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COMMITTEE STAFF REPORT TO THE CHAIRMAN AND RANKING MEMBER

REVIEW OF THE FDA'S APPROVAL PROCESS FOR THE VAGUS NERVE STIMULATION THERAPY SYSTEM FOR TREATMENT-RESISTANT DEPRESSION

PREPARED BY THE STAFF OF THE

COMMITTEE ON FINANCE
UNITED STATES SENATE

CHARLES E. GRASSLEY, *Chairman*
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I. Executive Summary

The United States Senate Committee on Finance (Committee) has exclusive jurisdiction over the Medicare and Medicaid programs. Accordingly, the Committee has a responsibility to the more than 80 million Americans who receive health care coverage under Medicare and Medicaid to oversee the proper administration of these programs, including the payment for medical devices regulated by the Food and Drug Administration (FDA). Given the rising health care costs in this country, and more importantly, in the interest of public health and safety, Medicare and Medicaid dollars should be spent on drugs and devices that have been appropriately deemed safe and effective for use by the FDA, in accordance with all laws and regulations.

In February 2005, Senator Charles Grassley (R-IA) and Senator Max Baucus (D-MT), Chairman and Ranking Member of the Committee, initiated an inquiry into the FDA's handling of Cyberonics, Inc.'s (Cyberonics) pre-market approval application to add a new indication—treatment-resistant depression (TRD)—to Cyberonics's Vagus Nerve Stimulation (VNS) Therapy System, an implanted pulse generator. The Chairman and Ranking Member initiated the inquiry in response to concerns that were raised regarding Cyberonics's VNS Therapy System for TRD. On July 15, 2005, the FDA approved the device for TRD.

The investigative staff of the Committee reviewed documents and information obtained and received from the FDA and Cyberonics and found the following:

- As the federal agency charged by Congress with ensuring that devices are safe and effective, the FDA approved the VNS Therapy System for TRD based upon a senior official overruling the comprehensive scientific evaluation of more than 20 FDA scientists, medical officers, and management staff who reviewed Cyberonic's application over the course of about 15 months. The official approved the device despite the conclusion of the FDA reviewers that the data provided by Cyberonics in support of its application for a new indication did not demonstrate a reasonable assurance of safety and effectiveness sufficient for approval of the device for TRD.
- The FDA's formal conclusions on safety and effectiveness do not disclose to doctors, patients or the general public the scientific dissent within the FDA regarding the effectiveness of the VNS Therapy System for TRD. The FDA has publicized differences of scientific opinion within the agency when it has announced other controversial regulatory decisions. Throughout the review of Cyberonics's application, the team of FDA scientists, medical officers, and management staff involved recommended that the device not be approved for TRD. However, at every stage of the review, the team was instructed by the

FDA official, who ultimately made the decision to approve the device, to proceed with the next stage of pre-market review.

- The FDA has not ensured that the public has all of the accurate, science-based information regarding the VNS Therapy System for TRD it needs. Health care providers relying on the FDA's public information on the safety and effectiveness of this device may not be able to convey complete risk information to their patients, because not all of the relevant findings and conclusions regarding the VNS Therapy System have been made available publicly.

The FDA has an important mission:

> The FDA is responsible for protecting the public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, our nation's food supply, cosmetics, and products that emit radiation. The FDA is also responsible for advancing the public health by helping to speed innovations that make medicines and foods more effective, safer, and more affordable; and helping the public get the accurate, science-based information they need to use medicines and foods to improve their health.[1]

As part of that mission, the FDA weighs the risks and benefits of a product, in this case a medical device, to determine if the product is reasonably safe and effective for use.

The facts and circumstances surrounding the FDA's approval process for the VNS Therapy System for TRD raise legitimate questions about the FDA's decision to approve that device for the treatment of TRD. While all implantable medical devices carry risks, it is questionable whether or not the VNS Therapy System for TRD met the agency's standard for safety and effectiveness. The FDA's approval process requires a comprehensive scientific evaluation of the product's benefits and risks, including scientifically sound data supporting an application for approval. Otherwise health care providers and insurers as well as patients may question the integrity and reliability of the FDA's assessment of the safety and effectiveness of an approved product. In the case of VNS Therapy for TRD, the FDA reviewers concluded that the data limitations in Cyberonics's application could only be addressed by conducting a new study prior to approval. However, in the present case, instead of relying on the comprehensive scientific evaluation of its scientists and medical officers, it appears that the FDA lowered its threshold for evidence of effectiveness. Contrary to the recommendations of the FDA reviewers, the FDA approved the VNS Therapy System for TRD and allowed Cyberonics to test its device post-approval.

In addition, given the significant scientific dissent within the FDA regarding the approval of the VNS Therapy System for TRD, the FDA's lack of transparency with respect to its review of the device is particularly troubling. The FDA has limited the kind and quality of information publicly available to patients and their doctors and deprived them of information that may be relevant to

[1] *http://www.fda.gov/opacom/morechoices/mission.html.*

their own risk-benefit analysis. Patients and their doctors should have access to all relevant findings and conclusions from the comprehensive scientific evaluation of the safety and effectiveness of the VNS Therapy System for TRD to enable them to make fully informed health care decisions.

II. Introduction

The United States Senate Committee on Finance (Committee) has exclusive jurisdiction over the Medicare and Medicaid programs. Accordingly, the Committee has a responsibility to the more than 80 million Americans who receive health care coverage under Medicare and Medicaid to oversee the proper administration of these programs. Given the rising health care costs in this country, and more importantly, in the interest of public health and safety, Medicare and Medicaid dollars should be spent on drugs and medical devices that have been appropriately approved by the Food and Drug Administration (FDA), based on a comprehensive scientific evaluation of the product's benefits and risks, in accordance with all laws and regulations.

On July 15, 2005, the FDA approved Cyberonics, Inc.'s (Cyberonics or the sponsor[2]) Vagus Nerve Stimulation Therapy System (VNS Therapy System) for a new indication, the first medical device for treatment-resistant depression (TRD). Medicare and Medicaid currently cover the VNS Therapy System, including programming and implantation of the device, for the treatment of epilepsy, the first indication for which the device was approved. Cyberonics expects that within a year both programs will also cover the device for TRD.[3]

Senator Charles Grassley (R-IA) and Senator Max Baucus (D-MT), Chairman and Ranking Member of the Committee, began an inquiry related to the VNS Therapy System for TRD in February 2005, after allegations of problems with the FDA's review of Cyberonics's device were brought to the attention of the Committee. To review these allegations, the Chairman and Ranking Member initiated an inquiry and sent a letter to the FDA regarding the FDA's review of Cyberonics's pre-market approval application supplement (PMA-S or application) for the use of the VNS Therapy System for TRD (the sponsor's PMA-S) in March 2005.

This Committee Staff Report to the Chairman and Ranking Member (Report) presents the information and findings compiled by the investigative staff of the Committee (Committee Staff) based on interviews and the review of documents and information obtained by and provided to the Committee regarding the VNS Therapy System. Appendices to the Report include: correspondence between the Chairman and Ranking Member and the FDA, documentation of the FDA's internal and external communications regarding the sponsor's PMA-S, and related materials posted on the FDA website. The Table of Contents contains a list of documents

[2] Under 21 C.F.R. §3.2, the term "sponsor" has the same meaning as "applicant," any person who submits or plans to submit an application to the Food and Drug Administration (FDA) for pre-market review. The sponsor is usually the manufacturer of the product under review, in this case a medical device manufacturer. Under 21 C.F.R. §812.3, a sponsor is also a person who initiates the clinical studies to determine the safety or effectiveness of a device.

[3] Dow Jones/AP, "FDA approves implant against depression," July 15, 2005, available at *http://www.chron.com/disp/story.mpl/tech/news/3268114.html,* last accessed on January 18, 2006.

in the Appendices. A timeline of major events related to the FDA's review of the sponsor's PMA-S for the VNS Therapy System are also included at the end of this Report.

III. Scope and Methodology

During the course of its inquiry, the Committee Staff obtained numerous documents related to the FDA's review of Cyberonics's PMA-S for the VNS Therapy System for TRD, including documents that contain clinical data submitted by the sponsor to the FDA as part of its application. The Committee Staff did not independently assess the validity of the data submitted or determine whether or not the sponsor met the FDA's standards for approval of the VNS Therapy System. The purpose of the Chairman and Ranking Member's inquiry was to address the allegations, examine the FDA's review of the sponsor's PMA-S, and consider whether or not Medicare and Medicaid dollars should be spent on a drug or device because it has received FDA approval.

In addition, several individuals who were interviewed by the Committee Staff raised concerns about the FDA's process for pre-market review and post-market surveillance of medical devices generally. A range of allegations regarding the FDA and Cyberonics as well as medical devices in general were brought to the attention of Committee Staff; however, this Report is limited to those allegations most germane to the Committee Staff's initial review of the FDA's approval process for the VNS Therapy System for TRD. Other allegations may be addressed at a later date. This Report focuses solely on matters and events related to the sponsor's PMA-S and how the FDA made the decision to approve the VNS Therapy System for TRD.

By letters dated March 11, April 19, May 17, May 27, July 7, and July 28, 2005, the Chairman and Ranking Member requested from the FDA documents and information related to the FDA's review and approval of the VNS Therapy System for TRD, as well as interviews with FDA staff involved in the review.[4] The Committee Staff review was conducted from February through September 2005.

In conducting the inquiry, the Committee Staff:

- Interviewed eleven FDA employees; six of whom were directly involved in the review of the VNS Therapy System for TRD and internal deliberations regarding the sponsor's PMA-S.
- Reviewed documents provided by the FDA, which were created during the course of the FDA's review of the sponsor's PMA-S.
- Reviewed documents from the sponsor, which were produced voluntarily to the Committee by the sponsor, including filings in support of its PMA-S, e-mail communications, meeting minutes, and other documentation of internal communications, as well as communications between the FDA and the sponsor related to the review of the VNS Therapy System for TRD.

[4] Letters from the Chairman and Ranking Member of the Committee to the FDA, *see* Appendix A.

- Examined FDA regulations regarding medical device review, documentation of contacts with sponsors, and conditional approvals.

IV. Background

A. Vagus Nerve Stimulation Therapy System

The VNS Therapy System is an implanted vagus nerve stimulator.[5] The FDA initially approved the VNS Therapy System in July 1997 for epilepsy to help reduce seizures that could not be fully or adequately controlled by drugs or surgery.[6] By letter dated July 15, 2005, the FDA approved the VNS Therapy System "indicated for the adjunctive long-term treatment of 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."[7]

The FDA website (*www.fda.gov*) provides an overview of the VNS Therapy System, which consists of a pulse generator that is surgically implanted under the skin of the left chest and an electrical lead that is connected from the generator to the left vagus nerve. Electrical signals are sent from the battery-powered generator to the vagus nerve via the lead. To turn the stimulator off, the patient holds a magnet over the pulse generator. The overview provides information regarding usage of the device:

> The device is to be used only in patients 18 years of age or over with treatment-resistant depression. These are patients who have been treated with, but failed to respond to, at least 4 adequate medication and/or [electroconvulsive therapy] ECT[8] treatment regimens prescribed by their physician. It is not intended to be used as a first-line treatment, even for patients with severe depression. It should be prescribed and monitored only by physicians who have specific training and expertise in the management of treatment-resistant depression and the use of this device. It should be implanted only by physicians who are trained in surgery of the carotid sheath and have received specific training in the implantation of the device. . . . The device cannot be used in patients who have had their vagus nerve cut or will be exposed to diathermy.[9]

According to the physician and patient labeling for the VNS Therapy System for TRD, commonly reported side effects associated with the use of the device in epilepsy patients and patients with depression include voice alteration, increased cough, dyspnea (shortness of breath), neck pain, and dysphagia (difficulty swal-

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[5] FDA's overview of the VNS Therapy System, *see* Appendix B; also available at *http://www.fda.gov/cdrh/mda/docs/p970003s050.html.*

[6] FDA's July 16, 1997, press release on the approval of the VNS Therapy System for the treatment of epilepsy, *see* Appendix F; also available at *http://www.fda.gov/bbs/topics/NEWS/NEW00576.html.*

[7] Approval letter issued to the sponsor on July 15, 2005, *see* Appendix B; also available at *http://www.fda.gov/cdrh/PDF/p970003s050a.pdf.*

[8] Electroconvulsive therapy is a type of shock therapy that involves a brief electrical shock that is applied to the head to induce a short seizure. For more information, *see http://www.nlm.nih.gov/medlineplus/ency/article/003324.htm.*

[9] Available at *http://www.fda.gov/cdrh/mda/docs/p970003s050.html; see also* Appendix B.

lowing).[10] Serious adverse events that have been reported include death, cardiac events, vocal cord paralysis, sleep apnea,[11] and worsening depression.

B. Major Events Related to the Approval of the Vagus Nerve Stimulation Therapy System for Treatment-Resistant Depression

On October 27, 2003, the sponsor submitted a PMA-S to the FDA to add treatment-resistant depression as a new indication for the VNS Therapy System. Once a device has been cleared through the PMA process, a device manufacturer can file additional information with the FDA as a supplement to the original PMA to demonstrate that an already-approved device is safe and effective for a new indication.[12] In the case of the VNS Therapy System, the original PMA was approved in 1997 for commercial distribution of the device for the treatment of epilepsy.

In 1997, Congress also passed the Food and Drug Administration Modernization Act (FDAMA) to streamline the FDA approval process for medical devices,[13] among other things, to "ensure the timely availability of safe and effective new products that will benefit the public." According to FDA guidance on the new provisions that were added to the Federal Food, Drug, and Cosmetic Act as a result of FDAMA, "While Congress wanted to reduce unnecessary burdens associated with the premarket clearance and approval processes, Congress did not lower the statutory criteria for demonstrating . . . reasonable assurance of safety and effectiveness."[14]

The FDA's standard for approval of an implantable device is "reasonable assurance of safety and effectiveness."[15] The FDA considers there to be a reasonable assurance of safety when it can be determined that the probable benefits to health that result from the use of the device as directed by the sponsor and accompanied by adequate instructions for use and warnings against unsafe use outweigh any probable risks.[16] The FDA considers there to be a reasonable assurance of effectiveness when, based upon valid scientific evidence, the use of the device in a significant portion of the target population according to the sponsor's instructions will produce clinically significant results.[17]

Once the FDA receives a PMA-S, a team of FDA scientists and medical officers is assigned to review the application. The review team assigned to Cyberonics's PMA-S consisted of more than a dozen FDA scientists and medical officers from the Center for De-

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[10] The Physician and Patient Labelings for the VNS Therapy System for TRD are available at *http://www.fda.gov/cdrh/PDF/P970003S050.html; see also* Appendix B.

[11] According to the National Institutes of Health's National Institute of Neurological Disorders and Stroke, sleep apnea is a common sleep disorder characterized by brief interruptions of breathing during sleep. For more information, *see http://www.ninds.nih.gov/disorders/sleep_apnea/sleep_apnea.htm.*

[12] 21 C.F.R. § 814.39(a)(1), *see* Appendix C; *see also* Congressional Research Service, *The U.S. Approval Process for Medical Devices: Legislative Issues and Concerns with the Drug Model,* RL32826 (March 23, 2005), available at *http://www.congress.gov/erp/rl/pdf/RL32826.pdf.*

[13] Pub. L. No. 105–115, 111 Stat. 2296, 2336–2338.

[14] Food and Drug Administration, "The Least Burdensome Provisions of the FDA Modernization Act of 1997: Concept and Principles; Final Guidance for FDA and Industry," October 4, 2002, *see* Appendix I; also available at *http://www.fda.gov/cdrh/ode/guidance/1332.pdf.*

[15] 21 C.F.R. § 860.7, *see* Appendix C.

[16] 21 C.F.R. § 860.7(d)(1), *see* Appendix C.

[17] 21 C.F.R. § 860.7(e)(1), *see* Appendix C.

vices and Radiological Health (CDRH)[18] and the Center for Drug Evaluation and Research (CDER).[19] This team included neurosurgeons, neurologists, psychiatrists, statisticians, epidemiologists, and adverse events analysts. Management staff of the Restorative Devices Branch, the Division of General, Restorative and Neurological Devices (DGRND), and the Office of Device Evaluation (ODE) in CDRH and the Division of Neuropharmacological Drug Products[20] and the Office of Drug Evaluation I in CDER were also involved in the review of the sponsor's PMA-S.

After a sponsor submits its PMA-S, the review team determines whether or not that sponsor provided the required administrative components of the PMA-S. The FDA has 45 days to make sure an application is administratively complete.[21] If an application is complete, the FDA formally files it and begins its substantive review. By letter dated December 15, 2003, the FDA informed Cyberonics that its PMA-S was suitable for filing[22] and granted expedited review because "the VNS Therapy System has the potential of providing therapeutic benefits . . . in the treatment of patients who are intolerant or resistant to other legally marketed therapies."[23] FDA guidance states that a device is appropriate for expedited review if the device is (1) intended to treat or diagnose a life-threatening or irreversibly debilitating disease or condition, and (2) addresses an unmet medical need.[24]

The CDRH website states that during the PMA review process, the FDA notifies a sponsor by major/minor deficiency letters of any information needed by the FDA to complete its review. In addition, a sponsor can request a meeting with the FDA within 100 days of the filing of its application to discuss the status of the FDA's review.[25] According to the FDA review team leader for Cyberonics's PMA-S, on February 4, 2004, 100 days after the sponsor filed its application, the FDA held a meeting with the sponsor to discuss concerns or questions related to the sponsor's PMA-S. The team leader stated that the sponsor did not address all the concerns discussed during the 100-day meeting; and that the 23 concerns not addressed were identified in a major deficiency letter that the FDA sent to the sponsor on March 1, 2004. In that letter, the FDA stat-

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[18] Members of the review team include staff from the Division of General, Restorative and Neurological Devices in the Office of Device Evaluation, the Division of Bioresearch Monitoring in the Office of Compliance, and the Division of Biostatistics and Surveillance and the Division of Postmarket Surveillance in the Office of Surveillance and Biometrics. *See* CDRH organizational chart, Appendix K.

[19] Members of the review team include staff from the Division of Neuropharmacological Drug Products in the Office of Drug Evaluation I.

[20] In the summer of 2005, the Division of Neuropharmacological Drug Products was split into two divisions within the Office of Drug Evaluation I, the Division of Neurology Products and the Division of Psychiatry Products.

[21] 21 C.F.R. § 814.42(a), *see* Appendix C.

[22] The filing date is the date on which the FDA received the sponsor's PMA-S, October 27, 2003.

[23] Letter to the Director and Senior Counsel, Regulatory Affairs, Cyberonics, Inc. signed by the Director of the Division of General, Restorative and Neurological Devices, Office of Device Evaluation, CDRH, December 15, 2003, *see* Appendix E.

[24] Food and Drug Administration, U.S. Department of Health and Human Services, "Guidance for Industry and FDA Staff: Expedited Review of Premarket Submissions for Devices," November 26, 2003, available at *http://www.fda.gov/cdrh/mdufma/guidance/108.html.*

[25] CDRH Device Advice website, *http://www.fda.gov/cdrh/devadvice/pma/review_process.html; see also* Appendix I.

ed that its review of the PMA-S could not continue until the sponsor addressed the 23 deficiencies described therein.[26]

Once a sponsor addresses the concerns and questions identified in a major deficiency letter, the review team can complete its initial review of the PMA-S and determine whether or not to proceed with an advisory panel to obtain input and recommendations from outside experts on the approvability of the device.[27] In the case of VNS Therapy, the Committee Staff were told that the review team did not believe that the sponsor had satisfactorily addressed all of the deficiencies. However, the Director of ODE, who became the Acting Director of CDRH in May 2004 and the Director in August 2004, instructed the review team to proceed with an advisory panel meeting. On June 15, 2004, the FDA Neurological Devices Panel was held to address several questions from the FDA regarding the sponsor's PMA-S, including whether or not the clinical data in the PMA-S provided a reasonable assurance of safety and effectiveness.[28] The panel recommended, by a vote of five to two, that the device be approved with the following conditions:

> (1) Patients should fail four or more traditional treatment modalities for TRD (*i.e.*, antidepressant medications or electroconvulsive therapy (ECT)) before using the VNS Therapy System for TRD.
>
> (2) The device should be implanted by surgeons with appropriate training.
>
> (3) Training regarding the programming of the device should be provided to primary care providers.
>
> (4) The product should have additional patient labeling to inform patients completely of the risks and benefits involved in having the device implanted and an identification card should be provided to patients that indicate they have the device implanted.

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[26] For example, the FDA stated that according to the National Depressive and Manic Depressive Association Consensus panel, "patients with mood disorders have inherently high placebo response rates, and without a placebo (control) or valid alternative method, . . . most findings are difficult to interpret." Because the sponsor's only placebo-controlled study failed, the FDA asked the sponsor to provide any additional information that would address the potential bias that may occur from a placebo effect. *See* Appendix E for the text of the major deficiency letter. A "placebo" is an inactive substance or treatment against which investigational treatments are compared for efficacy and safety. A "placebo-controlled study" is a study in which an inactive substance or treatment (placebo) is given to one group of patients, while the treatment being tested is given to another group. High placebo response rate, or "placebo effect" is a physical or emotional change, such as an improvement in health or alleviation of symptoms, that is not the result of any special property of the treatment received but may occur because individuals expect or believe that the treatment will work.

[27] *See* Congressional Research Service, *The U.S. Approval Process for Medical Devices: Legislative Issues and Concerns with the Drug Model,* RL32826 (March 23, 2005), available at *http://www.congress.gov/erp/rl/pdf/RL32826.pdf.* According to the CDRH Device Advice website on the PMA review process, all PMAs for a first-of-a kind device are generally referred to an advisory panel for review and recommendation. Once the FDA believes that "(1) the pertinent issues in determining the safety and effectiveness for the type of medical device are understood and (2) FDA has developed the ability to address those issues," future PMAs for that type of device are not taken before a panel unless there is an issue that can be best addressed through panel review. *See http://www.fda.gov/cdrh/devadvice/pma/review_process.html.* A copy of the review process overview is included in Appendix I.

[28] The other questions were: (1) whether or not data that are not derived from a randomized study affect the evaluation of the effectiveness of the VNS Therapy System for TRD, *i.e.*, a study where the subjects are randomly assigned to VNS Therapy and no VNS Therapy; (2) whether or not the clinical outcomes of one of the sponsor's major studies were the result of a "placebo effect"; and (3) whether or not the use of antidepressant medications and electroconvulsive therapy in conjunction with VNS Therapy impact the interpretation of the study results on the effectiveness of the VNS Therapy System for treatment-resistant depression. *See* Appendix G for the list of panel questions.

(5) A patient registry to collect clinical data should be established.

(6) The patient labeling should be revised regarding, among other things, the description of the 12 month open label follow-up study and the variable effect of treatment.[29]

The FDA considers an advisory panel's recommendations in deciding whether or not to approve a device; however, panel recommendations are not binding. In this case, although the advisory panel recommended conditional approval, the FDA issued a not approvable letter to the sponsor on August 11, 2004.[30] According to the FDA, a not approvable letter means that the FDA found the data provided by the sponsor insufficient to establish that there is a reasonable assurance that the device is safe and/or effective for the use(s) specified in the sponsor's application.

FDA regulations state that, after a sponsor receives a not approvable letter, the sponsor may amend its PMA as outlined in the not approvable letter, request an administrative review by filing a petition for reconsideration under 21 C.F.R. § 10.33, or withdraw its application.[31] The FDA Ombudsman for CDRH informed the Committee Staff that, in practice, the sponsor has several options if it wants to continue to seek approval for its product. The sponsor can submit an amendment to the PMA-S to address the problems identified in the not approvable letter; the sponsor can petition the FDA to reconsider its decision; the sponsor can appeal up the supervisory chain; or the sponsor can file a formal appeal of the decision to the dispute resolution panel.[32]

In this case, Cyberonics requested that the FDA reconsider the not approvable decision, but after examining additional data provided by the sponsor, the ODE Director concluded that there was no basis for reconsideration. Consequently, on September 23, 2004, the sponsor submitted an amendment to its PMA-S (Amendment) to address the deficiencies identified in the August 11, 2004 not approvable letter. The Amendment included analyses of additional data from studies conducted by the sponsor to examine the responses of TRD patients to VNS Therapy.

In addition to its Amendment, on September 10, 2004, the sponsor submitted a request for a Treatment Investigational Device Exemption (Treatment IDE) to the FDA. A Treatment IDE allows a device that is not yet approved for marketing to be used to treat patients with a serious or immediately life-threatening disease or condition when no comparable or satisfactory alternative device or treatment is available. "The purpose is to facilitate the availability of promising new devices to desperately ill patients as early in the device development process as possible, . . . and to obtain additional data on the device's safety and effectiveness."[33] The device must be under investigation in a clinical trial for the same use, or the clinical trials are completed but the sponsor is pursuing marketing approval of the device. The FDA conditionally approved the

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[29] The transcript of the June 15, 2004, Neurological Devices Panel meeting is available at *http://www.fda.gov/ohrms/dockets/ac/04/transcripts/2004-4047t1.htm.*

[30] Not Approvable Letter, *see* Appendix E.

[31] 21 C.F.R. § 814.44(f), *see* Appendix C.

[32] 21 C.F.R. § 10.75, *see* Appendix C; the Ombudsman and several other FDA staff informed the Committee Staff that the last option is rarely used.

[33] 21 C.F.R. § 812.36, *see* Appendix C.

sponsor's Treatment IDE on September 22, 2004. On October 1, 2004, the sponsor submitted an IDE Supplement to address deficiencies identified in FDA's conditional approval, and the FDA approved the IDE Supplement on October 15, 2004.

Over the next few months, the sponsor continued to meet and communicate with FDA officials regarding the Amendment. On December 1, 2004, the CDRH Director convened a meeting between members of the FDA review team and the sponsor's clinical, statistical, legal, and management staff. According to the team leader and DGRND Director, only four members of the review team were invited to the meeting; the management staff at the branch and division levels who were involved in the review of the sponsor's PMA-S were not invited to attend. The purpose of the meeting was to further discuss the deficiencies listed in the August 11, 2004, not approvable letter and consider options to obtain FDA approval, including options for another pre-market study or a commitment from the sponsor to conduct additional studies once the device was approved. After the meeting, the sponsor submitted proposals for a randomized, double-blind[34] comparison study to be conducted post-approval. Based on a review of communications and documents provided to and obtained by the Committee Staff, there were no pre-approval studies proposed or discussed with the sponsor after December.

In addition to the review of a sponsor's PMA, the FDA inspects the sponsor's operations and records to ensure that medical devices are designed, manufactured and distributed in compliance with the Current Good Manufacturing Practices (CGMP) requirements of the Quality System Regulation[35] and other standards. During an interview with Committee Staff, the ODE Director stated that it was not unusual for the FDA to clear a PMA but not approve the device because the sponsor fails an inspection. On December 22, 2004, the FDA issued a warning letter to the sponsor identifying a number of significant violations of the Quality System Regulation, including a failure to establish and maintain adequate procedures for validating device design, failure to completely investigate and evaluate the case of each adverse event, and failure to establish and maintain procedures for implementing corrective and preventive actions.[36] On January 21, 2005, the sponsor submitted its response to the warning letter, and on April 6, 2005, the sponsor was notified that its response was complete.

On February 2, 2005, the FDA issued an approvable letter to the sponsor, which superceded the not approvable letter issued on August 11, 2004.[37] An approvable letter is not a final approval. However, if the FDA determines that the sponsor has met the conditions outlined in the approvable letter, the device can be approved for the specified use. The conditions outlined in Cyberonic's approvable letter included conducting two post-approval studies: (1) estab-

[34] Patients are randomly assigned to different treatment groups, and neither the study investigator nor the patient knows to which treatment group the patient has been assigned.

[35] 21 C.F.R. Part 820.

[36] *See* Appendix E for the full text of the warning letter.

[37] According to FDA regulations, the FDA sends a manufacturer an approvable letter if the manufacturer's application substantially meets the requirements of FDA regulations, and the FDA believes it can approve the application if the manufacturer provides additional information or agrees to certain conditions specified by the FDA, such as product labeling and post-approval requirements, 21 C.F.R. § 814.44, *see* Appendix C.

lishing a registry of 1,000 TRD patients implanted with the vagus nerve stimulator and evaluating their response to the therapy for five years after implantation; and (2) conducting a randomized, double-blind comparison of different output of currents from the device in 450 TRD patients with follow-up for at least one year after implantation to determine the optimal dosage of stimulation in patients with TRD. The FDA also required the sponsor to submit revised physician and patient labelings for the VNS Therapy System for TRD and to address any deficiencies identified during FDA inspections of the sponsor's clinical study sites. In addition, the sponsor was informed that the PMA-S could not be approved until the FDA determined that the manufacturing facilities, methods, and controls complied with the conditions set forth in the sponsor's application and the applicable requirements of the Quality System Regulation.[38]

On July 15, 2005, the CDRH Director signed the approval letter for the VNS Therapy System for TRD. The approval letter allows the sponsor to begin commercial distribution of the VNS Therapy System for TRD; however, as specified in the February 2, 2005 approvable letter, the sponsor must meet certain conditions, including two post-approval studies.[39]

C. Post-Approval Events

Since the approval of the VNS Therapy System for TRD in July 2005, the sponsor has initiated efforts to secure reimbursement for the use of its device to treat TRD. In September 2005, the American Medical Association's Current Procedural Terminology[40] (CPT) Editorial Board approved the use of the same neurostimulator programming codes that are currently being used for VNS Therapy programming services for patients with epilepsy for the treatment of patients with TRD.

In addition, the BlueCross BlueShield Technology Evaluation Center (TEC), which provides scientific opinions regarding the clinical effectiveness and appropriateness of specific medical procedures, devices, and drugs, published its assessment of the VNS Therapy System for TRD in August 2005.[41] The TEC examined the available evidence on the effectiveness of the VNS Therapy System for TRD, including findings from three of the sponsor's clinical studies, and concluded that "Overall, the evidence supporting efficacy of VNS is not strong."[42] Based on the evidence it reviewed, the TEC determined that the VNS Therapy System did not meet

[38] *See* Appendix E for the full text of the approvable letter.

[39] *See* 21 C.F.R. § 814.82, Appendix C.

[40] CPT Codes describe the medical or psychiatric procedures performed by health care providers.

[41] D. Mark, "Vagus Nerve Stimulation for Treatment-Resistant Depression," August 2005, *see* Appendix J; also available at *http://www.bcbs.com/tec/vol20/20_08.html.*

[42] According to the TEC website (*http://www.bcbs.com/tec/*), the TEC uses five criteria to assess whether a technology improves health outcomes: (1) The technology must have final approval from the appropriate governmental regulatory bodies; (2) the scientific evidence must permit conclusions concerning the effect of the technology on health outcomes; (3) the technology must improved the net health outcome; (4) the technology must be as beneficial as any established alternatives; and (5) the improvement must be attainable outside the investigative settings.

all of its criteria for demonstrating that the device improves health outcomes, such as length of life and quality of life.[43]

D. Summary of Cyberonics's Clinical Studies

After a device is approved for marketing by the FDA, a potential new use for the device may be discovered through observations from additional clinical trials or by health care providers in the course of using the device as approved by the FDA or off-label to treat their patients.[44] According to the FDA review team leader on the sponsor's PMA-S, after the VNS Therapy System was approved for epilepsy in 1997, anecdotal reports of mood alteration were noted in some of the epilepsy patients implanted with the vagus nerve stimulator.

To investigate these reports, the sponsor conducted a pilot study (D–01) of 60 patients with treatment-resistant depression to examine their response rates to the device. D–01 was an open-label, nonrandomized, single-treatment arm study—all 60 patients were implanted with the device and were aware that they were receiving VNS Therapy. The study had no control groups, *i.e.,* patients without the device implanted or patients with an inactive device, so patient response rates could not be compared. VNS Therapy was used as an adjunctive treatment, so patients continued their antidepressant medication regimen during the study. The study consisted of a 12-week (after implantation) acute phase and a long-term follow-up. A health care provider-administered screening tool known as the Hamilton Rating Scale for Depression (HRSD) was used to rate the severity of depression; the higher the score, the more severe the depression. The sponsor defined a response to the VNS Therapy System as a 50 percent or greater reduction in the HSRD score. Based on this definition, at the end of 12 weeks, 18 of 59 patients (31 percent) responded to the device. After one and two years of VNS Therapy in conjunction with antidepressant medication and/or ECT treatment regimens, 25 of 55 (45 percent) and 18 of 42 (43 percent) patients, respectively, exhibited a response.[45]

As mentioned previously, a sponsor can file a supplement to an original PMA to obtain approval for a new indication for a device. To obtain FDA approval for the new indication, the sponsor must demonstrate a reasonable assurance that the device is safe and effective for the new indication. According to FDA regulations, reasonable assurance of effectiveness must be based on "valid scientific evidence."[46] Valid scientific evidence consists principally of well-controlled clinical investigations, which include assigning study subjects to tests groups that can be compared. The regulations specify four types of controls to which subjects receiving the treatment under investigation can be compared: (1) no treatment; (2) placebo control, *e.g.,* an implanted device that has not been acti-

[43] The TEC reviewed published and unpublished data related to the clinical outcomes of the VNS Therapy System for TRD. The sponsor's response to the TEC assessment is available on its VNS Therapy for TRD website at *http://www.vnstherapy.com/depression/hcp/ReimbursementIns/data.aspx.*

[44] Physicians use a device "off-label" when they prescribe an FDA-approved product for treatments other than those specified on the product labeling.

[45] *See* Appendix B, Summary of Safety and Effectiveness, p. 68, and Physician Labeling, p. 110.

[46] 21 C.F.R. § 860.7(e), *see* Appendix C.

vated used under conditions that resemble the conditions of use under investigation; (3) active treatment control, *i.e.,* comparison to an effective treatment; and (4) historical control, *i.e.,* comparison to a group of patients receiving no treatment or an established effective regimen who were observed at a previous time.[47]

To address the requirement of "valid scientific evidence," the sponsor conducted a second study, a randomized, placebo-controlled study (D–02), to examine the difference in responses to VNS Therapy over a 12-week period between patients with TRD whose devices were activated compared to those whose devices were not activated. In this first phase of D–02, also known as the acute phase, all study participants were implanted with the device, but 119 patients had the device activated (the treatment group) and 116 patients did not (the placebo control group). The patients were randomly assigned to the treatment group or the control group. Patients were allowed to continue the antidepressant treatments that they were already receiving, but changes to those treatment regimens were not allowed during the course of the study. After 12 weeks, based on the HSRD scores, about 15 percent of the treatment group responded compared to 10 percent of the control group; however, because the difference observed was not "statistically significant," any differences observed between the two groups of patients could have been due to chance rather than a response to the device.

The second phase of D–02 was a long-term follow-up. In this phase, all of the inactive devices that were implanted in the patients during the acute phase of D–02 were turned on, so the study lost its placebo control group. The sponsor used a population of 124 patients from a different study (D–04) to act as a comparison group. D–04 was a long-term, observational study, in which patient responses to the usual standard of care for people with a major depressive episode—antidepressant medications and/or ECT—were observed and noted by the study investigators.

In the long-term phase of D–02, there were no restrictions on changing patients' antidepressant treatment regimens during the course of the study, which were taken in conjunction with VNS Therapy. After 12 months, about 30 percent of the D–02 patients had a 50 percent or greater reduction in their HSRD scores. About 22 percent responded based on a different screening tool used by the sponsor to assess patient response rates, the Inventory of Depressive Symptomatology-Self-Report (IDS-SR). Unlike the HSRD, the IDS-SR is not administered by a health care provider. The response rates for the D–04 patients at 12 months were 12 percent (IDS-SR) and 13 percent (HSRD). In addition, the sponsor examined the level of sustained response in D–02 compared to D–04 patients and found a statistically significant difference between the two groups—13 percent of the D–02 patients evaluated had a sustained response compared to 4 percent in the D–04 group. Sustained response was defined as a 50 percent improvement or better in the IDS-SR scores at 9 months and 12 months.

[47] 21 C.F.R. § 860.7(f), *see* Appendix C.

In addition to the D–02/D–04 comparative study, the sponsor submitted data from three other studies to support its application for FDA approval to market the VNS Therapy System for TRD. D–03 was a Phase IV European post-market study in 47 patients with chronic or recurrent depression.[48] D–05 was not a clinical study but a videotape assessment of D–02 patients, and D–06 was a clinical study examining VNS Therapy in seven patients with bipolar disorder.

The FDA's not approvable and approval decisions regarding the safety and effectiveness of the VNS Therapy System for TRD were based primarily on the FDA's evaluation of data collected from the D–01, D–02 and D–04 studies.[49]

V. Discussion

A. FDA Official Overruled Review Team: Device Approved Despite Team's Objections

In February 2005, after the FDA issued an approvable letter to the sponsor, concerns were raised regarding FDA's review of the sponsor's PMA-S for the VNS Therapy System for TRD. Specifically, it was alleged that the CDRH Director signed an approvable letter despite strong objections from the FDA review team for the sponsor's PMA-S and the DGRND and ODE management staff involved in the review. The FDA reviewers concluded that based on the data provided to the FDA in the PMA-S, the sponsor did not demonstrate a reasonable assurance of safety and effectiveness for approval of the device for TRD. Nevertheless, the CDRH Director decided that the VNS Therapy System should be approved for TRD and the FDA issued an approval letter to the sponsor on July 15, 2005.[50]

In interviews with Committee Staff, the review team leader, the DGRND Director, the ODE Deputy Clinical Director, and the ODE Director all expressed concerns regarding the CDRH Director's decision to conditionally approve the VNS Therapy System for TRD. The review team recommended that the device not be approved for TRD because the team determined, over the course of about 15 months, the sponsor did not provide "a reasonable assurance that the probable benefits to health from use of the device for its intended uses and conditions outweigh the risks associated with its use."[51] According to an FDA medical officer who was involved in the review of the sponsor's PMA-S, "surgically implanted devices

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[48] The VNS Therapy System is approved in the European Union and Canada for use in the treatment of TRD.

[49] *See* Appendix B for the FDA's Summary of Safety and Effectiveness, which provides, among other things, additional results and details from these studies, pp. 68, 71–82.

[50] In the Preamble to a final rule amending the FDA's regulations governing the content and format of labeling for human prescription drug and biological products, the FDA recently asserted the following:

> Under the act and FDA regulations, the agency determines that a drug is approvable based not on an abstract estimation of its safety and effectiveness, but rather on a comprehensive scientific evaluation of the product's benfits and risks under the conditions of use prescribed, recommended, or suggested in the labeling.

Although the final rule relates to drug and biological products, the import of the policy statement articulated by the FDA bears directly on the facts, circumstances, and findings of this Report. *See* "Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products," 71 Fed. Reg. 3922, 3934 (January 24, 2006) (to be codified at 21 C.F.R. pts. 201, 314, and 601).

[51] Final review team memorandum, *see* Appendix D, p. 205.

carry known risks including infection, need for future removal of the device, and injury to structures in and around the operative site (specifically vagal and recurrent laryngeal nerve injury) as well as the risk of anesthesia, which is also significant. In order to outweigh these risks, a device must demonstrate efficacy."[52]

During interviews with Committee Staff, the FDA staff stated that decisions regarding the approval or non-approval of medical devices are typically made at the division level of CDRH, unless the device is the first of its kind or the device is being reviewed for a new indication. Under those circumstances, the ODE Director signs the letter of approval or non-approval, although the ODE Director informed Committee Staff that she typically reads only the review team's internal review memorandum before she makes a decision. The review memorandum documents a team's rationale for recommending approval or non-approval of a device. In the case of VNS Therapy for TRD, the review of the application was elevated from the division level (DGRND), to the office level (ODE), and finally to the center level (CDRH).

The review team's final review memorandum, dated January 6, 2005, recommended that the VNS Therapy System not be approved for TRD.[53] This memorandum was approved and signed by the team leader, the Restorative Devices Branch Chief, the DGRND Deputy Director and Director, and, atypically, included the signature of the ODE Director. The ODE Director informed Committee Staff that the internal review memorandum only provides signature lines for the team leader, branch chief, deputy division director and division director.[54]

Because the review of the sponsor's PMA-S had been elevated to the ODE level, the August 11, 2004, not approvable letter was signed by the ODE Director. During an interview, the ODE Director informed Committee Staff that she added her signature to the review team's January 2005 memorandum when she realized that the Center Director would likely be overriding the not approvable decision.[55] She explained that she wanted to make clear her concurrence with the rest of the review team that the VNS Therapy System for TRD should not be approved because the data provided by the sponsor were insufficient to meet the standard of reasonable assurance of safety and effectiveness.

The review team was not convinced that the additional data provided by the sponsor as part of its Amendment submission were sufficient for approval. After reviewing the data, the review team met on November 10, 2004, to discuss the submission and vote on whether the sponsor's application should be approved, conditionally approved, or considered not approvable. Aside from one abstention, the members of the review team who were present at the meeting unanimously recommended that the device not be approved.[56]

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[52] Post-panel meeting memorandum from a medical officer on the review team to the team leader for the Administrative File of the sponsor's PMA-S, June 22, 2004, *see* Appendix D, p. 202.

[53] Final review team memorandum, *see* Appendix D, pp. 215–216.

[54] Final review team memorandum, *see* Appendix D, p. 216.

[55] Final review team memorandum, *see* Appendix D, p. 216.

[56] *See* Appendix I for minutes from the November 10 meeting, which include summaries of the concerns and issues raised by team members representing other divisions and offices within CDRH as well as concerns raised by the Division of Neuropharmacological Drug Products within

Continued

In addition to the internal review memorandum and meeting minutes, the team leader and the ODE Deputy Clinical Director expressed concerns regarding approval of VNS Therapy for TRD in e-mail communications to other members of the team. After informing the team leader and several other members of the review team that the CDRH Director would be making the decision regarding approval, the ODE Deputy Clinical Director wrote in an e-mail dated December 22, 2004:

> It will be tough for most if not all of us to look at a post-approval study . . . since we don't agree with the approval decision.[57]

When the review team leader became aware that the CDRH Director was "leaning towards approval," he requested that the review of submissions related to VNS Therapy for TRD be reassigned to another FDA reviewer. In an e-mail dated December 27, 2004, he wrote:

> Considering my scientific recommendation of not approvable based on the lack of clinical data supporting a reasonable assurance of safety or effectiveness and my knowledge of the ethical uncertainty in how they may have collected data in their epilepsy registry, I believe I have little to contribute in either the proposed dosage study or the post-market registry.[58]

In another message from the ODE Deputy Clinical Director to the team leader and several other members of the review team dated January 25, 2005, he wrote:

> I think it is clear down here that [the CDRH Director] is going to approve VNS for Depression. . . . I know that both of you believe this product should not be approved (as do I) but [the CDRH Director] is asking us to at least make sure there is truth in the labeling and I think that can be done regardless of our individual takes on the approvable/not approvable decision.[59]

CDER staff involved in the PMA-S review were also concerned about the VNS Therapy System being approved by CDRH for TRD. In an e-mail dated January 12, 2005, a CDER medical reviewer stated:

> I am disturbed that VNS might actually get an approval for "TRD". In my opinion, they do not have adequate data and I don't understand how this can move forward. I think you feel much the same but what will happen if the post-approval study is negative? Will the device be withdrawn? And, more importantly, it seems this type of data should come before approval.

CDER. *See also* memoranda included in Appendix D for more detailed discussions of the concerns and issues raised by the review team members related to the sponsor's response to the August 11, 2004 not approvable letter.

[57] *See* Appendix F.

[58] Ibid.

[59] Ibid.

> I feel like I can't just sit back and watch this happen without asking if there is anything more we can do. . . . As an M.D. with an interest in science, it seems to me that such an approval would be akin to approving an experimental product and is this what the FDA does? [60]

Committee Staff interviewed the CDRH Director in April 2005 and asked questions relating to his decision to issue an approvable letter to the sponsor in February 2005 despite the recommendations of the review team and the management staff at the branch, division, and office levels of CDRH. According to FDA regulations, as explained to Committee Staff by members of the review team, an approval letter signed by the CDRH Director would reverse the ODE's August 11, 2004, not approvable decision. Therefore, if the CDRH Director approved the device for TRD, he would be required to document his rationale for approving the device in an internal override memorandum.[61] At the time of the interview, the CDRH Director informed Committee Staff that he had not made his decision regarding approval of the device, and therefore, had not yet drafted the override memorandum.

On July 15, 2005, the FDA approved the VNS Therapy System for use in TRD patients. By signing the approval letter, the CDRH Director overruled the comprehensive scientific evaluation of FDA review team for the sponsor's PMA-S, including more than 20 FDA scientists, medical officers and management staff. According to the CDRH Director's override memorandum dated June 12, 2005, he found the additional long-term data from the D–01 and D–02 studies that the sponsor submitted as an amendment to its PMA-S (Amendment) to be compelling support for approval of the device, contrary to the review team's conclusions regarding that data.

B. FDA's Public Materials Do Not Reveal the Extent of Scientific Dissent Regarding Effectiveness of the Device

The Summary of Safety and Effectiveness (Summary), which is posted on the FDA's website, is silent with respect to the level of scientific dissent within CDRH regarding the safety and effectiveness of the VNS Therapy System for TRD. It simply states that CDRH believes that the sponsor "has provided reasonable assurance of safety and effectiveness based on valid scientific evidence as required by statute and regulation for the approval of a Class III medical device." [62] However, throughout the review of the sponsor's PMA-S, the review team recommended to the CDRH Director that the device not be approved for TRD. Yet, at every stage of the review, the team was instructed by the CDRH Director to proceed with the next stage of pre-market review.

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[60] *See* Appendix F.

[61] 21 C.F.R. § 10.70 requires documentation of significant agency decisions in an administrative file. The administrative file must contain, among other things, "the recommendations and decisions of individual employees, including supervisory personnel, responsible for handling the matter," *see* Appendix C.

[62] Medical devices are classified based on the risk they pose when patients use or misuse them. There are three classes of devices, Class I, II, and III. Class III devices include devices that are life-supporting or life-sustaining, and devices that present a high or potentially unreasonable risk of illness or injury to the patient.

The Summary also presents a single conclusion from CDRH regarding the June 15, 2004, advisory panel's recommendation. It states that CDRH "concurred with the Panel's recommendation of June 15, 2004, and issued a letter to the sponsor on February 2, 2005, advising that its PMA was approvable subject to" specified conditions. However, CDRH did not initially concur with the Panel's recommendation of an approvable decision. A not approvable letter was issued by the FDA on August 11, 2004. FDA staff who were interviewed by Committee Staff explained that although the panel recommended approval with conditions, the review team considered the panel's discussion and deliberations as well as its recommendations in deciding whether or not the VNS Therapy System should be approved for use in TRD patients.[63] Based on the comments of the panel members[64] and the review team's evaluation of the PMA-S, the review team concluded that the data submitted by the sponsor with its PMA-S did not meet the standard of reasonable assurance of safety and effectiveness.

Several FDA management staff, including the CDRH Director, stated in interviews with Committee Staff that the CDRH Director is very rarely directly involved in the approval or non-approval of medical devices. They could recall only one other instance where the Center Director made the final decision regarding a device's approvability in the past decade. In that instance, the Center Director decided not to reverse the Office Director's decision. In the case of the VNS Therapy System, the FDA review team that evaluated the VNS Therapy System for TRD strongly disagreed with the CDRH Director's decision to approve that device, but despite the team's conclusions about the device, the CDRH Director decided independently to approve the VNS Therapy System for TRD.

Prior to Cyberonics's PMA-S submission on October 27, 2003, CDRH had expressed concerns about Cyberonics's acute D–02 data; however, the Center accepted the sponsor's application for review. According to an e-mail communication from CDER staff to CDRH staff, dated October 3, 2003, if a sponsor had submitted to CDER

[63] Although the panel recommended approval with conditions, one panel member stated in an e-mail to the Executive Secretary of the Neurological Devices Panel dated June 18, 2004, "If I were to have voted up front, I would have not approved the device." Another panel member said in an e-mail dated October 19, 2004, that she was not surprised that the FDA issued a not approvable letter despite the panel's recommendation. She stated, "This was not surprising in and of itself, given the less than impressive nature of the data as well as the extreme ambivalence about the approval as reflected in the deliberations of the panel. I certainly was very ambivalent myself." One of the two members who did not believe VNS Therapy should be approved stated in an e-mail to a supervisory medical officer in CDER dated June 17, 2004, that "The sponsor did not present convincing data that the treatment was effective, nor in my mind, that it was safe." *See* Appendix F.

[64] According to several members of the review team, the panel's recommendation was inconsistent with its discussion of the data on the risks and benefits of VNS Therapy. In particular, even though the panel members found that without a randomized, controlled study they could not determine how much of the response to VNS stimulation was due to a placebo effect or what impact concomitant medications and ECT had on interpreting the efficacy of the VNS Therapy System for TRD patients—two of the concerns that led the review team to recommend non-approval of the device—the majority of the panel members still concluded that the data provided a reasonable assurance of effectiveness. *See* Neurological Devices Panel Meeting Transcript, p. 343–357, 363–368, *http://www.fda.gov/ohrms/dockets/ac/04/transcripts/2004-4047t1.DOC.* The BlueCross BlueShield Technology Evaluation Center's evaluation of the evidence on the effectiveness of VNS for TRD also noted that "Although the FDA voted to approve VNS Therapy, a poll of committee members showed that approval was based on the safety of VNS Therapy rather than strong evidence of efficacy." In addition, the Executive Secretary of the June 15, 2005, panel informed Committee Staff that the June 15 meeting was "very unusual, emotional, not data driven," compared to more than a dozen panel meetings for which she was the executive secretary.

the type of data that Cyberonics's did for FDA review and approval of a drug, CDER would not have filed that sponsor's application. In that e-mail, the psychopharmacology expert in CDER who reviewed initial materials from the sponsor wrote:

> I am concerned that we are not getting our point across that the VNS for depression package that we reviewed represents a failed development program on face and that we would not file this as an NDA [New Drug Application[65]] if it were a drug. We realize that you may have a different threshold for approval when it comes to devices because of the nature of the different diseases on which our respective Divisions are asked to comment. However, we tend to view treatments for depression based on the disease and not on the therapeutic modality (psychotherapy, drug, ECT and now VNS). So it is artificial to us to consider one study for a device (that is negative on face) as sufficient to provide evidence for regulatory efficacy when we require positive studies for a drug.[66]

The CDER expert added that:

> The long term claims [of efficacy by the sponsor] are based on open-label data. We do not allow labeling claims based [on] open label studies that rely on historical controls in depression. Historical controls in depression are extremely unreliable.[67]

The FDA review team leader informed Committee Staff that the team was puzzled by the CDRH Director's decisions to proceed with each stage of the review of the sponsor's PMA-S despite the team continuously recommending that the FDA not approve the VNS Therapy System for TRD. According to the team leader and DGRND Director, the team recommended non-approval prior to the 100-day meeting, because the team did not believe the sponsor would be able to address the limitations of the clinical data provided in the PMA-S. The team leader and DGRND Director explained that the review team believed that the device could not be approved without the sponsor conducting a new randomized, controlled study to demonstrate effectiveness. Throughout the review of the sponsor's PMA-S, DGRND recommended to the sponsor that it conduct such a study prior to approval. However, the sponsor insisted each time that it was unnecessary and unethical to conduct such a study, at least not before FDA approval of the device.[68]

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[65] The vehicle through which drug manufacturers seek the FDA's approval of a new drug for sale and marketing in the U.S.

[66] *See* Appendix F.

[67] Ibid.

[68] According to an e-mail dated February 4, 2004, from a review team member to the team leader and Branch Chief, "Cyberonics spent an hour telling why it was completely impossible for them to do a placebo controlled long-term (or short-term) study . . . but then, completely out of the blue, promised that if we approved the device that they would do such a study post approval. I find this offer extremely puzzling since their argument centered around troubles with ethics, IRB cooperation, and patient recruitment. These are definitely not problems that would go away post approval." *See* Appendix F.

The team leader and DGRND Director acknowledged that randomized, controlled studies are not always required for FDA approval of devices, but the review team believed in the case of the VNS Therapy System, a randomized, controlled trial was necessary in order to distinguish improvement that is attributable to VNS Therapy from improvement that is attributable to other reasons, specifically, a placebo response or antidepressant treatments taken concurrently with VNS Therapy.[69] Nevertheless, Committee Staff were told that the CDRH Director, who was the ODE Director at the time, instructed the team to issue a major deficiency letter instead of a not approvable letter. The team leader said that the review team was surprised that the then-ODE Director would suggest a major deficiency letter without examining the sponsor's data. The CDRH Director, however, told Committee Staff that he asked for a deficiency letter because he prefers giving sponsors "a second bite at the apple," to address concerns.

The team leader and DGRND director stated that, after reviewing the sponsor's response to the major deficiency letter, the review team concluded that the sponsor had not addressed all of the deficiencies in its PMA-S and could not do so without conducting a new study. Consequently, the review team recommended that the device not be approved. Once again, the team was told to proceed with an advisory panel meeting to obtain recommendations on whether or not the FDA should approve the device. The DGRND Director told Committee Staff that she expressed her concerns to the then-ODE Director about convening an advisory panel, asking him what the FDA would do if the panel recommended approval despite the lack of sufficient effectiveness data, which is what occurred at the panel meeting. The then-ODE Director told Committee Staff that if the panel had agreed with the review team's assessment of the sponsor's clinical data, the panel's recommendation would provide additional support for a not approvable decision.

According to the ODE Deputy Clinical Director, soon after the June 15, 2004, advisory panel meeting, the ODE Director asked him to review the sponsor's application to advise her on whether or not the office should approve the VNS Therapy System for TRD. The Deputy Clinical Director informed Committee Staff that he was not initially involved in the review of the sponsor's PMA-S. He reviewed the transcript of the advisory panel meeting, the PMA-S file, and the review team's memoranda and supported DGRND's recommendation to not approve the device for TRD. In addition, after the not approvable letter was issued on August 11, 2004, the Deputy Clinical Director requested and reviewed additional patient response data from the sponsor and concluded in an e-mail to the ODE Director dated September 14, 2004:

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[69] Even before the sponsor submitted its PMA-S in October 2003, the DGRND Director had expressed concerns about the sponsor being able to demonstrate effectiveness after the failure of the sponsor's D–02 acute phase to show a difference in responses between those receiving VNS Therapy and those who were not. According to minutes from a meeting between the sponsor and the FDA on March 1, 2002, the DGRND Director stated that she was not convinced that the sponsor would not need a randomized, long-term study to demonstrate effectiveness. About two weeks prior to the sponsor's submission of the PMA-S, the FDA reiterated concerns about the data limitations during a conference call with the sponsor. *See* October 11, 2002, conference call minutes. *See* Appendix H for the March and October 2002 minutes.

> I do not see anything in the information which would convincingly make me decide to overrule the original Division/ Office decision.[70]

Committee Staff were informed that the team leader as well as the DGRND, ODE, and CDRH Directors received hundreds of letters and phone calls opposing the FDA's August 11, 2004, decision to not approve the device for treatment-resistant depression. FDA staff interviewed by Committee Staff stated that interactions with the sponsor were not collegial[71] and the company was more aggressive than other sponsors in pursuing FDA approval. According to the CDRH Director and Ombudsman, the sponsor also spoke with staff in the Office of the Secretary, Department of Health and Human Services, who in turn followed up with CDRH regarding the FDA's not approvable letter. As a result of the influx of letters and phone calls after the not approvable letter was issued, the CDRH Director informed Committee Staff that he kept then-FDA Commissioner Lester Crawford apprised of developments in the review of the sponsor's PMA-S during his bi-weekly meetings with the Commissioner.

On September 23, 2004, the sponsor submitted its Amendment, in response to the not approvable letter. The review team examined the data and information provided in the sponsor's Amendment submission and, on November 10, 2004, concluded that the not approvable decision should stand. However, according to the review team leader and the DGRND and ODE Directors, the CDRH Director decided to schedule a meeting with the sponsor in December 2004 to further discuss the sponsor's Amendment and what the sponsor could do to enable the FDA to reach approval of the VNS Therapy System for TRD. Only four members of the review team were invited to attend the meeting, and according to the team leader and DGRND Director, management staff were not invited to participate in the meeting.

When the Restorative Devices Branch Chief learned that the CDRH Director planned to hold a meeting with the sponsor that would not include the management staff involved in the sponsor's PMA-S review—the branch chief, the deputy division director, and the division director—he expressed his concerns to the team leader. In an e-mail dated November 24, 2004, he wrote:

> Don't know if you heard yesterday, but [the CDRH Director] has made a decision—of sorts. His plan is to have a meeting with the sponsor and the partial review team, for us to explain again why we came out to a different conclusion with the same data. I'll be meeting with [the ODE Director] today, and explain why I think that's a really bad idea, but chances are that's what'll happen.[72]

The CDRH Director stated to Committee Staff during his interview that the management staff were not intentionally excluded.

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[70] *See* Appendix F.

[71] According to the CDRH Director, DGRND's interactions with the sponsor were "terrible" and the staff felt "abused" in meetings with the sponsor. The ODE Director informed Committee Staff that she spoke with the Chief Executive Officer of Cyberonics at the end of a meeting and requested that he refrain from yelling at her review team.

[72] *See* Appendix F.

However, only the team leader and three other members of the review team were invited—a medical officer, the CDER psychopharmacology expert, and the ODE Deputy Clinical Director. The review team leader informed Committee Staff during an interview that he felt "outnumbered" by the sponsor's representatives. In addition, he wrote in his e-mail response to the Branch Chief dated November 29, 2004, that he was very troubled about the decision to hold a meeting without management and said such a meeting seemed "highly irregular." *See* Appendix F.

The CDER psychopharmacology expert on the review team also expressed his concern regarding the December 2004 meeting when he was told to limit his comments to the sponsor's clinical data and not discuss what types of studies CDER or the Center for Biologics Evaluation and Research would require for approval. He stated in an e-mail dated November 24, 2004:

> I am a little troubled by what appears to be a request that I not discuss the need for replicated controlled data in our upcoming discussion with Cyberonics and [the CDRH Director]. I am left with the impression that you may view our Division's opinion on the need for replicated controlled trial data as simply a bureaucratic policy difference between Centers. . . . This need for replicated controlled clinical trial data is a basic tenet of psychiatric clinical research. This need is based on sad experience. I suggest that the need for two randomized controlled trials should actually be the focus of this upcoming meeting.[73]

According to the CDRH Director and the Deputy Commissioner for Operations, the CDRH Director sought the Deputy Commissioner's advice on how to proceed with the review of the VNS Therapy System for TRD because of the Deputy Commissioner's expertise on antidepressants. During an interview with Committee Staff, the CDRH Director stated that he and the Deputy Commissioner discussed ways to obtain more data on the device, such as requesting the sponsor to conduct additional studies pre- or post-approval; however, the Deputy Commissioner did not advise him to approve or not approve the device. When he asked her impression of the sponsor's VNS Therapy for TRD, he said she was "lukewarm" about the device. According to the CDRH Director, the Deputy Commissioner said there could be something there, but the studies were flawed.

The Deputy Commissioner also informed Committee Staff that she spoke with the Director of the Office of Medical Policy regarding potential studies that the sponsor could conduct to generate more effectiveness data on its device. She suggested to the CDRH Director a "randomized withdrawal" study, *i.e.*, randomly withdrawing VNS treatment from D–02 patients that the sponsor labeled as "responders." According to the Deputy Commissioner, if the device works, the sponsor should observe a relapse in patients when their treatment is withdrawn. Alternatively, because patients usually can tell if the device is on, she suggested randomly reducing the output of the stimulator rather then fully withdrawing

[73] *See* Appendix F.

treatment. By e-mail dated December 23, 2004, the Director of the Office of Medical Policy also suggested to the CDRH Director a study that the sponsor "can and should do," a randomized withdrawal study.[74] However, he questioned whether or not the sponsor could "realistically" conduct such a study post-approval.[75] The Deputy Commissioner informed Committee Staff that the FDA received "push back" from the sponsor on the proposal.

On July 28, 2005, the Chairman and Ranking Member sent a letter to the FDA to question why the FDA's website did not address the level of scientific dissent within CDRH regarding the review and approval of the VNS Therapy System for TRD. FDA's response, dated August 9, 2005, states:

> The absence from the SSE of any discussion of internal discussions and the decision-making process that led to the approval reflects the policy of the Agency not to disclose pre-decisional and deliberative process information. . . . The reasons for this policy are to encourage open and frank discussions among colleagues and between subordinates and superiors at FDA and to protect against public confusion that might result from disclosure of reasons and rationales that were not in fact ultimately the grounds for the Agency's decision.[76]

A review of whether or not the FDA uniformly adheres to this policy, however, shows that enforcement of the policy appears to depend on the interests of FDA management rather than any stated interest in encouraging scientific debate or in protecting the public. The Committee Staff are aware of more than one instance in recent years where the FDA has forthrightly publicized internal dissent regarding safety and effectiveness.

While Committee Staff recognize that it is not uncommon for FDA reviewers to disagree about the findings and conclusions regarding the safety and/or effectiveness of a drug or device, the level of dissent regarding the approval of the VNS Therapy System for TRD goes far beyond that of "open and frank discussions." As the CDRH Director acknowledged to Committee Staff prior to his decision to approve the device, if he approved the device, the public would not be aware of his decision to overrule more than 20 FDA staff.

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[74] *See* Appendix F.

[75] By letter dated July 7, 2005, Chairman Grassley and Ranking Member Baucus asked the FDA whether or not an agreement or understanding was reached between the sponsor and the FDA regarding FDA approval of VNS Therapy for TRD if the sponsor agreed to voluntarily withdraw VNS Therapy for TRD should post-marketing studies fail to show efficacy. The FDA provided its response on July 20, 2005. *See* Appendix E. In that response, the FDA noted that "consideration of post-market controls is an important component of FDA's Pre-Market Approval program for devices." The FDA also stated that "there exists no agreement or understanding between FDA and Cyberonics, written or oral," and "such an agreement or understanding between FDA and Cyberonics has never been discussed." However, given the FDA's post-market authorities, "studies agreed to by Cyberonics do not reflect an inappropriate agreement by the Agency to permit the marketing of a device in exchange for a promise of withdrawal should the studies show the device to be ineffective."

[76] *See* Appendix E.

C. Not All Relevant Findings and Conclusions Regarding Safety and Effectiveness of the Device Were Made Publicly Available

Through its website, the FDA has made available to the public the approval letter for the VNS Therapy System for TRD, the Summary of Safety and Effectiveness (Summary), physician and patient labeling information for the device, and other information for consumers. The Committee Staff reviewed these materials as well as other information and documents obtained by and provided to the Committee from the FDA and the sponsor. Based on that review, the Chairman and Ranking Member questioned, by letter dated July 28, 2005, the FDA's decision not to disclose certain information regarding the effectiveness of the VNS Therapy System that appears relevant to those who are considering having this device implanted.[77]

In the July 28, 2005, letter, the Chairman and Ranking Member noted that during an interview conducted with the CDRH Director, prior to approval of the VNS Therapy System for TRD, the Director acknowledged that data from the only randomized, controlled study, the acute phase of D–02, failed to demonstrate the effectiveness of the VNS Therapy System for TRD. The Director's internal override memorandum dated June 12, 2005, states:

> With regard to effectiveness, I think it needs to be stated clearly and unambiguously that the short-term randomized comparison of VNS active to VNS sham[78] at 12 weeks failed to reach, or even come close to reaching, statistical significance with respect to its primary endpoint. I think that one has to conclude that, based on that data; either the device has no effect, or, if it does have an effect that in order to measure that effect a longer period of follow-up is required.[79]

However, the Director's comments regarding the effectiveness of the VNS Therapy System for TRD are absent from the Summary that is posted on the FDA's website. The Chairman and Ranking Member also noted in the July 28, 2005 letter to the FDA that the patient labeling of the VNS Therapy System for TRD does not make clear the Director's own conclusions regarding the sponsor's short-term clinical study. Instead of stating "clearly and unambiguously" that the "[VNS Therapy System for TRD] has no effect, or, if it does have an effect that in order to measure that effect a longer period of follow-up is required," the patient labeling for the VNS Therapy System for TRD states:

> At the end of the first 3 months, the proportion of patients who had at least a 50 percent reduction in depression symptoms was 15 percent in the group of patients receiving active stimulation, slightly better than for patients who were not receiving stimulation (10 percent of these patients had at least a 50 percent reduction in symptoms).

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[77] *See* Appendix A.

[78] A "sham" is used to resemble a treatment without actual use of the treatment. A placebo is an example of a sham control.

[79] *See* Appendix B.

> . . . This finding suggested that the full effects of VNS Therapy might require more than 3 months of treatment.[80]

On August 9, 2005, the FDA responded to the Committee and cited a different section of the patient labeling to show that the labeling acknowledges "the failure of the data to demonstrate short-term effectiveness."[81] The labeling states that "the 12 week acute studies did not show a significant difference between patients receiving VNS Therapy and those not receiving it." However, it does not explain that "did not show a significant difference" means that any differences observed between the two groups of patients could have been due to chance rather than a response to the device. Because it could not be determined if the effect of the device was real or due to chance, the CDRH Director concluded in his override memorandum that, based on the results of the short-term study, a longer study would be needed to determine whether or not the device is effective.

In response to the Chairman and Ranking Member, the FDA also stated that it would review the CDRH Consumer Information webpage (*www.fda.gov/cdrh/mda/docs/p970003s050.html*) regarding the approval of the VNS Therapy System for TRD to determine whether or not it could be revised to provide more helpful information to patients. By e-mail dated August 23, 2005, the FDA notified Committee Staff that it had revised its webpage. The current webpage, updated on August 12, 2005, includes additional information on when the device can be used:

> The device is to be used only in patients 18 years of age or over with treatment-resistant depression (TRD). These are patients who have been treated with, but failed to respond to, at least 4 adequate medication and/or ECT treatment regimens prescribed by their physician. It is not intended to be used as a first-line treatment, even for patients with severe depression.[82]

The FDA also added information regarding what the VNS Therapy System is intended to accomplish. Specifically, the CDRH Consumer Information webpage on VNS Therapy states:

> Based on the results of a clinical study of over 200 patients conducted in the United States, during the first 3 months of therapy, patients who had the device implanted and turned on did not show any significant advantage in response compared to patients in whom the device was implanted but not turned on.

The additional information regarding the short-term effectiveness data is similar to what is provided in the patient labeling. However, as presented, the information does not represent the gravity of the statement made by the CDRH Director in his override memorandum that the short-term study "failed to reach, or even come close to reaching, statistical significance with respect to its primary endpoint [of efficacy]." Nor does it represent the conclusions of the review team or the management staff at the branch,

[80] *See* Appendix D.
[81] *See* Appendix E.
[82] *See* Appendix B.

division and office levels who found the sponsor's data on the effectiveness of the VNS Therapy System for TRD to be "weak" and insufficient for FDA approval of the device.

In addition, because the review team's own assessment of the safety and effectiveness of the device is not available to the public, patients and physicians are not made aware of the reviewers' concerns regarding the safety of the VNS Therapy System for TRD in light of the team's conclusion that the device has not been shown to be effective. The review team stated in its final review memorandum dated January 6, 2005, "any safety risk associated with using a long-term implant, in the absence of a reasonable assurance of effectiveness data, is excessive."[83] The FDA review team also believed that the sponsor did not provide a reasonable assurance of safety because the safety data provided in the PMA-S did not allow an accurate assessment of any increased risks of using the device for TRD.

In the Preamble to a final rule on drug and biological products labeling, the FDA recently stated:

> The centerpiece of risk management for prescription drugs generally is the labeling, which reflects thorough FDA review of the pertinent scientific evidence and communicates to health care practitioners the agency's formal, authoritative conclusions regarding the conditions under which the product can be used safely and effectively in accordance with the act. . . .
>
> As FDA has long recognized, its role is not to regulate medical practice. The agency's actions nevertheless affect medical practice in a variety of ways. For example, FDA approval decisions affect the availability of drugs and medical devices. Also, FDA decisions as to the content and format of prescription drug labeling affect health care practitioner communications with patients, to the extent such labeling is relied upon by such practitioners to guide their discussions of risk with patients. FDA strongly believes that health care practitioners should be able to rely on prescription drug labeling for authoritative risk information and that health care practitioners should not be required to convey risk information to patients that is not included in the labeling.[84]

While these statements were made with respect to labeling for drug and biological products, they have implications for how and what information might be conveyed in device labeling. The FDA's position is that health care providers and their patients should be relying on the FDA for "authoritative risk information." However, the questionable aspects of the agency's regulatory approval process as evidenced in this Report suggest that health care providers relying on the FDA's authoritative information may not be able to convey complete risk information to their patients on the safety and effectiveness of the VNS Therapy System, because not all of

[83] Final review memorandum, *see* Appendix D, p. 207.

[84] "Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products," 71 Fed. Reg. 3922, 3969. (January 24, 2006).

the relevant findings and conclusions regarding this device have been made available.

Then-FDA Commissioner Crawford testified on July 26, 2005, before the House of Representatives Committee on Appropriations Subcommittee on Agriculture, Rural Development, Food and Drug Administration, and Related Agencies that he would make the FDA "a much more open and transparent organization." This pledge has been reiterated by the FDA in letters to the Committee on other matters. However, selective disclosure of the FDA's findings and conclusions regarding the safety and effectiveness of a device, in this case the VNS Therapy System for TRD, appears inconsistent with that pledge.

VI. Concluding Observations

The public relies on the FDA to weigh the risks and benefits of a new medical device or a new indication for a device to determine whether or not the device is reasonably safe and effective for use. FDA approval has long been considered the gold standard. However, the events and circumstances surrounding the FDA's review and approval of the VNS Therapy System for TRD—including the rare involvement of the CDRH Director and other high level FDA officials in the review of a device; the insistence of a single official to continue review of the PMA-S despite the repeated recommendations of over 20 FDA scientists, medical officers, and management staff to not approve the device throughout approximately 15 months of review; a "highly irregular" meeting between the sponsor and the FDA; and external pressure from the sponsor as well as hundreds of health care providers and TRD patients through letters, e-mails and phone calls—raise legitimate questions about the FDA's decision to approve that device for the treatment of TRD. In light of the significant scientific dissent within the FDA regarding the effectiveness of the VNS Therapy System for TRD and the conclusion not only of the review team for the sponsor's PMA-S but also of high level officials in the FDA that the effectiveness data were weak, concerns persist that the FDA's standard of reasonable assurance of effectiveness may not have been met.

The FDA has standards for approval that must be met so that there is some assurance that the products approved for commercial distribution are safe and effective when used as directed in the product labeling. As a result of the short lifespan of new devices, different standards for demonstrating effectiveness may apply for devices compared to drugs. An approved device can quickly be replaced by a newer model or by smaller, better, and more sophisticated devices. However, what remains the same in FDA's approval of a device or a drug is the requirement that data supporting a sponsor's application for approval be scientifically sound. Otherwise health care providers and insurers as well as patients may question the integrity and reliability of the FDA's assessment of the safety and effectiveness of an approved product. In the case of VNS Therapy for TRD, the FDA review team for the sponsor's PMA-S believed that conducting a new randomized, controlled study would be the only way that the sponsor could address the data limitations in its PMA-S and repeatedly recommended that the sponsor con-

duct the study prior to approval. However, the sponsor refused to conduct another randomized, controlled study pre-approval.

FDA approval does not mean that a device is risk-free or that it will work in every patient. The determination of a medical device's safety and effectiveness prior to approval is based largely on studies that are conducted in small populations. While valuable information about the effectiveness of a device can be gained and new risks are sometimes identified once the device is on the market and used by millions of people, the FDA should not be making devices available to the public if those devices have not reached the agency's standard for safety and effectiveness. With respect to the VNS Therapy System for TRD, however, it appears that instead of relying on the comprehensive scientific evaluation of its scientists and medical officers, the FDA lowered its threshold for evidence of effectiveness. The FDA approved the VNS Therapy System for TRD based on what its own reviewers considered to be weak data and allowed the sponsor to test its device post-approval, contrary to the recommendations of the review team.

In addition to questions about the effectiveness of VNS Therapy System in the population for which the device is intended, concerns exist about the potential off-label uses of the device. Because the FDA does not regulate the practice of medicine, once a device is on the market, it is available for widespread use. While there have been benefits derived from off-label uses, the safety and effectiveness of off-label uses are not known and therefore can pose serious health risks to patients. The circumstances are no different for the VNS Therapy System for TRD. The specific public safety concern related to off-label use of this device is the implantation of the device in children with TRD. For example, the VNS Therapy System for epilepsy is approved only for use in patients 12 years of age or older, but off-label use of the device has occurred in children as young as five years of age. There are risks with using the VNS Therapy System in children that do not exist among adults because implantation of the device involves wrapping a wire around the nerve of a growing child. In the case of TRD, the VNS Therapy System is approved only for patients 18 years of age or older.

The level of scientific dissent within the FDA regarding the effectiveness of the VNS Therapy System for TRD also raises concerns about the use of taxpayer dollars to pay for a $25,000 device, including implantation and programming, that over 20 FDA scientists, medical officers, and management staff believed should not be approved for the treatment of TRD. Whether or not a device is effective is not only a major public safety concern, but also a very important financial concern. The Medicare and Medicaid programs pay for health care services received by millions of Americans, so the Committee has a responsibility to ensure that the programs pay for medical devices approved based not on an abstract estimation of safety and effectiveness but on a comprehensive scientific evaluation of the product's benefits and risks, in accordance with all laws and regulations.

In addition, patients and their doctors, including Medicare and Medicaid beneficiaries, should have access to all relevant findings and conclusions regarding the safety and effectiveness of a device. The CDRH Director acknowledged during a media briefing on Feb-

ruary 2, 2006 that one of the FDA's "biggest challenges is in terms of providing useful information, and we understand that a lot of the concerns that have been raised over the course of the last few months to a year is with regard to the information that we present—the quantity of information and the timeliness of that information." Concerns remain about the lack of transparency regarding the approval process for the VNS Therapy System, which deprives doctors and their patients of information that may be relevant to a patient's care. All relevant findings and conclusions regarding the safety and effectiveness of the VNS Therapy System for TRD should be made available to patients and their doctors to enable them to make fully informed health care decisions and ensure all risks and benefits can be carefully weighed by those considering having the device implanted.