May 25, 2020

Sidney M. Wolfe, MD
Director
Public Citizen's Health Research Group
1600 20th Street NW
Washington, DC 20009

Re: Citizen Petition – Docket Number FDA-2006-P-0143 (2006P-0370/CP1)

Dear Dr. Wolfe:

This letter responds to your petition, dated September 6, 2006, regarding the Vagus Nerve Stimulation (VNS) device for the management of treatment-resistant depression (TRD). Your petition requests that the Food and Drug Administration (FDA or Agency) revoke its premarket application (PMA) approval of the VNS device for the management of TRD because you consider the device to be "ineffective" for TRD and because the device allegedly has not demonstrated a reasonable assurance that it is safe and effective for TRD. Your petition incorporates by reference your September 6, 2006, letter to the Centers for Medicare and Medicaid Services (CMS), and your May 11, 2005, letter to FDA, and you submitted a supplement to this petition dated September 12, 2006. FDA provided an interim response to your petition on March 2, 2007. FDA has reviewed the petition and supplement and is denying them under 21 C.F.R. § 10.30(e)(3). Below we summarize your petition and provide the bases for FDA's decision.

A. Background

The VNS device is a permanent implant consisting of a pulse generator and leads that deliver electrical stimulation to the vagus nerve. FDA approved Cyberonics, Inc.'s (Cyberonics) premarket approval (PMA) application (P970003) for the VNS device in 1997 as an adjunctive therapy for epilepsy to help reduce seizures that could not be fully or adequately controlled by surgery. On October 27, 2003, Cyberonics submitted a PMA supplement (P970003/S050) to FDA for the VNS device to add a new indication for the adjunctive long-term treatment of "treatment-resistant depression" (TRD), *i.e.*, chronic or recurrent depression for patients 18 years of age or older who are experiencing a major depressive episode and have not had an adequate response to four or more adequate antidepressant treatments.

Because the VNS device was a first-of-a-kind device for the management of TRD, FDA held a meeting of a panel of outside experts, the Neurological Devices Panel (Advisory Panel) on June

15, 2004, to consider the approvability of the VNS device as an adjunctive treatment for TRD.[1] The Advisory Panel voted five to two to recommend that FDA approve Cyberonics' PMA supplement with conditions.[2]

During its evaluation of Cyberonics' PMA supplement, FDA considered, in addition to its own analysis, the recommendations from the Advisory Panel, and the arguments made in your May 11, 2005 letter to FDA urging the Agency to reject Cyberonics' PMA supplement on the basis that the efficacy of the VNS device for the management of TRD had not been sufficiently established by the data provided by Cyberonics.[3] FDA disagreed with your assessment of the data provided by Cyberonics for the VNS device for TRD, and approved Cyberonics' PMA supplement on July 15, 2005.[4]

As a condition of approval of the PMA supplement, FDA required Cyberonics to conduct two post-approval studies (PAS): a one-year dosing study, and a five-year patient registry study to further characterize the optimal stimulation dosing and patient selection criteria for the VNS Therapy System for TRD and to evaluate long-term patient outcomes as well as predictors of response to therapy. Cyberonics has completed both studies, and their results, which are described in detail in section C 2, support the existence of a reasonable assurance of safety and effectiveness for the VNS device for the narrow subset of patients for which the device is indicated and provide further valid scientific evidence that this device is not ineffective.

Consideration of postmarket controls – such as the two PAS required by FDA's approval of the VNS device for the management of TRD – is an important component of FDA's PMA review of devices. Congress has directed the Agency to consider its postmarket authorities when making premarket determinations about the effectiveness of devices. Section 513(a)(3)(C) of the FD&C Act provides:

> In making a determination of a reasonable assurance of the effectiveness of a device for which [a PMA application] has been submitted, the Secretary shall consider whether the extent of data that otherwise would be required for approval with respect to effectiveness can be reduced through reliance on postmarket controls.[5]

Consistent with this Congressional directive, FDA evaluated a number of considerations in making its decision to approve the VNS device for the management of TRD, including Cyberonics' postmarket plan.

At the time of approval, FDA determined that the totality of the evidence demonstrated a reasonable assurance of safety and effectiveness of the VNS device for a narrow subset of patients, 18 years of age or older, with major depressive disorder who have chronic or recurrent

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[1] A brief summary of the Advisory Panel meeting is available at https://wayback.archive-it.org/7993/20170405192730/https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/NeurologicalDevicesPanel/ucm124784.htm

[2] *Id.*

[3] A copy of the May 11, 2005 letter is attached to the petition.

[4] *See* Approval Letter from FDA to Cyberonics, *available at* https://www.accessdata.fda.gov/cdrh_docs/pdf/P970003S050A.pdf.

[5] 21 U.S.C. 360c(a)(3)(C).

treatment-resistant depression and have failed at least four antidepressant treatments.[6] Although the VNS device was not shown to be effective for the management of TRD in a randomized controlled trial, a randomized controlled trial is only one way to collect valid scientific data.[7] The agency determined that Cyberonics provided reasonable assurance of safety and effectiveness of the VNS device for the management of TRD because it provided (1) data that were systematically collected and analyzed which showed that, in a definable subset of the at-risk, treatment-resistant target population, the use of the VNS device produced statistically and clinically significant improvement from baseline over one and two years;[8] and (2) evidence regarding the safety of the VNS device, as well as the risks of non-treatment in the subject population, which demonstrated that the probable benefits of the device outweighed any probable risks to the indicated population, which is an at-risk population resistant to conventional treatment.

B. Standard for PMA Withdrawal

You submitted your petition pursuant to Title 21 of the Code of Federal Regulations (CFR) 10.30 and requested that FDA "reverse the approval" of the VNS device for the management of TRD. Consequently, FDA interprets your petition as requesting that the agency withdraw its July 15, 2005 approval of Cyberonics' PMA supplement[9]. The Federal Food, Drug, and Cosmetic Act (FD&C Act) section 515(e)(1) and 21 CFR 814.46(a) set forth the standards for FDA's withdrawal of approval of a PMA, including, among others, the following:

- The device is unsafe or ineffective under the conditions of use prescribed, recommended, or suggested in the labeling of the device; or

- On the basis of new information with respect to the device, evaluated together with the evidence available when the application was approved, there is a failure to show reasonable assurance that the device is safe or effective under the conditions of use prescribed, recommended, or suggested in the labeling of the device.

As discussed below, the arguments and evidence presented in your petition do not establish any basis for the Agency to withdraw its approval of the VNS device for the management of TRD.

C. Bases for FDA's Decision

You argue in your petition that FDA should withdraw its approval of the VNS device for the management of TRD because the device is "ineffective," and because the device has not

[6] *See* 21 CFR 860.7(d)(1) and (e)(1).
[7] *See* 21 CFR 860.7(f)(1)(iv) (permitting scientific evidence to be collected through "[a] comparison of the result of treatment or diagnosis with a control in such a fashion as to permit quantitative evaluation").
[8] Cyberonics also provided comparative data against a reasonably matched control which also showed sustained improvement over time.
[9] Because it was submitted more than 30 days after FDA's approval of Cyberonics' PMA supplement, and does not reference 21 CFR 10.33, FDA does not interpret your petition as requesting that the Agency reconsider that approval of Cyberonics' PMA supplement. *See* 21 CFR 10.33 (stating that an "interested person may request reconsideration of part or all of [an Agency] decision" by submitting a petition "no later than 30 days after the date of the decision involved"). Therefore, the Agency is not reconsidering its approval of Cyberonics' PMA supplement.

demonstrated a reasonable assurance that it is safe and effective for TRD. The Agency disagrees with your contentions because (1) you have presented no evidence demonstrating that the VNS device is ineffective for the management of TRD, or any new evidence demonstrating a lack of a showing of reasonable assurance of safety and effectiveness for the device; and (2) the results of the two PAS required by the approval constitute additional valid scientific evidence supporting a reasonable assurance of safety and effectiveness for the VNS device for the management of TRD and FDA's decision to approve it for this use.

1. Failure to Demonstrate Ineffectiveness or Provide New Information Demonstrating a Lack of Reasonable Assurance of Safety and Effectiveness

In support of your petition requesting withdrawal of approval of the VNS device for TRD, you neither provide evidence demonstrating that the VNS device is ineffective under the conditions of use prescribed, nor provide new evidence (which includes a reevaluation of the data submitted by Cyberonics)[10] to establish that there is a lack of a showing of reasonable assurance that the device is safe or effective under the conditions of use prescribed. Instead, you reference the February 2006 report prepared by the United States Senate Committee on Finance titled, "Review of the FDA's Approval Process for the Vagus Nerve Stimulation Therapy System for Treatment-Resistant Depression," which details procedural irregularities and internal FDA disagreement prior to approval of the device for TRD. You contend that "given the highly irregular aspects of the approval process at the FDA, it is appropriate that the FDA revisits its ill-advised decision to approve VNS for TRD. To have an ineffective device on the market… does no favors for those suffering from TRD."[11] You also incorporate by reference your criticisms of Cyberonics' data that you previously submitted to FDA prior to approval of the device for TRD, and, from your letter to CMS, your criticisms of articles touting the benefits of VNS for TRD. Just because there was some disagreement among Agency personnel regarding whether to approve the VNS device for the management of TRD,[12] and even assuming there were also procedural irregularities during the approval process, it does not follow that the VNS device is ineffective for TRD, or that it lacks a reasonable assurance of safety or effectiveness. You do not explain how any of the findings in the Congressional report support withdrawal of approval under the applicable bases for withdrawal.

Your criticisms of the journal articles published after approval of the VNS device for TRD, and that were not a consideration in FDA's initial approval decision, also do not provide a basis for withdrawal of approval. The article by Rush A. J. et al., (Biological Psychiatry (2005), 58, 347-354), presents the result of a short-term (10-week) study and concludes that study did not yield definitive evidence of short-term efficacy for adjunctive VNS in treatment-resistant depression. However, the trial had a variety of issues that called into question its conclusions, including study design, study sample, and treatment delivery. Despite these issues, and the conclusions articulated in the study, the data showed that VNS was associated with greater symptom

[10] *See* 51 Fed. Reg. 26358 (July 22, 1986) ("[T]he 'new information' justifying withdrawal of approval under section 515(e)(1) of the act may be based on a reevaluation of the data and information upon with approval was based.").
[11] *See* Petition at 2.
[12] FDA makes many approval decisions yearly on medical devices. There are occasions when the final Agency decision to approve a device diverges from the recommendation of some of the individuals in the review process.

reduction, and the authors indicated that longer treatment with VNS may be necessary to achieve clinically meaningful benefits. Similarly, a one year treatment comparison study reported by George M.S. et al, (Biological Psychiatry (2005), 58, 364-373) showed VNS with treatment as usual for TRD was associated with a greater antidepressant benefit over 12 months.
Finally, with respect to your criticisms of Cyberonics' data in your May 11, 2005 letter to FDA, which you incorporate by reference into both of your September 6, 2006, letters to FDA and CMS, these letters are not new information, nor do they demonstrate that the VNS device is ineffective for the management of TRD – particularly in light of the data generated by the PAS. FDA considered these letters and the arguments contained therein prior to its approval of the VNS device for TRD, and FDA is not going to revisit them now. As explained above, this is not a reconsideration of FDA's 2005 PMA approval decision, but rather an evaluation of whether, at the present time, any grounds for withdrawal of approval under section 515(e) of the FD&C Act exist, and your letters present no basis for withdrawal.

2. Post-Approval Studies

As stated above, as conditions of FDA's approval, the Agency required Cyberonics to conduct two PAS to collect data on the long-term safety and effectiveness of the VNS device for the management of TRD.

In accordance with the conditions of FDA's approval, Cyberonics has completed both studies, and their results support the existence of a reasonable assurance of safety and effectiveness for the VNS device for the narrow subset of patients for which the device is indicated, and provide further valid scientific evidence that this device is not ineffective.

Cyberonics has completed a one-year dosing study of 331 patients.[13] The results of the dosing study fail to demonstrate a difference between different doses; however, the effectiveness results and the safety profile of the device are consistent with and confirm Cyberonics' premarket data. Cyberonics has also completed a five-year patient registry study which included 795 patients (494 patients receiving VNS therapy and 301 patients not receiving it), and submitted a 10-year final report dated July 30, 2015.[14] The final report suggests that the safety and effectiveness profile of the VNS device with respect to the VNS therapy group is better than that of the treatment as usual control (non-VNS treated group). Although the follow-up rate of subjects was only about 40-50%, patients in the VNS therapy group experienced a greater than 50% reduction in all-cause mortality and completed suicides as compared with patients in the control group. A total of 8 patients in the control group and 7 patients in the VNS therapy group died during the trial. Of these, 4 (57%) deaths were considered suicides, 2 in the control group and 2 in the VNS therapy group. A higher response rate based on the Montgomery-Asberg Depression Rating Scale was observed in the VNS therapy group vs. control group. Patients in the VNS therapy group experienced statistically significant benefits compared to patients in the control group for

[13] The final study results are available on the PAS webpage at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma_pas.cfm?t_id=102621&c_id=207#tt
[14] The final report is available at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma_pas.cfm?t_id=102621&c_id=21#tt

13 out of 15 clinical outcomes measured and for 2 of the 4 quality of life or health outcomes measured.

Conclusion

Based on the available evidence, FDA denies your petition to withdraw the indication of the VNS device for the management of TRD. Your petition demonstrates no grounds for the Agency to withdraw its approval of the VNS device for the management of TRD pursuant to section 515(e)(1).

If you have any questions, please contact Madhusoodana Nambiar by e-mail at madhusoodana.nambiar@fda.hhs.gov or (301) 796-5837.

Sincerely,

Ellen J. Flannery -S

Digitally signed by Ellen J. Flannery -S
Date: 2020.05.25 16:58:17 -04'00'

Ellen J. Flannery, J.D.
Deputy Center Director for Policy
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