Chapter 15

CDRH Proposes Final Rule for CES Devices - Again

January-July 2016

In Chapter 1, you were introduced to cranial electrotherapy stimulator (CES) devices which were the subject of the meeting of the Neurological Devices Panel on February 10, 2012. The 83-page FDA Executive Summary[1] prepared for the meeting includes the regulatory history which shows that the FDA devoted its attention to CES devices sporadically, beginning in 1977. It has been a strange sequence of events. Let's take a look.

1977 Classification Panel meeting
1978 Classification Panel meeting
1978 FDA proposed final rule to classify the devices in Class III
1979 FDA published **final rule to classify the devices in Class III**
1993 FDA published proposed rule to require premarket approval
1995 FDA published final rule to require premarket approval
1997 FDA published revocation of the requirement for a premarket approval application
2011 FDA published proposed rule to require premarket approval
2016 FDA published proposed final rule with Class II for two indications and Class III for one indication

According to the regulatory history[2], the FDA's consideration of CES devices began with two classification panel meetings (in 1977 and 1978) during which some panel members expressed concern that the effectiveness of CES devices had not been adequately established. However, they did not think the devices were particularly risky. They did not think there was enough information upon which to base a performance standard.

In 1995, when the FDA published the final rule to require a premarket approval application, it must have seemed the agency had done its job, and industry knew was expected of it. But it was not over.

Clearly, it has taken a long time for the FDA to nearly complete its process. They published the final rule classifying the devices into Class III in 1979. Fourteen years would pass before they proposed a rule to require premarket approval, and another two years until that rule was finalized. Then, two years later they revoked the requirement of a premarket approval

application. Another 14 years would pass before they returned to where they had been in 1993.

And we're not done yet!

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The FDA, in August, 2011, published a notice of a proposed rule to require a premarket approval application or a notice of completion of a product development protocol for CES devices. The notice also stated that manufacturers could submit a petition to reclassify the device. When petitions were submitted by three manufacturers, the agency scheduled the Panel meeting on February 10, 2012, which was discussed on Chapter 1.

On January 22, 2016, nearly four years later, the FDA published the proposed final regulations for CES devices[3]. The notice contained a big surprise: instead of Class II for all three indications for use, they decided that Class II was okay for anxiety and insomnia, but Class III would be needed for depression. Comments were solicited by April 21, 2016.

Why did the FDA decide that CES devices should be in Class III when prescribed for use in treating depression? The Federal Register notice provided the answer. I'll let excerpts from my formal comments on the proposed final regulation explain.

Comments on Docket Number FDA-2014-N-1209[4]

February 24, 2016

Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, rm. 1061
Rockville, MD 20852

Comments on FDA-2014-N-1209

The FDA proposes final regulations for the classification of Cranial Electrotherapy Stimulator (CES) devices for three indications for use: anxiety, insomnia, and depression. (For reference, CES devices were assigned Product Code JXK.)

The Federal Register notice[5] was published on January 22, 2016. The agency decided that Class II is appropriate for anxiety and insomnia, and that Class III is appropriate for depression. I must respectfully disagree with Class III in the case of depression.

The reason for putting CES into Class III for depression is stated in the last sentence of section XI B:

> "FDA believes that the risks to health identified in Section V for the use of CES devices for treating depression, in the absence of an established benefit- risk profile, presents a potential unreasonable risk of illness or injury."

Section V Risks to Health identifies five items: (1) Ineffective treatment, (2) Skin irritation, (3) Headaches, (4) Dizziness, and (5) Electrical shock and burns. Whether these risks rise to the level of unreasonable risk of illness or injury is a matter of opinion. In this case, I beg to disagree with FDA's position, as explained below.

The "absence of a benefit-risk profile" is a red herring. If we make a risk/benefit ratio, a tiny amount of risk might be considered unreasonable in a case where the benefit is extremely small or completely unknown. Mathematically, if the benefit is zero, the risk/benefit ratio is infinite. The fact is, we do not have numbers for either the risk or benefit to plug into the ratio. The general principle is to evaluate the risk and the benefit, making a judgment call whether the risk outweighs the benefit or the benefit outweighs the risk. Although it would be possible to set up a system to quantify risk in benefit in compatible units, I do not believe this has been done for CES devices for any of its indicated uses (or other medical devices, for that matter).

Instead, FDA should apply the facts in relation to the definition of Class III. At the Panel meeting on February 10, 2012, the Panel offered the opinion that CES devices are safe when used as directed, regardless of the indication for use. Moreover, the track record for safety, using data from MAUDE, as discussed below, does not support the conclusion that there is an unreasonable risk of illness or injury.

My argument is simple: I do not believe CES devices satisfy the legal definition of Class III for any of the listed indications for use. (I previously used this argument in Docket Number FDA-2012-P-0493.)

Statement of grounds

I assert that CES devices do not meet the requirements for Class III under the definition of Class III in the Federal Food Drug and Cosmetic Act (FFDCA). The definition of Class III in the FFDCA appears at Title 21 U.S.C. § 360c(1)(C) which states the following:

> (C) CLASS III, PREMARKET APPROVAL.—A device

which because—
(i) it (I) cannot be classified as a class I device because insufficient information exists to determine that the application of general controls are sufficient to provide reasonable assurance of the safety and effectiveness of the device, and (II) cannot be classified as a class II device because insufficient information exists to determine that the special controls described in subparagraph (B) would provide reasonable assurance of its safety and effectiveness, and ← NOTE "AND"
(ii)(I) is purported or represented to be for a use in supporting or sustaining human life or for a use which is of substantial importance in preventing impairment of human health, or
(II) presents a potential unreasonable risk of illness or injury,
is to be subject, in accordance with section 360e of this title, to premarket approval to provide reasonable assurance of its safety and effectiveness.

It is important to note that the definition has two parts, both of which must be satisfied for a device to be in Class III. Let us focus on the second part.

The definition requires that to be in Class III, the device "is purported or represented to be for a use in supporting or sustaining human life" OR
"for a use which is of substantial importance in preventing impairment of human health" OR
"presents a potential unreasonable risk of illness or injury."

Stripped of excess verbiage, a device is in Class III if

> "Insufficient information exists to determine that special controls would provide a reasonable assurance of the safety and effectiveness, AND [Emphasis added]

> the device is life-supporting or life-sustaining, or is for a use which is of substantial importance in preventing impairment of human health, or presents a potential unreasonable risk of illness or injury."

For a medical device to be in Class III, at least one of the three conditions in the second part of the definition must be satisfied, namely, (1) the device is life-supporting or life-sustaining, (2) the device is for a use which is of substantial importance in preventing impairment of human health, or (3) the device presents a potential unreasonable risk of illness or injury. **If none of these conditions is satisfied, the device should be precluded from being in Class III PreMarket Approval, the most demanding of the medical device classes.**

In the January 21 FR notice, FDA asserts CES devices used for depression do present a potential unreasonable risk of illness or injury. This assertion is not supported by the facts. All the reports in the MAUDE system do not add up to unreasonable risk. Moreover, this position contradicts the opinion of the expert Panel. The Neurology Panel at the meeting on February 10, 2012, responded to a series of questions, including question 6, part d, as follows: "Does the available scientific evidence adequately demonstrate the absence of unreasonable risk of illness or injury associated with the use of the device for its intended uses – anxiety, depression, and insomnia in adult substance abuse patients including also the indications that I just posted – and conditions of use?" After the Panel was polled, the Panel Chairman summarized as follows, at page 275 of the meeting transcript:

> "(d), available scientific evidence adequately demonstrate the absence of unreasonable risk, that was yes pretty uniformly throughout the Panel."

I agree with the Panel.

FDA disagrees with the Panel on the level of risk associated with CES devices used to treat the symptoms of depression. What is the basis for their disagreement? The January 21st Federal Register statement attributes it to the lack of a "benefit-risk" profile. The Panel, and the FDA, find the scientific evidence of the effectiveness of CES in the treatment of depression inadequate, yet the agency has permitted manufacturers to offer their devices for anxiety, insomnia, and depression for many years. Presumably, there have been practitioners willing to prescribe the devices for their patients during all those years so it seems likely that the devices have been in distribution in some quantity during that time, giving the public the opportunity to use them. Serious problems with the devices should have come to light by now.

Data from MAUDE

A current search of the MAUDE database reveals there were only 14 reports for JXK devices from January 1, 2000 through January 31, 2016. The most concerning of these reports was filed on February 16, 2015. The report (submitted by the patient's wife) stated the following:

> A psychiatrist recommended the fisher wallace stimulator for my husband's depression. My husband had been previously treated successfully for 24 years with antidepressants. He started using the stimulator at the end of (b)(6) 2014. He was told by the psychiatrist that he would be able to be weaned off his antidepressant. Once he was totally off the antidepressants and solely using the stimulator, he experienced extreme irritability and anxiety. The week before christmas, he started experiencing extreme depression and severe tiredness. On (b)(6) 2014, he took his own life. I feel that the reason that he took his life is due to the fisher wallace stimulator and the false claims of how well it works for depression. Each person has different types of depression caused by many different reasons. I do not believe that this stimulator is safe and effective on just any person diagnosed with depression. I also believe that patients need to be closely supervised while using this product. My husband, sadly, was not.

This is a sad case, but by itself should not be taken as an indictment of the technology. Without more information, it is impossible to say that the CES device was substantially or even partly responsible for the patient's decision to end his life.

The other thirteen reports contain complaints about hearing loss, tinnitus, headaches, and nightmares. These reports need to be evaluated in terms of the incidence of these problems. I do not know how many devices have been used, but would estimate that the incidence of complaints is quite small.

MAUDE reports are potentially useful, but they cannot be relied upon in many cases. The quality of the information contained in them is extremely variable.

The evidence is clear: CES devices do NOT present an unreasonable risk of illness or injury. They do not satisfy the definition of Class III and should not be regulated as Class III devices.

There are concerns by the Panel and the FDA about how effective CES devices are in treatment of depression. Under the proposed special controls, the agency may require the manufacturers of CES devices to provide clinical evidence to support their claims. This can make Class II nearly as demanding as having the device in Class III.

Respectfully submitted,

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As of September, 2017, over 300 comments have been posted at regulations.gov for Docket FDA-2014-N-1209. There are comments from doctors who report favorably on the use of CES in

their practices, as well as many supportive comments from patients. The vast majority of them urge the FDA to classify CES devices in Class II for all three indications for use.

We're still waiting for the FDA to respond.

End Notes for Chapter 15

[1] http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/NeurologicalDevicesPanel/UCM290787.pdf

[2] Ibid, pages 8-9

[3] Federal Register vol. 81 No. 14, Friday, January 22, 2016, pp 3751-3762

[4] Docket Number FDA-2014-N-1209-0025 at www.regulations.gov

[5] Federal Register, Vol. 81, No. 14, Friday, January 26, 2016, pages 3751-3762.