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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

MAR 13 2007

Food and Drug Administration  
Center for Devices and  
Radiological Health  
2098 Gaither Road  
Rockville, MD 20850

WARNING LETTER

VIA FEDERAL EXPRESS

Charles M. Smith  
President  
Cochlear Americas  
400 Inverness Parkway, Suite 400  
Englewood, CO 80112-5834

Dear Mr. Smith:

This Warning Letter is to inform you of objectionable conditions observed during the Food and Drug Administration (FDA) inspection conducted at Cochlear Americas from October 11 to 19, 2006 by an investigator from the FDA Denver District Office. The purpose of this inspection was to determine whether your activities as sponsor of the clinical study [redacted] complied with applicable federal regulations. The [redacted] is a device as that term is defined in section 201(h) of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. 321(h). This letter also requests prompt corrective action to address the violations cited, and discusses your written response to the noted violations.

The inspection was conducted under a program designed to ensure that data and information contained in requests for Investigational Device Exemptions (IDE), Premarket Approval applications (PMA), and Premarket Notification submissions [510(k)] are scientifically valid and accurate. Another objective of the program is to ensure that human subjects are protected from undue hazard or risk during the course of scientific investigations.

Our review of the inspection report prepared by the district office revealed serious violations of Title 21, Code of Federal Regulations (21 CFR) 812 – Investigational Device Exemptions. At the close of the inspection, the FDA investigator presented an inspectional observations Form FDA 483 for your review and discussed the observations listed on the form with you. The deviations noted on the Form FDA 483, your written responses, and our subsequent review of the inspection report are discussed below:

**Failure to include written procedures for monitoring in the investigational plan [21 CFR 812.25(e)].**

Pursuant to 21 CFR 812.25(e), sponsors are responsible for having written procedures for monitoring the investigation. Examples of your failure to adhere to the above stated regulation include, but are not limited to, the following:

The [redacted] clinical study (the [redacted] clinical study”) did not have a monitoring procedure during phase 1 of the clinical study.

Your response acknowledges that there was no written monitoring procedure in place during phase 1 of the [redacted] clinical study, and includes a written monitoring procedure that was put into place during phase 2 of the study. We note that although the date of the monitoring procedure is October, 2005, three of the 13 clinical sites with enrollees have not been monitored since then. Therefore, your corrective action appears to be inadequate in that the monitoring procedure has not been utilized at every site, making the corrective action plan ineffective. In addition, we note that the monitoring procedure that you have provided pertains only to the [redacted] clinical study. The purpose of a written monitoring procedure is to ensure data quality and integrity and investigator compliance for each investigational device study. Please ensure that you have a monitoring procedure for each FDA-regulated investigational device study that you sponsor.

**Failure to provide investigators the information they need to conduct the investigation properly and failure to ensure proper monitoring of the clinical investigation [21 CFR 812.40].**

Pursuant to 21 CFR 812.40, sponsors are responsible for providing investigators with the information they need to conduct the investigation properly and to ensure proper monitoring of the investigation. Examples of your failure to adhere to the above stated regulation include, but are not limited to, the following:

- a. You failed to provide investigators with the information that they needed to conduct the investigation properly. [redacted] occurred between 2004 and 2006 and was first documented in 2005. Five study subjects have experienced a complete [redacted] and there have been 12 subjects who have experienced [redacted]. A teleconference was not held until 2/28/06 to discuss [redacted] and only four of the 16 clinical investigators involved in the study participated in the teleconference. The adverse experience information was not formally communicated to all of the clinical investigators until May of 2006 when you notified all 16 clinical investigators of these cases of [redacted].

Your response states that the investigators received hearing loss information in the annual progress report that was submitted on 9/24/04. Your response is inadequate. According to exhibits collected during the inspection, the hearing loss was not documented until 2005; therefore it would have been impossible for this information to have been included

in a 2004 annual progress report. In addition, you did not provide a copy of the annual report referred to in your response.

b. You failed to provide investigators the information they needed to conduct the investigation properly. Although [redacted] had been documented since 2004, it was not until May of 2006 that you provided a revised version of the ICF for the [redacted] clinical study to all clinical sites and requested that the revised ICF be submitted to the sites' IRB for review and approval. The revised ICF contained important information regarding risk to subjects, i.e., [redacted]

Your response states that you have now received IRB approval letters for version 3.0 of the ICF from an additional two sites, and that you will continue your follow-up of the remaining sites. In addition, your response states that you will not enroll any new subjects or ship devices to sites unless you have received evidence of IRB approval of the revised ICF. Your response to this item appears adequate. However, please ensure that all subjects enrolled in the study are re-consented with the new ICF which includes information regarding [redacted]

c. You failed to ensure proper monitoring of the clinical investigation. At least five of the 72 subjects enrolled in the [redacted] clinical study did not sign the ICF prior to their preoperative study evaluation:

Subject [redacted]	evaluated on [redacted]	ICF signed [redacted]
Subject [redacted]	evaluated on [redacted]	ICF signed [redacted]
Subject [redacted]	evaluated on [redacted]	ICF signed [redacted]
Subject [redacted]	evaluated on [redacted]	ICF signed [redacted]
Subject [redacted]	evaluated on [redacted]	ICF signed [redacted]

Your response states that it is currently your policy to obtain informed consent prior to any study evaluations, and that you will not enroll any new subjects or ship devices until there is evidence that new subjects have been properly consented. Your response is inadequate in that you did not indicate when this policy was effective. Please provide a copy of this policy.

d. You failed to ensure proper monitoring of the clinical investigation in that you conducted monitoring visits of only one of the nine clinical sites participating in phase 1 of the [redacted] clinical study.

Your response states that you have identified a monitoring visit to another clinical site. In addition, your response states that you will conduct special monitoring visits at each investigational site that has not been monitored within the last six weeks. Your response to this deviation appears adequate.

**Failure to obtain a signed investigator agreement from each participating investigator [21 CFR 812.43(c)].**

Pursuant to 21 CFR 812.43(c), sponsors are responsible for obtaining a signed investigator agreement from each participating investigator. Examples of your failure to adhere to the above stated regulation include, but are not limited to, the following:

a. [redacted] M.D., was the clinical investigator at [redacted] (site [redacted]) from 2002 to 2005, and [redacted] two subjects. However, there is no investigator agreement signed by Dr. [redacted]

b. [redacted] M.D., did not sign an investigator agreement until [redacted]. However, he [redacted] subject [redacted] on [redacted] and activated the [redacted] on [redacted] and is listed on the ICF form that subject [redacted] signed on [redacted]

Your response to the above items states that Dr. [redacted] originally signed an investigator agreement on [redacted] but that this agreement was located after the FDA inspection, and that the investigator agreement that was shown to the FDA investigator during the inspection was a second agreement. Your response also states that in the future, you will not accept second signed investigators agreements. In addition, you state that it is your policy to not enroll subjects or ship devices until a signed investigator agreement has been received. Your response is inadequate in that you did not indicate when this policy became effective. Please provide a copy of this policy.

c. [redacted] M.D., performed a [redacted] study evaluation on subject [redacted] on [redacted]. However, Dr. [redacted] did not sign an investigator agreement until [redacted]

d. Subject [redacted] had a [redacted] study evaluation checklist visit on [redacted] and signed the ICF on [redacted]. However, the clinical investigator, [redacted] M.D., did not sign the investigator agreement until [redacted]

Your response to the above 2 items acknowledges that investigator agreements were not always signed prior to subject study evaluation. Please be aware that a clinical investigator must sign the investigator agreement prior to participation in any FDA-regulated device clinical study. As stated above, please provide a copy of your current policy regarding investigator agreements.

**Failure to maintain accurate, complete, and current records of disposition that describe the batch number or code marks of any devices returned to the sponsor, repaired, or disposed of in other ways by the investigator or another person, and the reasons for and method of disposal [21 CFR 812.140(b)(2)].**

Pursuant to 21 CFR 812.140(b)(2), sponsors are responsible for maintaining accurate, complete, and current records of disposition that describe the batch number or code marks of any devices returned to the sponsor, repaired, or disposed of in other ways by the investigator or another person, and the reasons for and method of disposal. Examples of your failure to adhere to the above stated regulation include, but are not limited to, the following:

There is no record of the disposition [redacted] units [redacted] and [redacted]

Your response states that you believe these [redacted] were shipped to the manufacturing facility in [redacted] due to expiry date. In addition, you indicate that the tracking system that you now have in place has assisted in tracking devices throughout the study, including final device disposition. Your response appears adequate.

Regarding Form FDA 483 observation 5, regarding lack of clinical investigator financial disclosures, your response states that you will not enroll new subjects or ship devices until you have received investigator financial disclosure information. Your response to this item appears adequate.

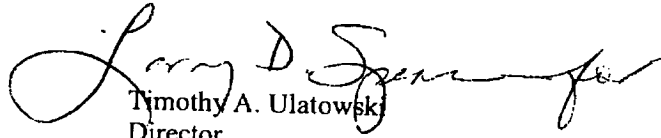
Regarding Form FDA 483 observation 6, regarding your failure to submit yearly progress reports, your response acknowledges that the annual progress report was not submitted during 2001. Your response also states that the annual progress report for 2005 was submitted late, on 3/1/06. Although your response states that you have introduced additional management oversight to ensure that annual progress reports are submitted to the IDE on time, no specific information was provided, therefore, your response is inadequate. Please provide the preventive measures that you have taken or plan to take to ensure that all annual progress reports are submitted as required.

The violations described above are not intended to be an all inclusive list of problems that may exist with your clinical study. It is your responsibility as a study sponsor to ensure compliance with the Act and applicable regulations.

Within fifteen (15) working days of receiving this letter, please provide written documentation of the additional actions you have taken or will take to correct these violations and prevent the recurrence of similar violations in current or future studies for which you are the study sponsor. Any submitted corrective action plan must include projected completion dates for each action to be accomplished. Failure to respond to this letter and take appropriate corrective action could result in the FDA taking regulatory action without further notice to you. Send your response to: Attention: Doreen Kezer, Food and Drug Administration, Center for Devices and Radiological Health, Office of Compliance, Division of Bioresearch Monitoring, 9200 Corporate Boulevard, HFZ-310, Rockville, Maryland 20850.

A copy of this letter has been sent to the Denver District Office, 6<sup>th</sup> and Kipling Street, P.O. Box 25087, Denver, Colorado 80225-0087. Please send a copy of your response to that office. If you have any questions, please contact Doreen Kezer at telephone number (240) 276-0125 or at e-mail address [doreen.kezer@fda.hhs.gov](mailto:doreen.kezer@fda.hhs.gov).

Sincerely yours,

A handwritten signature in cursive script, appearing to read "Timothy A. Ulatowski".

Timothy A. Ulatowski  
Director

Office of Compliance  
Center for Devices and Radiological Health