that a potential risk for the rTMS is that it has not been proven effective for the treatment of depression, the indication for which it received class II status. The final rule for rTMS failed to address effectiveness of the device, at all, leading one to question whether effectiveness was even considered in providing rTMS class II status. In fact, the final rule on rTMS failed to provide even one study to support FDA's finding of safety and effectiveness for rTMS. The determination for rTMS was signed by Nancy Stade, Deputy Director for Policy, Center for Devices and Radiological Health.

Two weeks later Ms. Stade signed off on the Proposed Rule which completely discounts a vast amount of science and research conducted on CES, determining that a device which has been demonstrated safe and effective through research and patient surveys for over 30 years should go through a PMA process. The risk to health of "worsening of the condition treated" was cited as justification for FDA's election to require a PMA application for CES manufacturers, a risk to health that EPI has not ever had reported to it by a customer in its thirty years of business. However, two weeks prior "ineffective treatment" was not considered sufficient justification to keep rTMS from being reclassified as class II.

A comparison of the amount of studies, and the results of those studies, for rTMS and CES would lead one to conclude that CES is just as safe, and more effective, than rTMS. Unfortunately, FDA did not review the data in that way, and the final rule for rTMS and Proposed Rule for CES, when compared together, leaves one wondering what the standard and expectations are for device manufacturers seeking approval to market from the FDA. As Congressman Barton correctly pointed out, "The Medical Device Review Process at the Food and Drug Administration (FDA) has become overly burdensome, unpredictable and inconsistent."

## **V. CONCLUSION.**

In its 2009 submission to the FDA, and in its 2011 submission providing additional data, EPI has provided FDA with valid scientific evidence showing that 99.9% of actual Alpha-Stim customers considered the device effective. EPI additionally provided FDA with valid scientific evidence establishing that 11 out of over 50,000 Alpha-Stim customers (less than 0.02%) reported adverse effects from using Alpha-Stim. EPI also provided FDA in its 2009 submission with 44 studies conducted on Alpha-Stim supporting the safety and effectiveness of the device. In 2011

EPI provided another 5 completed studies and 12 on-going studies on Alpha-Stim, all completed studies supporting a “reasonable assurance” as to the safety and effectiveness of the device. The Proposed Rule ignored all of the valid scientific evidence provided, including many well-controlled investigations, in determining that the “effectiveness of CES has not been established by adequate scientific evidence.” 76 Fed. Reg. 48065.

EPI hereby asks the FDA reconsider this determination, and that it review all of the research completed on CES. A review of all the valid scientific evidence provided in support of the safety and effectiveness of CES, “when considered as a whole,” will lead FDA to reach a conclusion that a reasonable assurance as to the safety and effectiveness of CES has been established. EPI asks FDA to review the science provided and review the results without seeking ways to exclude all valid scientific evidence provided. The Code of Federal Regulations does not ask the FDA to seek ways in which to exclude valid scientific evidence, the C.F.R. asks FDA to review all the valid scientific evidence provided, and then determine if, “as a whole” the evidence supports a conclusion that there is a reasonable assurance as to the device’s safety and effectiveness.

CES has over a forty year history in the United States, and EPI has been a part of that history for over 30 years. FDA has allowed CES devices to legally market their devices for anxiety, insomnia and depression since the start of FDA’s oversight of medical devices. CES devices have consistently proven themselves to be safe and effective for the treatment of anxiety, insomnia and depression. Thirty years of research on Alpha-Stim supports EPI’s position that CES should be categorized as a Class II device for anxiety, insomnia and depression, thereby permitting CES manufacturers to continue to market the device without the need for Premarket Approval.

Thank you for your time and consideration of this request. We hope that the information provided herein will prove beneficial in allowing you to reconsider the Proposed Rule.

Sincerely,

A handwritten signature in black ink that reads "Tracey B. Kirsch". The signature is written in a cursive, flowing style.

Tracey B. Kirsch  
President  
Electromedical Products International, Inc.

cc: The Honorable Mac Thornberry  
The Honorable Kay Bailey Hutchinson  
The Honorable John Cornyn  
The Honorable Joe Barton  
The Honorable Rick Perry  
The Honorable Michael Burgess  
The Honorable Gene Green  
The Honorable Craig Estes  
The Honorable James Keffer  
The Honorable Cory Gardner  
The Honorable Diana DeGette  
The Honorable Mike Ross  
The Honorable Edward Markey  
The Honorable John Dingell  
Larry R. Pilot, Esq.

The Honorable Cliff Stearns  
The Honorable Lee Terry  
The Honorable John Sullivan  
The Honorable Tim Murphy  
The Honorable Marsha Blackburn  
The Honorable Sue Myrick  
The Honorable Brian Bilbray  
The Honorable Phil Gingrey  
The Honorable Steve Scalise  
The Honorable Morgan Griffith  
The Honorable Jan Schakowsky  
The Honorable Kathy Castor  
The Honorable Donna Christensen  
The Honorable Henry Waxman

**ATTACHMENT "A"**

**EPI HISTORY WITH THE FDA**

<b>Alpha-Stim Model No. and 510(k) Or Other FDA Submission</b>	<b>Introduction Or FDA Submission Date</b>	<b>Hz Options</b>	<b>Current In <math>\mu</math>A</b>	<b>Timer Options</b>
Alpha-Stim 2000 K831144	November 1981	0.5, 1.0, 1.5, 2.0, 3.5, 8.0, 10, 20, 40, 80, 160, 320	25 - 500	6, 8, 12 seconds, 2, 5, 10 minutes, and continuous
Alpha-Stim 350 K831145 and K881753A	October 1982	0.5, 3, 5, 8, 10, 20, 40, 80, 120	25 - 500	3, 5, 10, 15, 20 minutes, and continuous
Alpha-Stim CS TENS: K896948 and CES: 903014E	February 1989	0.5, and 80	10 - 600	3, 10, 20, 60 minutes, and continuous
Alpha-Stim 100 (upgrade of Alpha-Stim CS) See FDA letter of July 25, 1997	February 1993	0.5, 1.5, and 100	10 - 600	10 seconds on alternating with 2 seconds off, 10, 20, 60 minutes, and continuous
Alpha-Stim SCS (upgrade of Alpha-Stim 100)	Fall of 1997	0.5	10 - 500	20 and 60 minutes
PMA	Submitted November 16, 1995	Still Pending		
515(i)	Submitted August 11, 1998			
515(i)	Submitted August 7, 2009			
515(i)	Submitted August 19, 2011			

Below is a historical review of EPI's dealings with the federal government, including the FDA. This historical perspective is provided so that all will understand why EPI is concerned with the treatment CES received in the Proposed Rule, and justification for its concern that a PMA application for CES will not be treated in a fair and impartial manner.

EPI introduced the original Alpha-Stim technology (Alpha-Stim 2000) to the market in November of 1981, EPI obtained 510(k) clearance to market for the Alpha-Stim 2000 for pain indications, including ear clip electrodes.

In October of 1982, EPI introduced the Alpha-Stim 350 to the market, which also received 510(k) clearance to market for pain indications, including ear clip electrodes.

On February 23, 1990, a standard 510(k) form letter was issued to EPI, permitting interstate marketing of Alpha-Stim CS for pain control (TENS).

On May 12, 1992, after 22 months of review, an FDA 510(k) letter was issued stating that the Alpha-Stim was substantially equivalent to pre-amendment CES devices, but could not be marketed. FDA also stated that it would stop other firms from marketing CES, which FDA failed to do until 3½ years later, in November of 1995. This letter was unprecedented as the FDA's regulations and the Food, Drug and Cosmetic Act call for marketing clearance when substantial equivalency is found through the 510(k) process.

On May 19, 1992, EPI responded to the FDA May 12, 1992, letter stating that the Alpha-Stim will be marketed as allowed by law due to the FDA finding of substantial equivalence, as a search of all sources, including the *Federal Register*, Title 21 of the Code of Federal Regulations, and the Commerce Clearing House Medical Devices Reporter failed to indicate any notice of rulemaking, public hearings, or other legally sufficient procedure to support FDA's determination that EPI could not market its device. No response was received to this marketing notification.

On August 31, 1993 the FDA published a proposed rule in the *Federal Register* to reclassify CES devices. The proposed rule states that "...within 90 days after the date of promulgation of any final rule requiring premarket approval for the device, commercial distribution of the device must cease."

On March 16, 1994 FDA sent a warning letter to EPI concerning marketing of Alpha-Stim as a CES device and threatening "action including, but not limited to, seizure, injunction, and/or civil penalties." A response was sent to FDA on April 1, 1994 by EPI, and FDA responded on April 13, 1994 stating EPI's response was satisfactory. At this point, EPI stopped marketing its technology for CES applications out of fear of FDA action.

On March 24, 1995, Dr. Harold Stecker of Health Directions, a competing CES manufacturer based in Morrisville, Pennsylvania, received a letter from FDA informing them that their CES

device “has been cleared” [for marketing] “for the intended use of relieving anxiety, depression, and insomnia”. The letter complained about uses for other applications.

EPI met with Blix Winston, Staff Officer, FDA Division of Small Manufacturers Assistance at a DSMA seminar in Houston. EPI then sent a letter on March 31, 1995 to FDA confirming a telephone conversation in which Mr. Winston stated that after consulting with Dr. Robert Munsner of FDA, EPI may market for CES without any indications.

On August 7, 1995, the FDA wrongfully listed EPI as “out-of-business” due to EPI’s move from California to Texas. For several years thereafter, Alpha-Stim shipments were detained at point of entry for weeks by the FDA due to continual confusion over whether or not EPI was “out of business”. EPI had properly notified FDA of its move from California to Texas, sending notice via certified mail.

On August 24, 1995, FDA published their Final Rule calling for a PMA for CES. On page 43969 under Analysis of Impacts, the Final Rule states that “because firms that distributed this device prior to May 28, 1976, or whose device has been found to be substantially equivalent to the CES device in commercial distribution before May 28, 1976, will be permitted to continue marketing cranial electrotherapy stimulators during FDA’s review of the PMA or notice of completion of a PDP, FDA certifies that the final rule will not have a significant economic impact on a substantial number of small entities.” EPI’s Alpha-Stim product has been found to be substantially equivalent to pre-amendment CES devices.

On October 31, 1995, two FDA investigators and one dual FDA and Texas Department of Health investigator conducted an on-site investigation of EPI. The investigation was extremely confrontational and the investigators abruptly left on two occasions when EPI chose to exercise its rights to have legal counsel present and elected to record the investigation. One FDA investigator stated that he was sorry that EPI could not run its own business, referring to the fact that EPI’s attorney was teleconferencing through the investigation. The investigators stated they were doing a routine inspection and were investigating a complaint. When asked about the nature of the complaint, the investigators refused to answer until the end of the investigation when they admitted the complaint was about the marketing of CES, and not an injury. The investigators informed EPI that it was listed in its records as “out of business”. The team of investigators subsequently promised to clear up the matter of EPI being listed as “out of business”. The investigators told EPI that Mr. Blix Winston’s assurances to EPI that it could market for CES without any indications had no meaning and that EPI was not permitted to market CES.

On the third day of the investigation, after leaving abruptly because a newspaper reporter was present, after being given “permission” by their supervisors to have the press present, one of the FDA investigators physically assaulted the reporter by pushing him in the chest and forcing him back into a wall. The reporter’s attempts to take photographs were apparently the reason for the assault. An investigation later ensued concerning the investigator’s actions, and he was handed a minor reprimand by the Texas Department of Health, but there was no apparent

comment to the actions of its investigator by the FDA, despite the fact the investigator was acting on FDA's behalf.

EPI completed the required PMA application and submitted it to FDA on November 16, 1995 for an anxiety indication. On December 22, 1995, FDA sent EPI a letter stating that FDA refused to file the PMA for evaluation. EPI officials met with FDA, at which time it was discovered that FDA's entire review was conducted by a mechanical engineer at the Office of Device Evaluation. Mechanical engineers have no training and background in science and psychiatry, and are not qualified experts in the field of CES. The reviewer quizzed EPI as to why the PMA did not include a waveform depiction and EPI pointed out the waveform depiction that was clearly represented in the PMA. Those in attendance were struck by the reviewer's seeming unfamiliarity with the PMA, leading them to question whether the reviewer had actually reviewed the PMA prior to the meeting.

On December 29, 1995, after a shipment of Alpha-Stim 100's had been detained by the FDA, EPI was again informed it was listed in the FDA records as "out of business", despite the numerous assurances EPI had received from FDA that this issue would be resolved.

On February 14, 1996, following FDA's refusal to file the PMA, EPI held a second meeting with FDA, at the FDA's Office of Devices Evaluation:

FDA advised EPI that the meeting was an "informal" one, and therefore it would not affect EPI's options. Harry Preuss, MD, from Georgetown University, sitting risk/benefit chair for the Investigational Review Board and Scientific Consultant for EPI, pointed out to FDA that he had reviewed the PMA and found that there was very little risk involved with the Alpha-Stim for CES. Dr. Preuss has a significant curriculum vitae that includes a nomination for appointment as FDA Commissioner in 1997 by Senators Daschle and Harkin, appointment to the National Institute of Health's Alternative Medicine Program Advisory Council and an appointment as a Fellow for the American Academy of Integrative Medicine. Dr. Preuss also pointed out that physicians and other licensed practitioners must prescribe this form of therapy, and that should insure proper use.

FDA indicated that there was a "regulatory language problem" between EPI and FDA, stating that the problem was with EPI's definition of "valid science". FDA pointed out that the CES studies did not have enough detail and that the underlying data was not available to allow FDA to draw conclusions. Dr. Preuss disagreed and reported that he has seen enough data to draw conclusions and that most of the studies "methods sections" contained ample detail to draw conclusions. FDA reported that if EPI provided additional information to FDA then the additional data would be seen as an amendment to the PMA changing the submission date to the date the amendment was received, and that would cause EPI to receive a major deficiency letter for filing a late submission. So any effort to clarify the submission for FDA was met with hostility.

EPI pointed out that its technology had been on the market for over 15 years and there were no substantive reports of adverse effects or complaints regarding the Alpha-Stim and CES. Dr. Preuss advised FDA that he was most impressed with the promising positive results reported in the two post marketing surveys conducted by EPI. FDA continued to state that it believed there was not enough detail in the studies to draw conclusions. EPI advised them that it did not sponsor any of the studies and therefore, could not implement the type of protocols FDA was requesting. However, EPI did indicate that it might have the ability to contact the researchers and obtain the raw data FDA was looking for. FDA again advised EPI that if it did that it would be considered an amendment to the PMA and therefore would be considered a new filing and EPI would have to cease marketing because the new filing would not have met the 90 day deadline for the PMA published in the Federal Register.

FDA advised EPI that it has the option to bring in all data FDA is requesting. EPI could focus on a small study and “tease out” the treatment effect. FDA noted that how CES is blinded in studies is important. EPI showed FDA the double blinding boxes EPI offers to researchers and explained how they worked. FDA responded in generalities about how blinding is important. FDA advised EPI that it can use studies for supportive information and that it needs to lead FDA through the studies and they should support the indication and labeling. EPI advised FDA that Alpha-Stim’s indication was identical to the ones used and approved by FDA for anxiolytic drugs such as Valium and Miltown.

FDA stated that EPI needs to explain why the measures used in the research are standard acceptable measures. The reviewer was unfamiliar with all methods of diagnosing and monitoring anxiety and she acknowledged that she has no expertise in the area of anxiety. This was obvious when the reviewer stated that there are 12 types of anxiety. EPI then explained that there are only two types of anxiety, state anxiety and trait anxiety, regardless of the patient population, after all, which mood altering psychiatric drugs are approved for specific populations? FDA stated it could not check these things out unless EPI specified for them to do so. Dr. Preuss mentioned that it was easy to establish these were acceptable criteria by calling another Agency employee with background expertise in this area. He said he confirmed the validity of the psychometric tests used in the research by simply asking a qualified psychiatrist at Georgetown University. FDA reported that the burden of proof was on EPI to explain these issues. EPI stated that it was entitled to have FDA assign someone qualified to review this area of medical science, that there was no way we could have presumed the PMA would have been reviewed solely by a mechanical engineer.

EPI then advised FDA of a training Tracey Kirsch, President of EPI, had recently attended in Houston, sponsored by the Small Manufacturers Assistance Division of FDA, on the topic of PMA and 510(k) preparation. Mrs. Kirsch pointed out that none of the issues raised by FDA in the refusal to file letter were covered in the training. Most importantly, Dr. George Koustenis, Acting Director of FDA’s Biostatistics Office, had explained at the training that all a PMA submission needs is one study with striking results. He advised

the 350 industry representatives attending the training session that if you are denied and have one of these studies then FDA's ruling should be appealed. FDA responded that it could be done with one study, but EPI must convince FDA that it had a study that was "striking". Additionally, FDA reported that if there was only one study then FDA would be required to conduct an "in-depth review." EPI advised FDA that it is confident that several of its studies could stand alone, but it would require a qualified, non-biased reviewer to see the obvious trends and consistencies in the research.

EPI showed FDA the section of the PMA which contained three distinct graphical depiction's of the waveform, one of the items FDA said was lacking, and FDA's response was simply to ask if the depictions contained a key. EPI then pointed out that the first line under the graphics was the key. FDA then advised EPI that it had not heard anything in the meeting to cause it to change its current position.

FDA advised EPI it had three available options:

1. Informal conference - which, EPI was told, is not informal at all;
2. Consider this meeting an informal conference and respond to the deficiencies. But, this would be considered an amendment and EPI would have to stop marketing; or
3. Withdraw the application and resubmit at a later date.

FDA requested EPI provide its decision within the next ten working days.

It was clear throughout this meeting that the reviewers assigned by FDA to CES had been handling the CES industry through the entire rulemaking process with little knowledge in the field. When asked about EPI's right to a panel of experts to review the PMA, FDA responded that if such a panel were convened, it would not have anyone that has any experience in our field anyway, although the panel would be experts in other fields.

On February 25, 1996, the *Mineral Wells Daily Index* published an investigative article about EPI's inability to convince the FDA to follow its congressional mandate. The reporter contacted many sources, including Congressman Charles Stenholm (D-TX), who said FDA was unquestionably superseding its congressional boundaries and openly sympathized with EPI's problems with FDA, saying, "they have a very traumatic story to tell."

On March 20, 1996, EPI sent a response to FDA refuting the conclusions reached in the December 22, 1995 letter. However, FDA phoned EPI's legal counsel to inform him that it continued to refuse to evaluate the PMA. This determination was based on FDA's conclusion that there was no scientific evidence supporting CES.

On June 5, 1996, the FDA contacted EPI's attorney suggesting that EPI would not be allowed to record a planned meeting with the public taxpayer supported agency "because it may chill the exchange of information."

In June 1996, another shipment was detained at the port of entry by the FDA because EPI was still listed as "out of business". After several days of negotiation with the FDA, EPI was promised FDA had updated its records and EPI would no longer have to worry about being listed as "out of business".

On July 2, 1996, Congressman Charles Stenholm (D-TX) visited EPI's facility, greeted by a host of local dignitaries and the press. He was shown a multi-media presentation about Alpha-Stim CES, and said "FDA owes this company a straight answer."

On August 2, 1996, EPI officials again met with FDA officials in Washington, D.C. EPI was hopeful FDA would finally agree to follow its congressional mandate, as outlined in the Food, Drug, and Cosmetic Act, and convene a true expert panel to judge the effectiveness of the Alpha-Stim when used for cranial electrotherapy stimulation (CES). EPI had submitted the premarket approval application to the FDA for CES at FDA's request. During the meeting, the FDA's Director of the Office of Device Evaluation, Dr. Susan Alpert, told EPI "there is no safety issue" concerning Alpha-Stim CES. Dr. Alpert questioned if there was enough data to prove CES effective. EPI's attorney was curious why, if there was no safety issue, was the Alpha-Stim listed as a Class III device? Alpert said the FDA would contact EPI in 2 weeks with their decision. On October 7, 1996, more than 2 months after the August 2 meeting, EPI received notification the FDA would file the PMA. The letter from Dr. Susan Alpert was dated October 1, 1996.

On August 27, 1996, another EPI shipment was detained by the FDA at the point of entry. With patients waiting for their prescribed devices, it took EPI two weeks of negotiation with the FDA to release its products. The FDA finally released the shipment of Alpha-Stim 100's for distribution on September 10, 1996. EPI's backlog of orders was growing so large, its distributors were becoming impatient about the company's ability to fill orders and some left the business. Austin Templar of the FDA's Dallas District Office explained to EPI that the shipment was detained because the computer had listed the product with "PMA on hold." The Alpha-Stim 100 had long been registered with the FDA, which issued a 510(k) as a TENS device for pain control. The PMA deals only with CES registration and has nothing to do with the device's existing 510(k) as a TENS device, which gives EPI the right to market its product for pain control.

On October 9, 1996, EPI was notified by the mechanical engineer that had initially rejected the company's PMA that FDA had destroyed some of the required six copies of the document. Each copy weighed over 18 pounds and cost thousands of dollars to copy. The reviewer requested that EPI overnight the documents to FDA. EPI informed her that it could not meet this request on such short notice as making copies was time consuming and expensive. EPI had specifically requested that FDA hold on to the PMA's in its February 1996 meeting, due to the cost and

time needed to make additional copies. EPI requested the mechanical engineer to go to the FDA's microfiche department to obtain the necessary copies.

On October 10, 1996, FDA informed EPI that the initial review of the PMA had been completed, even though it was missing the documents it had requested the day earlier, with a list of questions the FDA classified as major deficiencies. EPI was told that if it answered FDA's questions, then it would have to stop marketing because FDA would reset the clock on EPI's PMA submission to when the questions were answered, thus meaning EPI would have [theoretically] missed the deadline it worked day and night to meet. FDA suggested EPI quit marketing and pursue full-time research.

On October 19, 1996, the FDA detained another EPI shipment at customs.

On October 21, 1996, EPI was informed that an expert panel would convene in Washington, D.C., on December 2, 1996. It takes FDA an average of 33 months for most companies to reach the panel.

On November 12, 1996, EPI informed Congressman Charles Stenholm that the FDA had sent the EPI application to the Division of Neuropharmacological Drug Products (DNPD) for review. The Alpha-Stim 100 is a medical device, not a drug. Dr. Bruce Burlington, Director of the Center for Devices and Radiological Health at FDA, had repeatedly said publicly that devices would not be evaluated as drugs. FDA had apparently made an exception for EPI.

On November 13, 1996, EPI was notified that, of the four members of the "expert panel", no members of the panel had any experience with CES. The PMA submitted by EPI was 3 volumes comprised of 18 pounds, 6 ounces of paper, printed on both sides. The "expert panel" would not have a reasonable amount of time to study the PMA before its December 3rd meeting. It was at this point that EPI's attorneys reluctantly recommended that EPI file suit against the FDA.

On November 26, 1996, EPI filed suit against the FDA in federal district court. On November 27, 1996, the FDA postponed the expert panel slated for December 3rd. FDA said it did not know when the expert panel would be rescheduled.

On January 7, 1997, EPI's lawsuit was dismissed. The D.C. district court ruled the case should be heard by a federal appeals court. The judge made it clear the dismissal was procedural in nature and indicated there was merit to the suit. EPI planned to re-file the case in the appropriate federal court in an attempt to get the FDA to follow its own rules.

On January 28, 1997, FDA published an announcement in *The Federal Register* of its proposed rule, revoking their 1995 regulation requiring premarket approval applications (PMA) for CES devices. This allowed EPI the opportunity to reclassify CES from Class III status (significant risk) into Class I (general controls) or Class II (special controls). This was the basis for the EPI November, 1996 lawsuit against FDA. So in effect, FDA conceded to EPI's demands by this action. That FDA decision meant Americans could continue to use CES as a non-drug alternative

for the treatment of anxiety, insomnia and depression. All comments received by FDA were in favor of the reclassification, including one by Charles H. Kyper, who served as the Assistant Director for Reclassification and Compliance in the FDA's Center for Devices and Radiological Health Office of Device Evaluation from 1990 to 1993. EPI also learned from this February 7, 1997 letter from Mr. Kyper that the FDA decision of May 12, 1992, in which FDA told EPI that its product was essentially equivalent to pre-amendment devices, but that it still could not market, was completely unprecedented, and that Mr. Kyper disagreed with this, and that FDA abandoned this position once Mr. Kyper "cited the statutory provisions and other considerations that negated such a position." However, FDA never informed EPI that it revoked this position. As Mr. Kyper pointed out in his letter, this has caused EPI great harm, and a tremendous financial burden.

On February 24, 1997, FDA inspector Irma Solis visited Dr. Marshall Voris of the Delos Mind/Body Institute of Dallas, Texas where she sought the research records and devices used by Dr. Voris in his studies of the effect of CES on state and trait anxiety in convicted child molesters and pedophiles. Dr. Voris is an independent researcher. On March 18, 1997, FDA inspector Irma Solis again visited Dr. Marshall Voris of the Delos Mind/Body Institute concerning his CES research. Ms. Solis issued a Form FDA 483 of Inspectional Observations to Dr. Voris on May 5, 1997. FDA determined that Dr. Voris had needed their approval to do the anxiety research he conducted. Dr. Voris responded on May 20, 1997 asking, among other things, for an explanation of the legal basis for FDA's conclusion that treating or researching a subgroup of patients diagnosed with anxiety represents a new indication. Because the Form FDA 483 contains allegations that damage his reputation as a clinical researcher, Dr. Voris demanded a response and an immediate retraction. FDA finally exonerated Dr. Marshall Voris, and therefore indirectly EPI once more, on September 22, 1997 when it sent Dr. Voris a letter stating that the inspections of his facility were made to ensure that the data in the EPI PMA was scientifically valid. The letter stated that "there were no deviations from the regulations observed during the inspection."

On March 18, 1997, FDA inspector Yehuala A. Gessesse completed a comprehensive three day inspection of the EPI manufacturing plant. Originally scheduled as a PMA inspection, EPI's attorneys were unable to stop this unnecessary inspection even after the FDA published the proposed PMA revocation in the *Federal Register*. The inspection went well with only two minor and easily correctable concerns on the part of the FDA. One was that the engineer did not initial a schematic drawing, and the other was that the three digital multi-meters in use were not calibrated by a certified lab, although the FDA inspector, an engineer, did test the equipment and found it to be functioning within specifications.

FDA exonerated EPI in writing on June 28, 1997 in a Certificate to Foreign Government No. 69858 stating, in part, that the Alpha-Stim 100 micro-current stimulator and cranial electrotherapy stimulator may be marketed in, and legally exported from, the United States, and as of the last inspection the EPI plant appeared to be in substantial compliance with current good manufacturing requirements.

FDA further exonerated EPI in writing on July 25, 1997 when a replacement 510(k) letter was sent from Philip J. Phillips, Deputy Director, Office of Device Evaluation, Center for Devices and Radiological Health, allowing EPI to market the Alpha-Stim for anxiety, depression, and insomnia.

EPI was then mandated to and did submit a five volume reclassification petition 515(i) to FDA on August 11, 1998 in order to remain on the market after that date, another major regulatory burden on a small business. As of 2011 there has been no response from FDA to the mandated 515(i).

In 1997, EPI was granted the CE Mark for compliance with the Medical Device Directive (MDD) (European approval to market) for the indications of pain, anxiety, insomnia and depression. The comprehensive regulatory review by an accredited European Union notified body found Alpha-Stim safe and effective enough to sell directly to the public without a prescription, as has the State Food and Drug Administration (SFDA) of China and every other regulatory body that has examined the Alpha-Stim and its science, except for FDA.

On September 14, 1999, FDA conducted another routine inspection of EPI. This inspection lasted 6 hours (including a lunch break). No 483 notice of violations was issued. Since 1999, FDA has inspected EPI on a bi-annual basis, and no major infractions, or serious injuries from use of Alpha-Stim, have been found by, or reported to, FDA. EPI has continued to market its Alpha-Stim CES technology throughout the United States and the world.

On April 15, 2005, EPI was awarded a 5 year Federal Supply Schedule (FSS) contract (V797-4800a) that was based on a waiver issued to EPI. The waiver was given due to a “non-availability” determination.

In 2007, Bernard Berne, MD, PhD., of the Neurodiagnostic and Neurotherapeutic Devices Branch of the Office of Device Evaluation, Center of Devices and Radiological Health a division of the FDA, indicated to EPI officials at a meeting of the American Psychiatric Association that “The only reason you (EPI) are in business is because you are not selling much.”

On August 7, 2009, EPI was awarded a 5 year extension to its FSS contract.

On September 2, 2009, a telephone call was received from the Department of Veterans Affairs, National Acquisitions Office, advising EPI that the National Acquisitions Office had received a complaint that EPI products are “Made in China”. EPI was notified that its FSS contract would be cancelled because products “Made in China” are prohibited on the Federal Supply Schedule, due to the Trade Agreements Act. The contracting officer reported that his office did not have the authority to grant the original waiver in 2005 and “missed it” again in August 2009 upon contract renewal.

On October 1, 2009, EPI obtained written notification that its FSS contract will be modified effective November 1, 2009. Instead of complete cancellation of the contract, the accessory items that are made in a designated country are allowed to remain on the FSS. Those three items are the AS-Trodes 6 (AT), Alpha Conducting Solution (ACS) and Alpha Conducting Solution Refill (ACSR). If manufacturing is moved to a location in a designated country, EPI can request the return of the removed items to the contract. EPI has not committed any deviations from its original agreement with the US Government to prompt these actions and was assured that the original waiver granted was an administrative error in the National Acquisitions Office. EPI has moved its manufacturing facility to Oklahoma and will be seeking a full reinstatement of the FSS contract.

Alpha-Stim devices and remaining accessories may continue to be purchased by the U.S. Department of Veterans Affairs and U.S. Department of Defense through “open market” procurement or pay cards. As of 2011 the U.S. Government is the biggest consumer of Alpha-Stim devices. This Proposed Rule has resulted in many practitioners, researchers, scientists and patients commenting on the docket against FDA’s Proposed Rule. Such comments are based on the commentators’ review of CES research, contributions to CES literature, or their use of the Alpha-Stim in their practice or for personal use, or both. Some of the strongest comments in support of Alpha-Stim have come from practitioners within the U.S. military. The experiences of qualified psychiatrists and psychologists who are tending to Service Members in need of care should be taken seriously by FDA.

## ATTACHMENT “B”

Below is a brief overview of anxiety, depression and insomnia, and an explanation of how CES can be a safe and effective treatment for all three indications:

**1. *Anxiety:*** Anxiety disorders are a group of mental disturbances having anxiety as a core symptom. Anxiety is found to some degree in nearly all forms of illness, in all patient populations and is ubiquitous in pain patients. Viewed in terms of possible causation, anxiety can be etiologic or reactive, and is often masked or unrecognized and therefore untreated. When this is the case, the illness may be labeled *intractable* and the healthcare practitioner may move into higher dosage levels of pharmaceuticals that often remain ineffective. Although mild temporary anxiety known as state or situational anxiety can be an unavoidable commonplace experience in daily life, and are often significant enough to require treatment by practitioners (*e.g.*, for preoperative fear) these situational symptoms of anxiety do not necessarily develop into a chronic anxiety disorder. Anxiety disorders are also associated with a wide range of physical illnesses, medication side effects, including psychiatric medications, and other psychiatric disorders.

Anxiety disorders are the most common mental illness affecting 27.4 million people in the U.S. According to *The Economic Burden of Anxiety Disorders*, a study commissioned by the Anxiety Disorders Association of America, anxiety disorders incurred an economic burden of approximately \$63.1 billion a year in 1998 dollars, with 54% of that amount spent on non-psychiatric medical treatment costs. People with an anxiety disorder are three to five times more likely to seek medical attention and six times more likely to be hospitalized than non-sufferers. Post traumatic stress disorder (PTSD) and panic disorder are forms of anxiety that have the highest rates of medical care and PTSD has proven refractive to drug therapy in United States Service Members and Veterans who are currently the primary users of Alpha-Stim CES therapy.

These disorders are a serious societal problem because of their potential interference with work, schooling, and family life. They have also been shown to contribute to alcohol and substance abuse and other major psychiatric disorders in the United States. Thus, it is unreasonable for FDA to exclude these, or any other patient populations from evaluating the science behind CES for anxiety when the co-morbidity is so high to be nearly universal in the populations FDA excluded (technically, FDA excluded all populations as they found a way to throw all studies out so they need not review them).

The Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) refined the classification of anxiety based upon recent discoveries about the biochemical and post-traumatic origins of some types of anxiety. The present definitions are based on the external and reported symptom patterns of anxiety disorders rather than exclusively and implicitly on their biochemical or physiologic etiology. Because panic disorders and agoraphobia occur in a wide variety of anxiety disorders, the DSM-IV-TR takes care to define both at the beginning of the Anxiety Disorder section since neither can be classified (or coded in billing) as a separate

disorder on its own but in combination with or without each other or some other diagnostic, classifiable feature such as social phobias.

Anxiety Disorders may be distinguished as follows:

**Table 1: Summary of DSM-IV-TR Anxiety Disorder Classifications**

- 300.01 Panic Disorder Without Agoraphobia
- 200.21 Panic Disorder With Agoraphobia
- 300.22 Agoraphobia Without History of Panic Disorder
- 300.29 Specific Phobia (specific type such as Animal Type, etc.)
- 300.23 Social Phobia
- 300.3 Obsessive-Compulsive Disorder
- 309.81 Posttraumatic Stress Disorder
- 308.3 Acute Stress Disorder
- 300.02 Generalized Anxiety Disorder
- 293.84 Anxiety Disorder Due to a General Medical Condition
- \_\_\_\_. \_\_ Substance-Induced Anxiety Disorder
- 300.00 Anxiety Disorder Not Otherwise Specified

**Panic Disorder** is defined as “a discrete period of intense fear or discomfort, which four (or more) of the following symptoms develop abruptly and reached a peak within 10 minutes: (1) palpitations, pounding heart, or accelerated heart rate, (2) sweating, (3) trembling or shaking, (4) sensations of shortness of breath or smothering, (5) feeling of choking, (6) chest pain or discomfort, (7) nausea or abdominal distress, (8) feeling dizzy, unsteady, lightheaded, or faint, (9) derealization or depersonalization, (10) feeling of losing control or going crazy, (11) fear of dying, (12) paresthesias, or (13) chills or hot flushes. Panic disorder is not population-specific. There are no excluded populations known for this form of anxiety based on race, color, age, gender, religion or national origin.

**Agoraphobia** is defined as: (1) anxiety about being in places or situations from which escape might be difficult or embarrassing in case one experiences panic in situations like being away from home alone, being in a crowd, standing in a line, being on a bridge, or traveling in a private or public transport. The situations are avoided or else endured with marked stress and the anxiety or phobic avoidance are not better explained by another mental disorder including any of the listed Anxiety Disorders. Agoraphobia is not population-specific. There are no excluded populations known for this form of anxiety based on race, color, age, gender, religion or national origin.

**Generalized anxiety disorder (GAD).** GAD is the most commonly diagnosed anxiety disorder and occurs most frequently in young adults and children. It involves excessive anxiety and worry, and difficulty controlling worry along with one of six other features including (1) restlessness, (2) easily fatigued, (3) difficulty concentrating, (4) irritability, (5) muscle tension, and (6) sleep disturbance. Generalized anxiety disorder is not population-specific. There are no

excluded populations known for this form of anxiety based on race, color, age, gender, religion or national origin.

**Panic disorders with or without agoraphobia.** The chief characteristic of panic disorder is the occurrence of panic attacks and the fear of their recurrence. In clinical settings, agoraphobia is usually not a disorder by itself, but is typically associated with some form of panic disorder. As previously described, those with agoraphobia are afraid of places or situations in which they might have a panic attack and be unable to leave or to find help or emotional security. About 25% of people with panic disorder may develop obsessive-compulsive disorder (OCD). These are not population-specific. There are no excluded populations known for these forms of anxiety based on race, color, age, gender, religion or national origin.

**Phobias.** These include specific phobias and social phobia that are found in both children and adults. A phobia is an intense and irrational fear of a specific object or situation that evokes profound negative responses and compels the person to avoid it. Some phobias are related to activities or objects that involve some risk (*e.g.*, flying or driving) but many are focused on harmless animals or other objects.

**Specific Phobia** used to be called Simple Phobia. Exposure to the phobic stimulus usually provokes an immediate anxiety response which may take the form of a situational panic attack. The person usually recognizes that the fear is unreasonable or excessive and the stimulus is either avoided or tolerated with extreme anxiety or stress. Specific phobias can be tied to specific animals or natural situations such as heights, storms, or water. Many of the specific phobias originate in childhood. **Social phobia**, also called Social Anxiety Disorder, involves a fear of being humiliated, embarrassed, judged, or scrutinized. It manifests as a fear of performing certain functions in the presence of others (*e.g.*, public speaking) or can include most social situations and normal developmental activities such as dating. Phobias are not population-specific. There are no excluded populations known for these forms of anxiety based on race, color, age, gender, religion or national origin.

**Obsessive-compulsive disorder (OCD).** This disorder is marked by unwanted, intrusive, persistent thoughts characteristically coupled with repetitive behaviors that reflect the patient's response to, or attempts to control the escalating intrusive ideas. OCD affects between 2-3% of the population. The disorder may have either obsessions, compulsions, or both. The person attempts to control, ignore, or suppress the unwanted thoughts and behaviors and almost always recognizes at some point in the illness that they are excessive or unreasonable. The symptoms may cause marked distress, waste a lot of time, and generally interfere with and obstruct the person's quality of life. Obsessive-compulsive disorder is not population-specific. There are no excluded populations known for this form of anxiety based on race, color, age, gender, religion or national origin.

**Stress Disorders.** These include **Post Traumatic Stress Disorder (PTSD)** and **Acute Stress Disorder** as well as **Combat Stress Disorder**. Stress disorders are symptomatic reactions to traumatic events in a person's life. The challenges of civilian life can frequently produce stress

disorders. These events involve the threat of either real death or serious injury which becomes recorded in the individual's memory in some way and then re-experienced over and over again in waking imagery or in dreams. Repetitive internal replay of the distress produces both psychological and physiological effects which cause the individual, as with some soldiers, to make many different attempts at avoiding the memories and dreams. The interest in life and any sense of a positive future become very weak. Life can become a series of different alarm and arousal states that include (1) difficulty falling or staying asleep, (2) irritability or outbursts of anger, (3) difficulty concentrating, (4) hyper-vigilance, and (5) exaggerated startle response. Panic disorder is not population-specific. Stress is ubiquitous in modern life. There are no excluded populations known for this form of anxiety based on race, color, age, gender, religion or national origin.

**Anxiety Disorders Due To Known Medical Conditions.** These disorders can include intense anxiety, panic attacks, or obsessions and compulsions. The severity of the anxiety disorder is often directly proportional to the physiological consequences and life pattern disruption of the general medical condition. There are no excluded populations known for anxiety due to medical conditions based on race, color, age, gender, religion or national origin.

**Substance-Induced Anxiety Disorder.** These include the same features as the disorders accompanying medical conditions but also includes complicating factors such as substance intoxication or withdrawal states as well as toxicity states related to the use of prescribed medications. Most prominent conditions include the use and abuse of substances that can involve the sympathetic nervous system while producing hyper-stimulated physiologic responses and emotional states of anxiety (*e.g.*, caffeine, amphetamines). Substance abuse patients all suffer from anxiety, depression and insomnia to some extent and substance abuse patients are not population-specific. This population of anxiety patients includes all populations without regard to race, color, age, gender, religion or national origin.

**Anxiety Disorder Not Otherwise Specified. (NOS)** This category includes conditions featuring prominent anxiety or phobic avoidance that do not meet the criteria for any of the previously described disorders. NOS disorders do not meet criteria for any specific Anxiety Disorder, Adjustment Disorder with Anxiety, or Adjustment Disorder with Mixed Anxiety and Depressed Mood. One example might be a person who has a clinically significant social phobia because of a general medical condition such as Parkinson's disease or a dermatological disorder. It is particularly prevalent in conditions such as fibromyalgia where the diagnostic criteria is not universally recognized causing some patients to be anxious about how others will view them in the context of their disorder. Once again, no anxiety disorder is population-specific. There are no excluded populations known for any form of anxiety based on race, color, age, gender, religion or national origin.

All *DSM-IV* anxiety disorder diagnoses include criteria and indices of severity. To meet criterion for a clinically relevant disorder, the anxiety must be severe enough to significantly interfere with the patients' occupational or educational functioning, social activities, interpersonal relationships, or other customary activities of daily living. This often forms the basis for

inclusion into studies of CES, pharmaceuticals or other modalities used in the treatment of anxiety disorders.

Anxiety disorders vary widely in frequency of occurrence in the general population, age of onset, family patterns, and gender distribution. In general, the stress disorders and anxiety disorders caused by medical conditions or substance abuse are less age and gender specific. While OCD affects males and females equally, GAD, panic disorder, and specific phobias all affect women more frequently than men. GAD and panic disorders are more likely to develop in young adults, while phobias and OCD can and frequently do begin in childhood. Yet there are no excluded populations known for anxiety populations based on race, color, age, gender, religion or national origin.

Although there is no psychiatric test that can provide definite diagnoses of anxiety disorders, there are several psychometric tests that are used to evaluate the intensity of a patient's anxiety and some of its associated features. These same tests are also used in both pharmaceutical and cranial electrotherapy stimulation (CES) research. Physiological parameters are another way to diagnose and measure progress in anxiety patients, be it for clinical progress notes or to ascertain differences in research. Many psychometric and physiological tests have been employed in the 150+ completed studies of CES. In aggregate, results seen with Alpha-Stim CES have been impressive with only a few exceptions as to be expected from such a large and diverse, yet continuously confirming body of scientific literature.

It is important for patients with severe anxiety symptoms to get help. Anxiety doesn't always go away by itself; it can progress to panic attacks, phobias, and as part of a larger constellation of features known as anxiety-depressive spectral disorders, lead to episodes of depression and even suicide. In addition, many anxious patients may turn to illicit drugs or alcohol in an attempt to self-medicate their symptoms. Moreover, since children learn ways of coping with anxiety from their parents, adults who get help for anxiety disorders are better prepared to contribute to family dynamics that teach their children healthy coping patterns than adults who remain untreated and install abusive habits to their children. Parents who are having difficulty coping with their own patterns of anxiety often have difficulty with effectively nurturing their children and helping them develop a healthy sense of self-esteem.

The spectrum of anxiety disorders are clearly bidirectionally comorbid with insomnia and depression, and CES is also emerging as a complementary and stand-alone treatment for pain related disorders. It is safe to assume that our healthcare culture will usually prescribe a medication such as a minor tranquilizer or SSRI as the first treatment of choice for a number of anxiety disorders, including panic attacks. But all of the pharmacological interventions employed for anxiety disorders tend to be dependency provoking, expensive, and depression-facilitating by virtue of the fact that they depress the central nervous system. CES has been clearly proven in numerous studies across several patient populations to be a safe and effective option for the treatment of the entire spectrum of anxiety disorders. Certain anxiety disorders such as panic attacks which are incipient and not chronically severe may respond to CES as the least complex, least expensive, and most efficacious treatment modality. People who suffer

from anxiety attacks can carry around an Alpha-Stim because it is no bigger than a cell phone. This allows them to abort an attack when it occurs but may also reduce the attacks because it removes the fear that the attack will cause them to have to seek emergency care. CES works faster than drugs which require time to metabolize.

2. **Depression:** According to NIH findings, one in 20 American adults experience major depression in a given year. The Depression and Bipolar Support Alliance report that 16 million people suffer from depression annually, with twice as many women afflicted as men. They estimate that as many as 25% of women suffer from depression serious enough to require treatment at least once in their lifetime. The National Alliance on Mental Illness indicates that “major depression is the leading cause of disability in the United States and many other developed countries, and affects 15 million American adults or about 5 to 8% of the adult population in a given year.”

Many other comorbid disabilities—such as cardiovascular events—can accompany depression. Depression may also result in chronically elevated levels of stress hormones, such as cortisol and epinephrine, and thus represents a condition that diverts metabolism away from tissue repair when needed for healing. Feelings of helplessness or of being out of control of one’s life also impair the immune system, increasing susceptibility to a wide spectrum of pathologies from infections to cancer.

Aside from the general population, chronic pain patients almost invariably suffer depression as a direct result of their pain and accompanying disability. Almost any chronic illness, especially ones with no clearly effective treatment, have a high incidence of comorbid depression. Based on these descriptions of the physical manifestations of depression, it is clear that it can have a devastating effect in the pain patient and others with chronic diseases.

While depression is a common term for describing how one feels, the technical psychiatric definition goes beyond just a feeling of sadness. For such a commonly-used term, it behooves us to scrutinize some technical definitions and terms. Depression is a mental state characterized by feelings of sadness, loneliness, despair, low self-esteem, and self-reproach; accompanying signs include psychomotor retardation or, at times, agitation, withdrawal from interpersonal contact, and vegetative symptoms such as insomnia and anorexia. The term refers to either a mood that is so characterized or a mood disorder.

**Mood disorder** is now the preferred term in both the World Health Organization’s (WHO) 10th revision of International Statistical Classification of Diseases and Related Health Problems (ICD-10) and the American Psychiatric Association’s DSM-IV. Official mood disorder categories in current use include **bipolar disorders** (with manic or hypomanic, depressive, or mixed episodes) and **major depressive disorders** and their respective attenuated variants known as **cyclothymic** and **dysthymic disorders**. Many of the older terms such as atypical depression, endogenous depression, and involuntional melancholia are included within major depressive disorders. The older depressive neurosis has been replaced and absorbed by dysthymic disorder.

The specific psychiatric criteria for a **Major Depressive Disorder**, require that “five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning. At least one of the symptoms is either depressed mood or loss of interest or pleasure and the symptoms are not obviously secondary to a general medical condition or mood-incongruent delusions or hallucinations.”

**The symptoms are:**

1. Depressed mood most of the day, nearly daily, and/or irritable mood in children and adolescents.
2. Markedly diminished interest or pleasure in most activities.
3. Significant weight loss when not dieting—or weight gain.
4. Insomnia or hypersomnia nearly every day.
5. Psychomotor agitation or retardation.
6. Fatigue or loss of energy.
7. Feelings of worthlessness or excessive or inappropriate guilt.
8. Diminished ability to think or concentrate, or indecisiveness.
9. Recurrent thoughts of death beyond a fear of dying, recurrent suicidal ideation, or a suicide attempt or specific plan.

Summary of DSM-IV-TR Depressive Disorders:

**TABLE 2: DSM-IV-TR DIAGNOSES FOR DEPRESSION**

- 296.xx Major Depressive Disorder
  - .2x Single Episode
  - .3x Recurrent
- 300.4 Dysthymic Disorder
- 311 Depressive Disorder Not Otherwise Specified (NOS)
- 293.83 Mood Disorder Due to a General Medical Condition.  
Specify with Depressive Features/With Major Depressive-Like Episode/with Mixed Features.  
\_\_\_\_. \_\_ Substance-Induced Mood Disorder  
Specify type as in 293.83 or With Onset During Intoxication/With Onset During Withdrawal
- 296.90 Mood Disorder Not Otherwise Specified
- 309.0 Adjustment Disorder With Depressed Mood
- 309.28 Adjustment Disorder With Mixed Anxiety and Depressed Mood

**Treatment Protocols.** The National Institutes of Health (NIH) describes depression as a serious medical condition that affects thoughts, feelings, and the ability to function. Depression is labeled a treatable disorder of the brain, with 80% of patients responding to treatment. The NIH, as well as other researchers, declare depression to be mainly a biochemical problem and, therefore, the first line of treatment should be psychopharmaceutical intervention, possibly accompanied by psychotherapy, counseling, exercise, or other wellness techniques. In the following sections, we will focus on three basic modalities in the treatment of depression: psychoanalysis-related, pharmaceutical, and microcurrent cranial electrotherapy stimulation.

**Psychoanalytic Foundations.** The absolute foundation of all psychological treatments for depression comes from the principles of psychoanalysis, and this applies to all mental health professionals. By the 1960s, the basic precepts of psychoanalysis were so thoroughly inculcated into the fabric of Western society (at least with the upper middle and upper classes), that the notions of depression representing mental pain and possibly anger turned against the self were widely (mis)understood and used in treatment. In fact, there was even a somewhat popularized book published titled, *Americanization of the Unconscious*. However, the same decade saw the beginnings and popularization of various types of behavior therapies. With current managed care, psychoanalysis as a technique has become more of a foundation science of consciousness for less prolonged, behaviorally and cognitively-oriented systems of psychotherapy. Psychiatric residents are taught elements from much briefer techniques such as Albert Ellis's Rational Behavioral Therapy (RBT), Aaron Beck's Cognitive Behavioral Therapy (CBT), and Weissman and Klerman's Interpersonal Therapy (IPT). Most of the methodologies used for depression in today's mental health teaching utilize psychodynamic principles but focus on briefer, time-limited, task- or sector-oriented psychotherapy systems as well as a large variety of group and peer related interventions.

**Rational Behavior Therapists recognize four specific steps required for depression to occur:**

1. A disappointment occurs due to an unfortunate or unexpected event;
2. One experiences frustration at the disappointment and dwells on it at length;
3. When nothing can be done to change the situation, and one can not manage to let go of it, a feeling of hopelessness and helplessness ensues;
4. The final step is what cognitive therapists refer to as lying exaggerations. Typical of these are, "This is the story of my life. No one has ever loved me and no one ever will," or "Everyone has someone to love them except me. I am no good for anybody, not even myself. I would be better off dead."

Rational Behavior Therapy can treat depression by assisting the patient in examining any one of these steps, usually step one or step four, and the depression hopefully becomes manageable as the patient learns to better understand these feelings. The biggest problem the therapist has is in identifying the specific trauma that started the most recent depressive episode. That is because depressed people obsess and dwell on similar events in their history and run reel after reel of mental depression tapes that maintain the affliction. The strategy is to examine recent history to decipher what started the latest episode so that, once it is clear and exposed to rational thinking, the depression may be reduced.

Operationally, the difficulty with all the cognitive and behavioral approaches can be a lack of real communications about feelings on the part of both therapist and patient. There is the also the potential of mistaking depression as a singular issue or mainly a psychological problem that can be isolated from the physical body.

**Pharmacological Mechanism of Action:** The biochemical model recognizes levels of depression from mild, to moderate, to so severe that it affects every part of the person's life. The biomedical model maintains that all these levels require medication. As a result,

antidepressants are often prescribed and typically include at least one of the following pharmaceuticals: Prozac, Paxil, Zoloft, Effexor, and Serzone. One important issue not always addressed is how long treatment for depression should be continued, given that there are physiologic consequences to prolonged manipulation of neurotransmitters by such drugs.

Neurotransmitters tend to attain balance by mutual regulation activities. Once a person encounters a sympathetic dominant situation that cannot be gotten out of by fleeing or fighting (e.g., bad job, worse marriage), the body adjusts to a new homeostatic stress level and this will affect the balance between neurotransmitters. Psychological symptoms such as anxiety, depression, panic attacks and phobias are often the result.

Depression is thought to involve many neurotransmitters including dopamine, norepinephrine and serotonin, among others. Most physicians and researchers theorize the mechanism of depression in terms of the “hardwired” neurological system in which the axon terminals secrete neurotransmitters from the pre-synaptic membrane into the inter-synaptic space to bind to a post-synaptic membrane. The neurotransmitter that is not bound by the post synaptic membrane will either undergo reuptake by the pre-synaptic membrane or it can be metabolized by monoamine oxidase or catechol-o-methyl transferase for elimination from the system.

The biochemical model views depression as being the byproduct of insufficient serotonin activity or inadequate serotonin level, and the neurotransmitter effects can be increased in several ways. A chemical can be added to the system to block the re-uptake into the pre-synaptic membrane, leaving more serotonin in the synaptic space. This is how the SSRI drugs are thought to work. Alternatively, a MAO inhibitor may be administered so that the serotonin in the synaptic space is not metabolized by monoamine oxidase and thereby remains available longer. A serotonin mimicking drug may stimulate the post synaptic membrane and serotonin activity.

This treatment approach comes from the theory of the hardwired (neuron-to-neuron), point-to-point hookup of traveling neuronal impulses, in which the synapses form the networks and define the neural circuits that, in turn, define and dictate performance.

It is now known that, in addition to the nervous system, cellular receptors throughout the body respond to ligands (molecules that bind to a receptor) such as serotonin flowing in the intercellular space outside the neural network. Manipulating levels of serotonin in the two percent of neuronal communications in the brain that are targeted in the treatment patterns as just described may actually influence the behavior of cells throughout all parts of the body in unknown ways. Depression is now often thought of as a mood produced by various neuropeptide ligands that activate cells simultaneously throughout the brain and the rest of the body.

At all times, feedback mechanisms work to regulate mutual relationships between the individual neurotransmitters so that a higher or lower level of one neurotransmitter will be

balanced or neutralized by a coupled feedback process on one or more corresponding neurotransmitters to reestablish physiological equilibrium. This is accomplished by the down-regulation by other neurotransmitters, when any one neurotransmitter is over-produced.

When a reuptake inhibitor is added to the system, a temporary surplus of the targeted neurotransmitter occurs and neurons that control the production of other neurotransmitters react automatically to bring the surplus neurotransmitter back into homeostasis. Thus chemicals that mimic endorphins at the post synaptic receptors (e.g., alcohol and benzodiazepines) stimulate the feedback mechanisms to down-regulate endorphin production. The substance abstinence syndrome results when the alcoholic, the heroin addict, or the long term diazepam (Valium) user attempts to come off the endorphin mimicking drug because the newly down-regulated endorphin production cannot balance the unchecked norepinephrine production causing the symptoms.

It is for this reason that neuroscience researchers advise that medications, such as SSRIs, should only be used short term to manage an acute problem, theorizing that longer use may throw the system into imbalance and produce harmful and sometimes long lasting iatrogenicity. **Cranial electrotherapy stimulation** is based on the concept that the biophysics underlying the body's biochemistry also plays a significant role in regulating brain processes. CES treats depression by passing tiny electrical currents through the brain. The microcurrent, delivered in a specific waveform, moves electrons through the brain at a variety of frequencies, collectively known as harmonic resonance. This normalizes the electrical activity of the brain as measured by an electroencephalogram (EEG). The patient undergoing CES treatment will often report a pleasant, relaxed feeling of well-being. Improvement is usually experienced during treatment, but may be seen hours later, or even the day after treatment. Depression control is generally experienced after three or more weeks of daily treatment.

Alpha-Stim CES is applied via ear-clip electrodes that attach to the ear lobes. The only thing felt by the patient may be a slight tingling sensation at the site of the electrodes. The duration of application is 20 to 60 minutes every day, every other day, or on a PRN basis. The treatment session may be in a practitioner's office or performed by the patient at home with a small portable device. In this regard, CES can be an ideal treatment for enhancing a patient's sense of mastery over depression because CES also emphasizes having the patient take the initiative on a daily basis. This involves several behavioral steps beyond merely passively swallowing a pill. CES still requires more education of clinicians and their patients about the modality and a fair and unbiased evaluation by FDA would certainly contribute to the public health in this regard.

CES can be utilized as an adjuvant treatment without fear of drug interaction. It's important to stress that add-on use of CES with one antidepressant drug can often prevent the need for using multiple antidepressants, as is too frequently the case in the currently accepted clinical treatment of depression and has recently been proven to be no more effective than monotherapy. CES is far more cost-effective for the American healthcare system than the long-term use of expensive SSRI's.

CES can occasionally be a single, time limited treatment of many forms of depression with or without concomitant medication. Depressive disorders require competent medical evaluation to rule out a primary or comorbid substance-related effect or a primary or comorbid treatable medical illness. This should be done by a competent, licensed physician, not by FDA. Although CES is nearly free of significant adverse effects, there is the possibility of usually mild cutaneous irritative effects at the electrode site which can limit treatment compliance in depressed patients. The other crucial factor is patient compliance and acceptance of the modality. Neither CES nor antidepressants should be employed for treatment without continuing and competent healthcare supervision because of emerging suicidality as some depressions lift. CES should always be considered as an add-on to medications before considering the more invasive Vagal Nerve Stimulator (VNS) or Deep Brain Stimulation (DBS), or even repetitive Transcranial Magnetic stimulation (rTMs) because CES is less expensive, safer and potentially as efficacious or more so, with minimal side-effects.

CES should always be considered a first line of treatment or, at least, an add on to medication for the treatment of depression. It should certainly be given serious clinical consideration in patients before resorting to the electroconvulsive therapy that the NIH has suggested on their web site as appropriate for those 20% of patients who do not respond to the use of even combinations of antidepressant medications, a common practice that was recently proven to have no additive effect. A more conservative—and perhaps wiser—approach to the treatment of depression (as with the treatment of anxiety disorders) would be to consider CES as a viable add-on or replacement for pharmacotherapy in milder depressions. For both moderately severe and severe depressions, CES should be considered as an add-on modality because of the potential for: (a) synergizing the efficacy of the drug (s), and (b) reducing the overall adverse effects of psychopharmaceuticals in patients who can tolerate and be compliant with CES. CES has no known adverse metabolic interactions with the various hepatic isoenzymes responsible for metabolizing SSRI's, other antidepressants, or any other commonly prescribed medications. CES will generally become more cost-effective than pharmaceuticals after the first 4-6 months of use.

Results of studies indicate that the effect sizes for FDA approved antidepressant drugs are low to low moderate at best, and the adverse effects that those manufacturers report in the Physician's Desk Reference—such as hypertension, nervousness, insomnia, sexual incompetence, seizures, liver and kidney dysfunction, among others—are often prominent. Further, physicians are warned that the use of some of these medications in patients, treated concomitantly with MAO inhibitors, can prove fatal in some circumstances. In fact, the FDA has required their most severe black box warnings on selective serotonin reuptake inhibitors (SSRI's) due to potentially adverse side-effects. In light of the low-to-moderate effectiveness indicated by analysis of the manufacturers' own studies together with documented side-effects and potential for drug interactions—especially among pain patients already on other potent drugs—the effectiveness of CES and lack of side effects make this an excellent option for the treatment of depression, alone or in combination with other antidepressants regardless of patient populations because there are no excluded populations known for depression based on race, color, age, gender, religion or national origin as hypothesized by FDA.

3. **Insomnia:** Primary insomnia is a complaint lasting for at least one month, of difficulty initiating and/or maintaining sleep or of the presence of non restorative sleep as defined by the Diagnostic and Statistical Manual of Mental Disorders. Primary insomnia is categorized as a Primary Sleep Disorder, under the category of **Dyssomnias** in the DSM-IV-TR. The diagnostic criteria for primary insomnia is summarized in Table 3. There are no excluded populations known for insomnia based on race, color, age, gender, religion or national origin as hypothesized by FDA.

**Table 3: Summary of DSM-IV-TR Diagnostic Criteria for Primary Insomnia**

- A. Difficulty initiating or maintaining sleep, or nonrestorative sleep, for at least one month.
- B. Sleep disturbance (or associated daytime fatigue) causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.
- C. Sleep disturbance does not occur exclusively during the course of Narcolepsy, Breathing-Related Sleep Disorder, Circadian-Rhythm Sleep Disorder, or a Parasomnia.
- D. Sleep disturbance does not occur exclusively during the course of another mental disorder such as Major Depressive Disorder, Generalized Anxiety Disorder, or a delirium.
- E. The disturbance is not due to the direct physiological effects of a substance (such as a drug of abuse or a medication) or a general medical condition.

The International Classification of Sleep Disorders Revised (ICSD-R) uses the term **psychophysiological insomnia** for a complaint of insomnia, and for the associated decreased functioning during wakefulness. The ICSD-R defines insomnia of six months duration as chronic.

The DSM criteria suggest that the diagnosis of insomnia is not a simple matter but reflects the now widely-accepted use of polysomnography (PSG) which has enlarged the scope of differential diagnosis when assessing insomnia. The DSM-IV-TR categorizes all sleep disorders as either **dyssomnias** or **parasomnias**. Parasomnias include diagnoses of Nightmare Disorder, Sleep Terror Disorder, Sleep-walking Disorder, or *not otherwise specified* conditions such as REM sleep behavior disorder and sleep paralysis. Sleep paralysis can be an exaggeration of a relatively nonpathologic hypnagogic event, or can be a common component of Narcolepsy, which itself is one of the dyssomnias. A list of some common dyssomnias as shown in Table 4 illustrates the diversity of dyssomnias.

**Table 4. Listing of DSM-IV-TR Main Dyssomnias**

- A. 307.42 Primary Insomnia
- B. 307.44 Primary Hypersomnia
- C. 347.00 Narcolepsy
- D. 780.57 Breathing-Related Sleep Disorder
- E. 327.xx Circadian Rhythm Sleep Disorder
  - .31 Delayed Sleep Phase Type
  - .35 Jet Lag Type
  - .36 Shift Work Type

Estimates of the number of people in the U.S. who suffer from insomnia range from 18 million to 24 million in adulthood, and up to 20% in later life, or seven million in people 65 years of age and older, with women being more likely to develop insomnia than men.

Theoretically, *nonrestorative* or *nonrefreshing* sleep is definable as some impairment in daytime functioning but is not always easy to demonstrate clinically. It has been difficult to demonstrate systematic impairment of daytime function in insomniacs. Some PSG studies have shown clear differences between the sleep of insomniacs and normal subjects. However, there is one large study which demonstrates extensive overlap in PSG indicators of sleep between insomnia patients and normal controls. So controversy exists whether patients with insomnia complaints and response to hypnotics differ from controls in any PSG measures of sleep and daytime function.

The significance of insomnia also relates to whether it occurs at the beginning, the end, or in the middle of the course of the usual sleep period. Traditionally, insomnia has been classified into three main types: **delayed sleep onset**, **impaired sleep continuity**, and **early-morning awakening**. Insomnia can be a feature of many major psychiatric disorders but is not regarded as a necessary diagnostic criterion for any particular disorder. Insomnia can be the sole symptom of depression, and can be a risk factor for the development or recurrence of some psychiatric disorders. Paradoxically, sleep loss can be both a symptom and a treatment of major depression.

The primary function of sleep is to ensure adequate cortical function when awake. Two processes interact in normal sleep production. The sleep homeostatic drives the sleep-wake schedule toward a balanced requirement (prolonged wakefulness incurs a *sleep debt*), and an internal circadian timer regulates the 24 hour biological clock's sleep-wake cycle. Together, the two processes regulate not only the amount of sleep but the quality of sleep as well. The two processes also differ across the life span, with young children requiring longer periods of sleep with more rapid eye movement (REM) sleep than do adults as the homeostatic drive declines with age.

There is no absolute technique for falling asleep and staying asleep. Sleep is generally regarded as a passive process in which internal and external cues act as setting autonomic conditions for sleep. According to the inhibition model, there is both a physiological de-arousal, and a cognitive de-arousal, allowing sleep to occur.

Sleep will usually not occur during cognitive arousal. According to Freud, the first step in becoming an insomniac is to worry that one will not sleep when one goes to bed. Recent research has borne out the fact that worries of any kind, but certainly a fear of not falling asleep and worrying about the resulting consequences of this for one's life the next day, clearly deactivates the cognitive de-arousal required for sleeping.

When asked what kinds of thoughts they have when they attempt to sleep, insomniacs provide a long list, typically including planning, thinking things out, especially with a negative emotional content, fear of not sleeping, plus concentrating on worrisome changes that are operative in their lives. When people who have no problems falling asleep are asked what they think about when they go to bed at night, many answer something to the effect of, “nothing especially.”

While medications are often used to treat insomnia, those that are of the benzodiazepine and related chemical structures have limited usefulness over the long range, since they tend towards tachyphylaxis (rapidly decreasing response following initial doses) and produce tolerance. The use of cognitive behavior therapy for enhancing sleep is often suggested since it may identify the things that the insomniac is doing to defeat the brain’s attempt to de-arouse. Although Alpha-Stim CES has proven to help all phases of sleep related disorders it does so by increasing Alpha brain waves as measured in several EEG studies so the reason for improving sleep is reducing anxiety, stress and cognitive ruminations.

People also sleep poorly due to illnesses, especially pain, depression, chronic medication effects, sleep apnea, anxiety, other stress related disorders, and other sleep disorders that can be diagnosed with PSG and alleviated with Alpha-Stim CES. These should all be addressed and evaluated as part of any therapy that is provided to the insomniac.

There have been more than 20 sleep studies of CES for insomnia as the primary diagnosis or as a secondary diagnosis to addictions or other forms of stress or pain related disorders. These studies demonstrate that CES can be an excellent treatment for insomnia in those patients who can accept and adapt to the modality. CES also has the additional benefit of helping to reduce dependence on drugs. This has been recognized by the United States Army where Alpha-Stim CES is being used in the theatre of war, at Army and VA medical centers, and the DOD has invested in two Alpha-Stim insomnia studies that are underway now.

And of course all sleep disorders, like anxiety, depression and pain, affect all populations without regard to race, color, age, gender, religion or national origin