



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service  
Food and Drug Administration

310544

Dallas District  
3310 Live Oak Street  
Dallas, Texas 75204-6191

March 23, 2001

Ref: 2001-DAL-WL-13

**WARNING LETTER**

**CERTIFIED MAIL**  
**RETURNED RECEIPT REQUESTED**

Mr. Robert (Skip) P. Cummins  
President and Chief Executive Officer  
Cyberonics, Inc.  
16511 Space Center Blvd., Suite 600  
Houston, Texas 77058

Dear Mr. Cummins:

During an inspection of your firm located in Houston, Texas, on January 22 to 25, 30 and February 1, 2001, our investigator determined that your firm manufactures the NeuroCybernetic Prosthesis (NCP®) System, a vagus nerve stimulator indicated for use as an adjunctive therapy in reducing the frequency of seizures in adults and adolescents over 12 years of age with medically intractable partial seizures. The NCP® System includes a pulse generator, programming wand, programming software, bipolar leads, tunneling tool, and accessory pack. These products are medical devices as defined by Section 201(h) of the Federal Food, Drug, and Cosmetic Act (the Act).

The inspection revealed that your devices are misbranded within the meaning of Section 502(t)(2) of the Act in that medical device reporting procedures were not implemented and maintained and information was not submitted to FDA as required by the Medical Device Reporting Regulation (MDR), as specified in Title 21, Code of Federal Regulations (CFR), Part 803. Specifically:

1. Failure to submit reports within 30 days whenever the manufacturer receives or otherwise becomes aware of information, from any sources, that reasonably suggests a device marketed by your firm may have caused or contributed to a death or serious injury, as required by 21 CFR 803.50(a)(1). For example, approximately 60 events, received by your firm between 3/15/99 and 12/20/00, that suggest your device may have caused or contributed to a death and 102 infection events received between 1/98 and 12/00 were not reported to FDA until 2/22/01 after completion of the inspection.

Page 2 – Mr. Robert (Skip) P. Cummins, President and Chief Executive Officer  
Cyberonics, Inc.  
March 23, 2001

Our inspection revealed that your MDR event files either were incomplete or do not contain sufficient records of investigations to change the alleged association between the devices and the deaths or to support your decision making process that these death events were or were not reportable within the 30-day reporting time frame [see FDA-Item 1 and 2]. Your firm can not postpone its decision to report the event while it continues to deliberate or collect additional information. Therefore, your firm must submit a report for each event within the 30-day time frame. If subsequent information or evaluation alters your firm's decision, then a supplemental report should be submitted to update the status of the MDR report.

Regarding the infection events, your firm indicated to our investigator that adverse events in which the NCP® Systems were explanted due to the occurrence of infections were known events that are addressed in the device labeling; thus, no MDR reports had been submitted prior to the inspection. We have concluded that these infection events meet the reporting threshold and therefore should have been submitted to FDA because the explanation the NCP® System amounts to medical or surgical intervention to preclude impairment of a body function or permanent damage to a body structure. Events described in medical device labeling are not exempt by statute or the MDR regulation from the reporting requirements set forth in 21 CFR 803.

2. Failure to establish and maintain MDR event files [21 CFR 803.18(b)(1)(i)] and failure to investigate and evaluate the cause of MDR reportable events [21 CFR 803.50(b)(2)]. For example, records of investigation for MDR reportable events were not complete to show that reasonable efforts were made to obtain missing information, evaluate returned devices, and determine the relationship of the devices to the reported incidents [FDA-483 Item 1 and 2].
3. Failure to establish and maintain procedures for implementing corrective and preventive action [21 CFR 820.100]. For example:
  - (a) Field reports of death events were not classified as complaints and lacked adequate treatment data (e.g., missing programming history, incomplete patient follow-up forms, no follow-up on product returns) to allow for effective data analysis [FDA-Item 3].
  - (b) The firm's CAPA procedures do not address how results from trending analysis are to be used to initiate corrective action for lead anomalies (i.e., lead breaks, high impedance) [FDA-483 Item 4].

This letter is not intended to be an all-inclusive list of deficiencies at your facility. It is your responsibility to ensure adherence to each requirement of the Act and regulations. The specific violations noted in this letter and in the FDA-483 issued at the closeout of the inspection may be symptomatic of serious underlying problems in your firm's manufacturing and quality assurance systems. You are responsible for investigating and determining the causes of the violations identified by the FDA. If the causes are determined to be systems problems, you must promptly initiate permanent corrective actions.

Page 3 – Mr. Robert (Skip) P. Cummins, President and Chief Executive Officer  
Cyberonics, Inc.  
March 23, 2001

You should take prompt action to correct these violations. Failure to promptly correct these violations may result in regulatory action being initiated by the Food and Drug Administration without further notice. These actions include, but are not limited to, seizure, injunction, and/or assessing civil money penalties. Also, until these violations are corrected, and FDA has documentation to establish that such corrections have been made, federal agencies will be advised of the issuance of this Warning Letter so that they may take this information into account when awarding government contracts.

We acknowledge the receipt of your firm's response, dated February 22, 2001, provided to us at the district meeting on February 23, 2001, and additional responses faxed on March 1 and 12, 2001, responding to the inspectional observations (FDA-483, copy attached) issued to Ms. Annette Zinn, Director and Senior Counsel, Regulatory Affairs, at the completion of the inspection. As part of your firm's corrective action plan to address the system-level issues, your firm has now submitted all death (83) and infection (116) events to FDA, made some organizational changes, hired additional senior management staff, revised and added procedures, provided updated employee training to address the shortcomings in the areas of complaint handling and CAPA activities, and plan to utilize a third party auditor to facilitate improvement in your quality systems. We consider your responses to be adequate and will verify the effectiveness of your corrective action at the next scheduled inspection.

Further responses should be sent to Mr. Thao Ta, Compliance Officer, at the above letterhead address. If you have any questions regarding this letter, please contact Mr. Ta at (214) 655-5310.

Sincerely yours,



for

Michael A. Chappell  
Dallas District Director

Enclosure(s)

cc: Mr. Alan D. Totah  
Vice President of Regulatory Affairs and Quality Assurance  
Cyberonics, Inc.  
16511 Space Center Blvd., Suite 600  
Houston, Texas 77058

Ms. Annette M. Zinn  
Director and Senior Counsel, Regulatory Affairs  
Cyberonics, Inc.  
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