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DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

21 CFR PART 882

[DOCKET NO. 93N-0027]

58 FR 45865
8/31/93

NEUROLOGICAL DEVICES; EFFECTIVE DATE OF REQUIREMENT FOR PREMARKET APPROVAL OF CRANIAL ELECTROTHERAPY STIMULATORS

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule; opportunity to request a change in classification.

SUMMARY: The Food and Drug Administration (FDA) is proposing to require the filing of a premarket approval application (PMA) or a notice of completion of product development protocol (PDP) for the cranial electrotherapy stimulator, a medical device. The agency is also summarizing its proposed findings regarding the degree of risk of illness or injury designed to be eliminated or reduced by requiring the device to meet the statute's approval requirements and the benefits to the public from the use of the device. In addition, FDA is announcing an opportunity for interested persons to request the agency to change the classification of the device based on new information.

DATES: Written comments by (insert date 60 days after date of publication in the FEDERAL REGISTER); requests for a change in classification by (insert date 15 days after date of publication in the FEDERAL REGISTER). FDA intends that, if a final rule based on this proposed rule is issued, PMA's will be required to be submitted within 90 days of the effective date of the final rule.

*Comply
11/1/93
request for change
in classification
9/15/93*

43N-0027

ADDRESSES: Submit written comments or requests for a change in classification to the Dockets Management Branch (HFA-305), Food and Drug Administration, rm. 1-23, 12420 Parklawn Dr., Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT:

Robert F. Munzner,
Center for Devices and Radiological Health (HFZ-450),
Food and Drug Administration,
1390 Piccard Dr.,
Rockville, MD 20850,
301-594-1744.

SUPPLEMENTARY INFORMATION:

I. BACKGROUND

Section 513 of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 360c) requires the classification of medical devices into one of three regulatory classes: class I (general controls), class II (special controls), and class III (premarket approval). Generally, devices that were on the market before May 28, 1976, the date of enactment of the Medical Device Amendments of 1976 (the amendments) (Pub. L. 94-295), and devices marketed on or after that date that are substantially equivalent to such devices, have been classified by FDA. For the sake of convenience, this preamble refers to both the devices that were on the market before May 28, 1976, and the substantially equivalent devices that were marketed on or after that date as "preamendments devices."

Section 515(b)(1) of the act (21 U.S.C. 360e(b)(1)) establishes the requirement that a preamendments device that FDA has classified into class III is subject to premarket approval. A preamendments class III device may be commercially distributed without an approved PMA or notice of completion of a PDP until 90 days after FDA promulgates a final rule requiring premarket approval for the device, or 30 months after final classification of the device under section 513 of the act, whichever is later. Also, a preamendments device is not required to have an approved investigational device exemption (IDE) (21 CFR part 812) contemporaneous with its interstate distribution until the date identified by FDA in the final rule requiring the submission of a PMA for the device.

Section 515(b)(2)(A) of the act provides that a proceeding to promulgate a final rule to require premarket approval shall be initiated by publication of a notice of proposed rulemaking containing: (1) The proposed rule; (2) proposed findings with respect to the degree of risk of illness or injury designed to be eliminated or reduced by requiring the device to have an approved PMA or a declared completed PDP and the benefit to the public from the use of the device; (3) an opportunity for the submission of comments on the proposed rule and the proposed findings; and (4) an opportunity to request a change in the classification of the device based on new information relevant to the classification of the device.

Section 515(b)(2)(B) of the act provides that if FDA receives a request for a change in the classification of the device within 15 days of the publication of the notice, FDA shall, within 60 days of the publication of the notice, consult with the appropriate FDA advisory committee and publish a notice denying the request for change of classification or announcing its intent to initiate a proceeding to reclassify the device under section 513(e) of the act. If FDA does not initiate such a proceeding, section 515(b)(3) of the act provides that FDA shall, after the close of the comment period on the proposed rule and consideration of any comments received, promulgate a final rule to require premarket approval, or publish a notice terminating the proceeding. If FDA terminates the proceeding, FDA is required to initiate reclassification of the device under section 513(e) of the act, unless the reason for termination is that the device is a banned device under section 516 of the act (21 U.S.C. 360f).

If a proposed rule to require premarket approval for a preamendments device is made final, section 501(f)(2)(B) of the act (21 U.S.C. 351(f)(2)(B)) requires that a PMA or a notice of completion of a PDP for any such device be filed within 90 days of the date of promulgation of the final rule or 30 months after final classification of the device under section 513 of the act, whichever is later. If a PMA or a notice of completion of a PDP is not filed by the later of the two dates, commercial distribution of the device is required to cease. The device may,

however, be distributed for investigational use if the manufacturer, importer, or other sponsor of the device complies with the IDE regulations. If a PMA or a notice of completion of a PDP is not filed by the later of the two dates, and no IDE is in effect, the device is deemed to be adulterated within the meaning of section 501(f)(1)(A) of the act, and subject to seizure and condemnation under section 304 of the act (21 U.S.C. 334) if its distribution continues. Shipment of the device in interstate commerce will be subject to injunction under section 302 of the act (21 U.S.C. 332), and the individuals responsible for such shipment will be subject to prosecution under section 303 of the act (21 U.S.C. 333). FDA has in the past requested that manufacturers take action to prevent the further use of devices for which no PMA has been filed and may determine that such a request is appropriate for the cranial electrotherapy stimulator (CES).

The act does not permit an extension of the 90-day period after promulgation of a final rule within which an application or a notice is required to be filed. The House Report on the amendments states that "the thirty month 'grace period' afforded after classification of a device into class III * * * is sufficient time for manufacturers and importers to develop the data and conduct the investigations necessary to support an application for premarket approval." H. Rept. 94-853, 94th Cong., 2d sess. 42 (1976).

A. Classification of the Cranial Electrotherapy Stimulator

In the FEDERAL REGISTER of September 4, 1979 (44 FR 51770), FDA issued a final rule (§ 882.5800 (21 CFR 882.5800)) classifying the CES into class III. The preamble to the proposal to classify the device (43 FR 55716, November 28, 1978) included the recommendation of the Neurological Device Classification Panel (the panel), an FDA advisory committee, regarding the classification of the device. The panel recommended that the device be in class III (premarket approval) for all uses. The panel members believed that there had been no clear demonstration of the effectiveness of CES's for treating any condition. In addition, the panel believed that it is not possible to establish an adequate performance standard for this device because the characteristics of the electrical current necessary for effectiveness are not known, and that general controls would not provide sufficient control over these characteristics. The panel believed that the device presents a potential unreasonable risk of illness or injury to the patient if the practitioner relies on the device and it is ineffective in treating the patient's illness. The panel recommended, therefore, that the device be subject to premarket approval to ensure that manufacturers demonstrate satisfactory performance of the device and thus ensure its safety and effectiveness.

The panel members based their recommendation on testimony presented to the Panel and on the results of a study performed by the National Research Council (NRC) on the safety and

effectiveness of devices used for electroanesthesia and electrosleep (Ref. 32). After reviewing the results of 88 published studies on cranial electrotherapy stimulation, NRC concluded that the device had not been shown to be effective in treating any of the conditions for which it was prescribed.

In the FEDERAL REGISTER of January 6, 1989 (54 FR 550), FDA published a notice of intent to initiate proceedings to require premarket approval for 31 class III preamendments devices. Among other things, the notice describes the factors FDA takes into account in establishing priorities for proceedings under section 515(b) of the act for promulgating final rules requiring that preamendments class III devices have approved PMA's or declared completed PDP's. Using those factors, FDA has determined that the CES identified in § 882.5800 has a high priority for initiating a proceeding to require premarket approval. Accordingly, FDA is commencing a proceeding under section 515(b) of the act to require that the CES has an approved PMA or a PDP that has been declared completed.

B. Dates New Requirements Apply

In accordance with section 515(b) of the act, FDA is proposing to require that a PMA or a notice of completion of a PDP be filed with the agency for the cranial electrotherapy stimulator within 90 days after promulgation of any final rule based on this proposal. An applicant whose device was in commercial distribution before May 28, 1976, or whose device has been found by FDA to be substantially equivalent to such a

device, will be permitted to continue marketing the CES during FDA's review of the PMA or notice of completion of the PDP. FDA intends to review any PMA for the device within 180 days, and any notice of completion of a PDP for the device within 90 days of the date of filing. FDA cautions that, under section 515(d)(1)(B)(i) of the act, FDA may not enter into an agreement to extend the review period for a PMA unless the agency finds that "* * * the continued availability of the device is necessary for the public health."

FDA intends that, under § 812.2(d) (21 CFR 812.2(d)), the preamble to any final rule based on this proposal will state that, as of the date on which a PMA or a notice of completion of a PDP is required to be filed, the exemptions in § 812.2(c)(1) and (c)(2) from the requirements of the IDE regulations for preamendments class III devices will cease to apply to any CES which is: (1) Not legally on the market on or before that date; or (2) legally on the market on or before that date but for which a PMA or notice of completion of PDP is not filed by that date, or for which PMA approval has been denied or withdrawn.

If a PMA or a notice of completion of PDP for the CES is not filed with FDA 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. The device may be distributed for investigational use only if the requirements of the IDE regulations regarding significant risk devices are

met. The requirements for significant risk devices include submitting an IDE application to FDA for its review and approval. An approved IDE is required to be in effect before an investigation of the device may be initiated or continued. FDA, therefore, cautions that IDE applications should be submitted to FDA at least 30 days before the end of the 90-day period to avoid interrupting investigations.

C. Description of Device

A CES is a therapeutic device that applies electrical current to a patient's head to treat insomnia, depression, anxiety, or any other use for which these devices may have been promoted prior to enactment of the amendments. The device consists of a pulse generator which delivers an electrical stimulus conducted by electrical cables to electrodes in contact with the skin. It differs from electroconvulsive therapy devices in that electrical output is not intended for the purpose of causing an epileptiform convulsion.

Throughout the literature numerous terms and acronyms have been adopted to describe cranial electrotherapy, i.e., the application of electric current to the head for therapeutic effects. They include electrosleep, electrotherapeutic sleep, cranial electrotherapy stimulation, cerebral electrotherapy (CET), transcranial electrotherapy (TCE), transcerebral electrotherapy (TCET), and electric cerebral stimulation. For simplicity, the term "cranial electrotherapy stimulator (CES)" is

used throughout this proposal, although references cited may employ other names.

There are a number of variations in the output waveform characteristics of CES's identified in the literature. A typical device may apply a waveform which is either monophasic or biphasic. The waveform may consist of rectangular pulses or may be sinusoidal. Current amplitude is typically in the range of 20 microamperes to 4 milliamperes. Typical use employs a pair of electrodes placed either directly on the eyelids or the brow with a second pair of electrodes placed over the mastoids. The forehead electrodes are usually cathodic, while those on the mastoids are usually anodic, although this arrangement is sometimes reversed. Treatment sessions cited in the literature vary from 15 minutes for 5 consecutive days to 2 hours daily for a period of several months. The average duration of exposure time in most studies was 30 minutes per session, repeated for 10 sessions. No systematic study was identified in the reviewed literature that attempted to determine the physiological effect of these various output waveform characteristics or the advantage of one combination over another.

D. Proposed Findings With Respect to Risks and Benefits

As required by section 515(b) of the act, FDA is publishing its proposed findings regarding: (1) The degree of risk of illness or injury designed to be eliminated or reduced by requiring the CES to have an approved PMA or a declared completed

PDP; and (2) the benefits to the public from the use of the device.

E. Risk Factors

1. Worsening of the condition being treated

If a patient is treated with a CES device in lieu of conventional therapy and the CES is not effective, the patient's psychological condition may worsen. There have been reported cases in which patients were adversely affected by treatment (Refs. 2, 6, 7, and 16). Achte et al. (Ref. 2) reported complications in 4 of their 24 patients in whom no direct effect on insomnia was observed. One case involved a patient suffering from hysterical neurosis who was reported to have suffered hysterical convulsions during treatment. Another patient was affected with a psychotic depression. Feighner et al. (Ref. 6) reported that eight patients diagnosed with either primary anxiety neurosis or insomnia showed significant improvement initially, but within the first month after treatment seven of those patients relapsed. Furthermore, Feighner et al. reported that four of six patients who were diagnosed with primary depression were dropped from the study because of significant worsening of depressive symptoms. Two of these four patients were hospitalized due to active suicidal ideation. Similar experiences were reported in the remaining references listed above (Refs. 7 and 16).

2. Headaches

Reported cases of adverse effects of CES devices include headaches following treatment with electrical stimulation (Refs. 2, 18, and 34).

3. Potential risk of seizure

The degree of risk associated with various electrical stimuli has not been studied systematically. It is well known, however, that the transmission of electrical current through the brain can induce epileptiform seizures (Ref. 1). Although no instances of seizure associated with CES's have been reported to FDA, the lower limits of electrical stimulation, which could potentially induce a seizure, have not been investigated.

4. Skin irritation

Both electrodes and the conductive medium used with the electrodes may cause skin irritation and burns (Ref. 17).

5. Blurred vision

Pressure from the electrodes when using a mask may cause blurred vision after treatment (Refs. 4, 9, 12, and 16).

6. 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 (Refs. 14 and 15).

F. Benefits of the Device

Investigators who have studied the effectiveness of cranial electrotherapy stimulation have reported varying, and often contradictory, results. The majority of the literature published in the English language regarding cranial electrotherapy is an assortment of anecdotal commentary, historical background, uncontrolled studies, and technical reviews.

Most of the scientific studies reviewed by FDA contained insufficient information regarding their protocol and design. Most of the studies failed to satisfy one or more of the minimum design requirements for a valid scientific study. These requirements include complete protocol description, adequate controls, randomization, blinding methods, full patient accountability including followup data, and reliable safety and effectiveness evaluation criteria. After an extensive literature search, FDA identified a number of studies (Refs. 3, 5, 6, 9, 10, 11, 13, 16, 19, 20, 21, and 23 through 32) in which some type of randomized controlled design was employed. However, many of these studies did not discuss in sufficient detail why the blinding methods employed were reliable, accurate, and without bias (Refs. 3, 6, 9, 10, 16, 19, 23, 28, 29, 30, and 31). In some cases it was unclear whether both the operator and the evaluator were blinded. Other studies were found to have only single-blind designs (Refs. 20, 24, and 27).

Six studies in the reviewed literature (Refs. 5, 11, 21, 25, 26, and 32) described randomized, controlled, double-blind

designs. Four of these six studies, however, did not provide sufficient followup data to show whether any effect continued after the initial treatment (Refs. 5, 21, 25, and 26). Ellison et al. (Ref. 5) reported a statistically significant difference ($p < 0.05$) between a stimulated group and a nonstimulated group of opiate dependent subjects in opiate withdrawal symptoms rated on the Himmelsbachs scale. However, the second experiment reported by Ellison et al. revealed that the withdrawal symptoms returned once the stimulation ceased, where four out of five subjects not stimulated for a second 24 hours experienced withdrawal symptoms within 3 to 4 hours of the cessation of stimulation.

Rosenthal (Ref. 21) reported an evaluation of a CES in a double-blind clinical study of 22 patients diagnosed with neurotic anxiety and depression. Although Rosenthal reported that 8 of the 11 patients who received active treatment showed marked improvement, there was little information describing how the patients were clinically evaluated and what criteria were used to determine a rating of improvement. Additionally, no followup data were provided on those patients who received active treatment.

Schmitt et al. (Ref. 25) investigated 60 individuals with alcoholism and other chemical dependencies to evaluate the effects of CES treatments on organic brain syndrome. Forty patients were assigned to either active ($N=30$) or sham ($N=10$) CES treatments and the remaining 20 patients participated in the standard treatment program. All patients were pretested and

posttested on the Revised Beta Examination IQ Test and on three subscales of the Weschler Adult Intelligence Scale (WAIS). In addition to the lack of any followup data on these patients, Schmitt et al. provided no justification or validation of the Revised Beta Examination IQ Test and WAIS subscales for measuring cognitive brain dysfunction. Moreover, due to the small sample size the power of the administered tests appears to be inadequate to draw any conclusions regarding treatment effect.

Smith (Ref. 26) studied the effects of cranial electrotherapy stimulation on 100 male patients with alcoholism in a randomized controlled study using the Revised Beta Examination IQ Test as the criterion variable for brain dysfunction. Smith provided insufficient information in terms of the statistical evaluation made, the validation of the measure used, or the explanation of results. Additionally, there were insufficient followup data and, therefore, no meaningful conclusions can be drawn from this study.

The remaining two studies (Refs. 11 and 32) both included a 2-week followup to determine the effective duration of the treatment. Hearst et al. (Ref. 11) studied 28 patients diagnosed with prominent anxiety and depression in a sham controlled, double-blind study to determine the effectiveness of cranial electrotherapy stimulation as a treatment modality.

Assessment of clinical change for symptoms of anxiety, insomnia, and depression was based on patient and physician global ratings and patient self-rating scores. Global ratings by

both the physicians and the patients showed no statistically significant difference between the active group and the sham group, and consisted of somatic complaints, anxiety, depression, and overall status.

Hearst et al. used the National Institute of Mental Health self-rating symptom scales (SRSS) to evaluate individual symptoms of anxiety, depression, and somatic complaints. At the end of the 5-day treatment there was no statistically significant difference in the self-rating scores for anxiety or somatic symptoms between the active group and sham group. Although there was a statistically significant difference in the depression scores of the two groups at the end of treatment, that difference was no longer present at the 2-week followup.

Although Hearst incorporated the minimum design requirements for a valid scientific study, including double-blinding, randomized controls and followup data, significant information was not reported, especially with regard to the statistical methods used in assessing results. Similarly, neither the assessment criteria used for the global ratings nor the criteria used for the numeric results based on the SRSS were reported. Further, there was no indication that objective evaluation criteria were implemented to ensure reliable patient diagnoses.

Weiss (Ref. 32) studied cranial electrotherapy stimulation in 10 volunteers who were diagnosed with sleep onset insomnia after being monitored with an electroencephalograph (EEG) for

three successive nights in a sleep laboratory. Although the study was double-blinded with randomized controls, the authors failed to identify the electrical stimulus characteristics used. Although the data obtained from the study are encouraging with regard to the use of cranial electrotherapy stimulation as a potential treatment for sleep-onset insomnia, the small sample size would not demonstrate statistical significance for treatment effect.

FDA has concluded from a review of the scientific literature that the effectiveness of CES's has not been established by adequate scientific evidence.

G. Need For Information For Risk/Benefit
Assessment of the Device

FDA classified the cranial electrotherapy stimulator into class III because it determined that insufficient information existed to determine that general controls would provide reasonable assurance of the safety and effectiveness of the device or to establish a performance standard to provide such assurance. FDA has determined that the special controls that may now be applied to class II devices as under the Safe Medical Devices Act of 1990 also would not provide such assurance. FDA has weighed the probable risks and benefits to the public from the use of the device and believes that the information obtained from studies which have evaluated CES's does not provide reasonable assurance of the safety and effectiveness of these devices. FDA believes that CES's should undergo premarket

approval to establish effectiveness for any intended use and to determine whether the benefits to the patient are sufficient to outweigh any risk.

II. PMA REQUIREMENTS

A PMA for this device must include the information required by section 515(c)(1) of the act and § 814.20 (21 CFR 814.20) of the procedural regulations for PMA's. Such a PMA should include a detailed discussion, with results of preclinical and clinical studies, of the risks identified above and the effectiveness of the device for which premarket approval is sought. In addition, the PMA must include all data and other information relative to: (1) Any risks known, or that should be reasonably known, to the applicant that have not been identified in this document; (2) the effectiveness of the specific CES that is the subject of the application; and (3) summaries of all existing preclinical and clinical investigations on the safety and effectiveness of the device for which premarket approval is sought.

Valid scientific evidence to be included in the PMA should be obtained from well-controlled clinical studies, with detailed information from long-term followup of the study patients, in order to provide reasonable assurance of the safety and effectiveness of the cranial electrotherapy stimulator for its intended use. In addition to the basic requirements described in § 814.20(b)(6)(ii) for a PMA, the description of the clinical protocol(s) should include sufficient detail to indicate whether

the protocol(s) meet the following criteria deemed necessary by FDA to provide reasonable assurance of the device's safety and effectiveness for its intended use.

A. General Requirements

The study protocol for a CES must contain a clear statement of the hypothesis to be tested, including: (1) An identification of the stages of the disease or condition to be treated, based on a recognized classification, so that improvement or deterioration can be measured; (2) a statement whether the device is intended to be used alone or as an adjunctive treatment; (3) an identification of the physiological effects which the device produces; and (4) an identification of the primary and secondary variables to be analyzed to demonstrate effectiveness. The protocol should be supported by background literature on previous uses of the device and proposed mechanisms for its effect. The protocol should address the clinical utility of the device in terms of the risk-to-benefit ratio of the device for its intended use. Pilot studies are recommended to characterize the primary and secondary variables associated with the use of the device. Primary variables used for measurement of safety and effectiveness should be clearly defined.

B. Study Sample Requirements

The subject population must be well defined. Ideally, the study population should be as homogeneous as possible in order to minimize selection bias and reduce variability. Otherwise, an

excessively large population may be necessary to achieve statistical significance. Independent studies producing comparable results at multiple study sites using identical protocols are necessary to demonstrate repeatability. Justification must be provided for the sample size used to show that a sufficient number of patients were enrolled to attain statistically and clinically meaningful results. Inclusion and exclusion criteria should be formulated based on the subjects' demographics and eligibility criteria. Eligibility criteria for the subject population should include the subjects' potential for benefit, the ability to detect a benefit in the subject, the absence of both contraindications and any competing risk, and assurance of subject compliance. In a heterogeneous sample, stratification of the patient groups participating in the clinical study may be necessary to analyze homogeneous subgroups and thereby minimize potential bias. All endpoint variables must be identified and a sufficient number of patients from each subgroup analysis must be included to allow for stratification by pertinent demographic characteristics.

C. Phases of Study

The study should consist of four phases: enrollment, baseline, treatment, and followup. During enrollment the sampling methods and intervals must be predetermined and kept constant and identical for all patients at all sites. Patients should be screened to assure they conform to the established inclusion criteria and that their medication and other forms of

therapy are stabilized. Once patients are enrolled, multiple baseline measurements should be obtained for all variables to be examined. The treatment phase should incorporate standard measures for each study variable. The primary study variables should be measured using several standard methodologies. Multiple measurements throughout the treatment phase may be necessary to determine sample variance. During each followup interval the variables should be measured again and analyzed for treatment effect. Followup must be complete and of sufficient duration to reasonably assure safety and effectiveness.

D. Study Design

The study should be a randomized double-blind design where all subjects of the study population are assigned concurrently by some method of randomization to either an active group or a placebo control group. The preferred method for subject enrollment into a study is randomization by a central monitor. The individuals responsible for the analysis and interpretation of the data obtained from the study should not have any pre-exposure to the study population. Blinding, therefore, is needed both of the subject population and of those individuals whose study functions require interaction with the subject population. All potential sources of error, including selection bias, information bias, misclassification bias, comparison bias, or other potential bias must be evaluated and minimized. The study must clearly measure any possible placebo effect.

Treatment effects should be based on objective measurements. The validity of these measurement scales must be shown to ensure that the treatment effect being measured reflects the intended use of the device.

Adherence to the protocol by subjects, investigators, and all other individuals involved is essential and requires monitoring to assure patient compliance, physician compliance, and blinding. Subject exclusion due to dropout or lost to followup greater than 20 percent may invalidate the study due to bias potential; therefore, initial patient screening and intensive compliance of the final subject population will be needed to minimize the dropout rate. All dropouts must be accounted for and the circumstances and procedures used to ensure patient compliance must be well documented.

Endpoint assessment cannot be based solely on a statistical value. Instead, the clinical outcome must be carefully defined to distinguish between the evaluation of the proper function of the device versus its benefit to the subject. Statistical significance and clinical utility of the device must be demonstrated by the statistical results. However, under certain restricted circumstances, a clinically significant result may be acceptable without statistical significance.

Observation of all potential adverse effects must be recorded and monitored throughout the study and the followup period. All adverse effects must be well documented and evaluated.

E. Statistical Analysis Plan

The involvement of an expert in biostatistics is necessary to provide proper guidance in the planning, design, conduct, and analysis of a clinical study, and to estimate the required number of patients based on the number of variables to be examined, the subgroup analyses to be conducted, and the expected treatment effect. The study should be designed to obtain statistical and clinical significance of the primary and secondary variables at the alpha level of 0.05 and a beta of 0.20 for each primary variable. Nonparametric tests may be required when analyzing data if the basic assumptions for parametric tests cannot be met.

In addition to this generalized guidance, the investigator is expected to incorporate additional requirements necessary for a well-controlled scientific study. These additional requirements are dependent on what the investigator intends to measure or what the expected treatment effect is based on the intended use of the device.

Applicants should submit any PMA in accordance with FDA's "Guideline for the Arrangement and Content of a PMA Application." The guideline is available upon request from Document Control, Center for Devices and Radiological Health, Food and Drug Administration, 1390 Piccard Dr., Rockville, MD 20850.

III. REQUEST FOR COMMENTS WITH DATA

FDA is providing a 60-day period for interested persons to submit to the Dockets Management Branch (address above) written comments regarding this proposal and its findings. Two copies of

any comments are to be submitted, except that individual may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the Dockets Management Branch between 9 a.m. and 4 p.m., Monday through Friday.

IV. OPPORTUNITY TO REQUEST A CHANGE IN CLASSIFICATION

Before requiring the filing of a PMA or a notice of completion of a PDP for a device, FDA is required by section 515(b)(2)(A)(iv) of the act and § 860.132 (21 CFR 860.132) to provide an opportunity for interested persons to request a change in the classification of the device based on new information relevant to its classification. Any proceeding to reclassify the device will be under the authority of section 513(e) of the act.

A request for a change in the classification of the CES is to be in the form of a reclassification petition containing the information required by § 860.123, including new information relevant to the classification of the device, and shall, under section 515(b)(2)(B) of the act, be submitted by (insert date 15 days after date of publication in the FEDERAL REGISTER).

The agency advises that, to ensure timely filing of any such petition, any request should be submitted to the Dockets Management Branch (address above) and not to the address provided in § 860.123(b)(1). If a timely request for a change in the classification of the CES is submitted, the agency will, by (insert date 180 days after submission deadline for petition), after consultation with the appropriate FDA advisory committee

and by an order published in the FEDERAL REGISTER, either deny the request or give notice of its intent to initiate a change in the classification of the device in accordance with section 513(e) of the act and 21 CFR 860.130 of the regulations.

V. REFERENCES

The following references have been placed on display in the Dockets Management Branch (address above) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. Abrams, R., Electroconvulsive Therapy, Oxford University Press, pp. 92-116, 1988.
2. Achte, K. A. et al., "On Electrosleep Therapy," Psychiatric Quarterly, 42:17-27, 1968.
3. Barabasz, A. F., "Treatment of Insomnia in Depressed Patients by Hypnosis and Cerebral Electrotherapy," American Journal of Clinical Hypnosis, 19(2):120-122, 1976.
4. Brown, C. C., "Electroanesthesia and Electrosleep," American Psychologist, 30(3):402-410, 1975.
5. Ellison, F. et al., "Opiate Withdrawal and Electro-stimulation: Double-

Blind Experiments," Encephale, 13(4):225-229, 1987.

6. Feighner, J. P. et al., "Electrosleep Therapy: A Controlled Double-Blind Study," Journal of Nervous and Mental Disease, 157:121-128, 1973.

7. Flemenbaum, A., "Cerebral Electrotherapy (Electrosleep): An Open Clinical Study With a Six-Month Followup," Psychosomatics, 15:20-24, 1974.

8. Frankel, B. L., "Research on Cerebral Electrotherapy (Electrosleep): Some Suggestions," American Journal of Psychiatry, 131:95-98, 1974.

9. Frankel, B. L. et al., "Ineffectiveness of Electrosleep in Chronic Primary Insomnia," Archives of General Psychiatry, 29:563-568, 1973.

10. Gomez, E. and A. R. Mikhail, "Treatment of Methadone Withdrawal With Cerebral Electrotherapy (Electrosleep)," British Journal of Psychiatry, 134:111-113, 1979.

11. Hearst, E. D. et al., "Electrosleep Therapy: A Double-Blind Trial," Archives of General Psychiatry, 30(4):463-466, 1974.

12. Koegler, R. R. et al., "Medical and Psychiatric Use of Electrosleep: Transcerebral Electrotherapy," Diseases of the Nervous System, 32(2):100-104, 1971.
13. Kotter, G. S. et al., "Inhibition of Gastric Acid Secretion in Man by the Transcranial Application of Low Intensity Pulsed Current," Gastroenterology, 69(2):359-363, 1975.
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15. Krauthamer, V. et al., "Morphological and Electrophysiological Changes Produced by Electrical Stimulation in Cultured Neuroblastoma Cells," Bioelectromagnetics, 12:299-314, 1991.
16. Levitt, E. A. et al., "A Clinical Trial of Electrosleep Therapy With a Psychiatric Inpatient Sample," Australian and New Zealand Journal of Psychiatry, 9(4):287-290, 1975.

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33. "An Evaluation of Electroanesthesia and Electrosleep," NRC, FDA Contract 70-22, Task Order No. 20 (NTIS PB 241305).
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VI. ENVIRONMENTAL IMPACT

The agency has determined under 21 CFR 25.24(a)(8) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore,

neither an environmental assessment nor an environmental impact statement is required.

VII. ECONOMIC IMPACT

FDA has examined the economic consequences of this proposed rule in accordance with the criteria in section 1(b) of Executive Order 12291 and finds that this proposal would not be a major rule as specified in the Order. The agency believes that only a small number of firms will be affected by this proposed rule, and the agency certifies under the Regulatory Flexibility Act (Pub. L. 96-354) that the proposed rule will not have a significant economic impact on a substantial number of small entities. An assessment of the economic impact of any final rule based on this proposal has been placed on file in the Dockets Management Branch (address above) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

VIII. COMMENTS

Interested persons may, on or before (insert date 60 days after date of publication in the FEDERAL REGISTER), submit to the Dockets Management Branch (address above) written comments regarding this proposal. Two copies of any comments are to be submitted, except that individuals may submit one copy. Interested persons may, on or before (insert date 15 days after date of publication in the FEDERAL REGISTER), submit to the Dockets Management Branch a written request to change the classification of the CES. Two copies of any request are to be

submitted, except that individuals may submit one copy. Comments or requests are to be identified with the docket number found in brackets in the heading of this document. Received comments and requests may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

List of Subjects in 21 CFR Part 882

Medical devices.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, it is proposed that 21 CFR part 882 be amended as follows:

PART 882--NEUROLOGICAL DEVICES

1. The authority citation for 21 CFR part 882 is revised to read as follows:

AUTHORITY: Secs. 501, 510, 513, 515, 520, 522, 701 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 351, 360, 360c, 360e, 360j, 360^(e)l, 371).

2. Section 882.5800 is amended by revising paragraph (c) to read as follows:

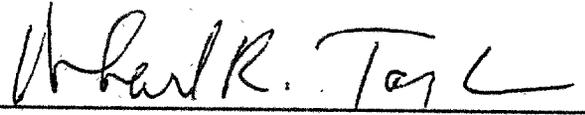
§ 882.5800 Cranial electrotherapy stimulator.

* * * * *

(c) Date premarket approval application (PMA) or notice of completion of product protocol (PDP) is required. A PMA or a notice of completion of a PDP is required to be filed with the Food and Drug Administration on or before (insert date 90 days after date of publication in the FEDERAL REGISTER of the final

rule based on this proposed rule), for any cranial electrotherapy stimulator that was in commercial distribution before May 28, 1976, or that has on or before (insert date 90 days after date of publication in the FEDERAL REGISTER of the final rule based on this proposed rule) been found to be substantially equivalent to the cranial electrotherapy stimulator that was in commercial distribution before May 28, 1976. Any other cranial electrotherapy stimulator shall have an approved PMA or declared completed PDP in effect before being placed in commercial distribution.

Dated: August 25, 1993.



Michael R. Taylor
Deputy Commissioner for Policy

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