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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

WARNING LETTER

JUL 12 2005

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

FEDERAL EXPRESS

Jack F. Cahill  
President-Surgical Division  
Encore Medical Corporation  
9800 Metric Boulevard  
Austin, Texas 78758

Dear Mr. Cahill,

During an inspection of your firm located in Austin, Texas on January 11, 2005 through February 1, 2005, our investigator(s) determined that your firm manufactures Encore Reverse Shoulder Prosthesis. These products are devices within the meaning of section 201(h) of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. § 321(h)). The purpose of this inspection was to determine if your activities as the sponsor of the study for the Encore Reverse Shoulder Prosthesis, IDE [redacted] complied with applicable FDA regulations. The Reverse Shoulder Prosthesis is a device as defined in Section 201(h) of the Federal Food, Drug, and Cosmetic Act (The Act) [21 U.S. C. § 321(h)].

Our inspection revealed that your firm introduced the Reverse Shoulder Prosthesis (RSP) into interstate commerce without approval or clearance from FDA in violation of the Act. We acknowledge that you subsequently obtained IDE approval for the RSP in [redacted]. However, the inspection documented that you modified the design approved in the IDE when you introduced into interstate commerce devices that were intended to be used with the Reverse Shoulder Prosthesis before submitting and obtaining approval for an IDE supplement. The inspection also documented deviations from the requirements of Title 21, Code of Federal Regulations (21 CFR), Part 56 – Institutional Review Boards, Part 50 – Protection of Human Subjects, and Part 812 – Investigational Device Exemptions. These deviations were listed on the Form FDA 483, “Inspectional Observations,” that was presented to and discussed with you, Craig Smith, Albert E. Alonso, Perry Barrs, Jose L. Naveira, and Christie Shumaker, at the conclusion of the inspection. Each of these violations is discussed below.

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

The deviations noted on the FDA 483, as well as Mr. Alonso’s written response, dated March 15, 2005, to the FDA 483 items are discussed below.

**A. Introduction of the Reverse Shoulder Prosthesis into Interstate Commerce Without Approval or Clearance**

The inspection revealed that you shipped the Reverse Shoulder Prosthesis (RSP) into interstate commerce before obtaining marketing clearance or approval for the RSP, which is a violation of the law. Specifically, these devices were adulterated under section 501(f)(1)(B) of the Act [21 U.S. C. § 351(f)(1)(B)] because you did not have an approved application for premarket approval, (PMA), in effect pursuant to section 515(a) [21 U.S. C. § 360e(a)] of the Act, and you did not have an approved application for investigational device exemption (IDE) under section 520(g) of the Act [21 U.S. C. § 360j(g)] when these devices were shipped. These devices were also misbranded under section 502(o) of the Act [21 U.S. C. § 352(o)] because you did not notify the agency of your intent to introduce the device into commercial distribution, as required by section 510(k) of the Act [21 U.S. C. § 360(k)]. For a device requiring premarket approval, the notification required by section 510(k) of the Act is deemed satisfied when a PMA is pending before the agency. 21 C.F.R. 807.81(b).

The inspection also revealed that you shipped modified devices intended to be used with the Reverse Shoulder Prosthesis (RSP), which modified the design of the RSP approved for use in IDE [redacted]. These devices were not the subject of an approved IDE supplement and were not covered by the exemption from PMA requirements provided by the IDE for the RSP device. Consequently, these devices were also adulterated under section 501(f)(1)(B) of the Act [21 U.S. C. § 351(f)(1)(B)], and violated the IDE regulation requiring submission of a supplemental application prior to implementing a change to the investigational plan, 21 C.F.R. 812.35, causing them to be adulterated under section 501(i) of the Act [21 U.S. C. § 351(i)] as well.

Our review indicates that you introduced the RSP and devices intended to be used with the RSP that modified the RSP approved for use in IDE [redacted] into interstate commerce as follows:

1. From November 2, 1998, to October 28, 2002, 120 of the RSPs were shipped and implanted into patients prior to the date you received IDE approval for these devices. Your firm did not receive conditional approval of the IDE [redacted] for the RSP until October 29, 2002.

Mr. Alonso's response, dated March 15, 2005, indicates that previous management at Encore Medical Corporation provided the 120 RSPs to an orthopedic surgeon as custom devices prior to the date you received IDE approval for these devices. Mr. Alonso also indicated that your training of employees on the custom device requirements and the use of custom devices was based on your understanding of the regulation.

Your response that the RSPs were distributed as custom devices is inadequate. The distributed/implanted devices are off-the-shelf devices and do not meet the

requirements for custom devices as described in 21 CFR 812.3(b). A custom device is a device that meets a narrow and specific set of statutory requirements. According to the definition of a custom device in 21 CFR 812.3(b), a custom device is a device that deviates from devices generally available or from an applicable premarket approval requirement in order to comply with the order of an individual physician; is not generally available to, or generally used by other physicians; and is not generally available in finished form for purchase or for dispensing upon prescription. In addition, the regulation states that a custom device is intended for use by an individual patient named in the order of a physician or dentist, and is to be made in a specific form for that patient, or is intended to meet the special needs of the physician or dentist in the course of professional practice. The RSPs distributed were not made in a specific form for a specific patient; hence, the RSP is not a custom device. A device must meet all portions of the custom device definition in order to be considered a custom device.

Your firm's response also does not address whether or not you notified patients who received the RSP prior to initiation of the study that they received an investigational device as defined in 21 CFR 812.3(g) and if you obtained informed consent from these patients.

2. Between March 10, 2003, and November 12, 2004, ten subjects were implanted with the RSP, [REDACTED] without 510(k) clearance or PMA approval. This device was not submitted for approval as part of the original IDE study. Further, you did not submit the RSP/[REDACTED] in an IDE supplement for use as part of the clinical study. Our records show that you submitted a premarket notification [REDACTED] for the RSP, [REDACTED] on October [REDACTED], 2003. A letter dated June 10, 2004, was sent to you stating that 30 days had elapsed since the Agency's request for additional information, and that in accordance with our regulations, 21 CFR 807.87(l), the Agency considered your 510(k) withdrawn. Therefore, this device has not received 510(k) clearance. This letter also states the following: "You may not market this device until you have received a letter from FDA allowing you to do so. If you market the device without FDA clearance/approval, you will be in violation of the Federal Food, Drug, and Cosmetic Act."

Mr. Alonso's response, dated March 15, 2005, states that the practice of providing the RSP/[REDACTED] to surgeons has been stopped and that the entire inventory has been destroyed so that these devices will not be used until an IDE supplement is obtained.

In addition to this response, please address what procedures have been or will be implemented to ensure other devices without an approved IDE, an approved PMA, or cleared 510(k) are not distributed in the future. Mr. Alonso's response does not address devices distributed and implanted into subjects. Please address the following concerns: (1) How will you retrieve the adulterated RSP/[REDACTED]

[redacted] that may still be in distribution; (2) How will you notify clinical investigators and IRBs that they received an uncleared or unapproved device; and (3) How will subjects implanted with the device be notified that they were implanted with a device that had not received FDA clearance or approval? Mr. Alonso's response does not address whether you have audited your distribution records to determine if other uncleared or unapproved devices were distributed and, if so, your procedures for disposition of these devices.

3. Subject [redacted] was implanted with the RSP [redacted] (Catalog Number [redacted]) and the RSP [redacted] (Catalog Number [redacted]), which were not covered under the approved IDE study at that time. In addition, these devices do not have 510(k) clearance or PMA approval. Based on the list of Research and Development numbers and corresponding manufacturing catalog numbers that you provided to our investigator, it appears as though you subsequently submitted the RSP [redacted] (Catalog No. [redacted]) in a supplement to IDE [redacted] on December 30, 2004, which was approved on March 18, 2005. It does not appear that the RSP [redacted] (Catalog Number [redacted]) was ever submitted in an IDE supplement for approval as part of the IDE.

Mr. Alonso's March 15, 2005, response explains that the patient had a failed implant manufactured by another company and that the patient required revision surgery. He conveys that the devices in the field have been returned and are now accounted for in your business information technology (IT) system. Mr. Alonso further states that investigators will be re-educated on your protocol and strict control over RSP devices will now be exercised to ensure their appropriate use. In addition, Mr. Alonso's response indicates that you have submitted an IDE supplement for these larger sizes of the RSP [redacted] and RSP [redacted].

In addition to the above response, please address how you will ensure that devices without an approved IDE, an approved PMA, or cleared 510(k) are not distributed in the future both for patients that may be enrolled in an Encore study and for patients that are not enrolled in an Encore study. Please inform us of the date that you submitted the IDE supplement for the larger sizes of the RSP [redacted]. Also, confirm if the RSP [redacted] referenced in this charge is the same device that was subsequently submitted in your IDE supplement dated December 30, 2004. If it is not, please inform us of the date of the IDE supplement that includes this device.

Please document how your clinical investigators will be re-educated and explain your procedures for proper control and segregation of devices to ensure their appropriate use. Explain how you intend to notify clinical investigators and IRBs that they received an uncleared or unapproved device, and how subject [redacted] and any other subjects who received uncleared or unapproved RSP devices will be notified that the devices used have not received FDA clearance or approval. In addition, please document device accountability in terms of released versus returned devices.

4. Twelve subjects who were entered into the IDE study for the RSP had revision surgery that included implantation of devices that were not included as part of the approved IDE and that did not have 510(k) clearance or PMA approval. Seven of these subjects had physician's orders on file and 5 subjects did not have physicians' orders on file.

Mr. Alonso's response, dated March 15, 2005, acknowledges this and states that missing records were a result of human error and insufficient monitoring. Mr. Alonso states that a new procedure

This response is inadequate in that it appears as though all twelve of the subjects referenced in this observation received uncleared or unapproved RSP devices as "custom" devices. However, these devices appear to be off-the-shelf devices and do not meet the requirements for custom devices as described in 21 CFR 812.3(b) and as previously discussed. Again, please address how you will ensure other devices without an approved IDE, an approved PMA, or cleared 510(k) are not distributed in the future as custom devices.

#### **B. Investigational Device Exemption**

**Failure to obtain Investigational Review Board (IRB) approval prior to initiating the study. [21 CFR 812.20(a)(1) and (2), 812.30(a), 812.40, and 812.42]**

Pursuant to 21 CFR 812.40, the sponsor is responsible for ensuring that IRB approval is obtained for an investigation involving a device, such as the Encore Reverse Shoulder Prosthesis.

Examples of failure to adhere to the regulations include, but are not limited, to the following:

1. You failed to ensure that clinical investigators participating in the study obtained IRB approval prior to the use of the investigational device. [21 CFR 812.40 and 812.42] IDE

however, no clinical sites were notified of the requirement to obtain IRB approval for this supplement.

Mr. Alonso's response acknowledges this violation as an oversight on the part of previous employees. Mr. Alonso also stated that in order to correct this failure, IRBs are being contacted directly to ensure future compliance and that new staff has been hired to address FDA requirements. This response appears acceptable. Please provide documentation that IRBs were contacted along with their

responses. In addition, please provide documentation that employees were hired and trained to address the FDA requirements.

**Failure to adhere to investigational device exemption (IDE) requirements including ensuring control of the investigational device, monitoring the study properly, obtaining investigator agreements, and maintaining records relating to the investigation. [21 CFR 812.40, 812.43, 812.45, and 812.140(b)]**

Examples of failure to adhere to these requirements include, but are not limited to, the following:

1. You failed to properly monitor the investigation [21 CFR 812.40] in that you failed to ensure that devices specified in the IDE were used as per protocol. RSPs specified in [redacted] were used outside the IDE study, specifically, subjects [redacted] were implanted with RSPs but were not enrolled in the study.

Mr. Alonso acknowledges this violation and states that your old system was not sufficiently rigorous to control inventory. According to Mr. Alonso's response you are changing your IT systems to account for all IDE and custom devices as well as assuring that all site coordinators, sales representatives, and investigators have received written notification requiring that documentation of subject informed consent be obtained and submitted to the Encore Clinical Affairs department prior to distribution of any RSP IDE devices. This corrective action appears acceptable. Please provide documentation showing that subjects and IRBs were notified.

2. The protocol entitled [redacted] Your records document that, of the [redacted] participating in the study, [redacted]

Mr. Alonso states that all existing sites will be trained by the end of June and Encore is hiring additional staff to address this as well as other noted deficiencies and that no new sites will be added until an [redacted] is conducted. This corrective action appears inadequate. Please indicate the specific year you plan to complete training of all existing sites and your progress to date. In your response, please indicate if sites where a [redacted] was not conducted are no longer participating in the study until your [redacted] and training have been completed.

3. You failed to maintain investigational device accountability for two Reverse Shoulder Prothesis [redacted] [21 CFR 812.43(b)] Specifically, there was no accounting for [redacted] one each from lot number [redacted] (Catalogue No. [redacted]) [redacted] (Catalogue No. [redacted])

Mr. Alonso states that updated SOP # [REDACTED] and entitled [REDACTED]

This corrective action appears acceptable.

4. You failed to obtain financial disclosure statements from each clinical investigator participating in the IDE [REDACTED] [21 CFR 812.43(c)(5)].

Mr. Alonso states that a financial disclosure agreement has been prepared, and Encore is in the process of obtaining signed statements from all of their investigators. This response appears acceptable. Please provide a copy of the financial disclosure agreement that has been prepared. In addition, please respond with an update of the status of signed statements obtained from your investigators.

5. You did not have records documenting IRB approval for [REDACTED] clinical sites for IDE [REDACTED]. This supplement requested [REDACTED]

Mr. Alonso states that this observation is the result of an oversight on the part of previous departmental employees and that in order to ensure compliance in the future the IRBs are being contacted directly and new staff has been hired to address FDA requirements. This response appears acceptable. Again, please provide documentation that IRBs were contacted, their responses, and the training documentation of your employees hired to address these issues.

For your information, we note from an inspection at Dr. Frankle's site that several devices were shipped and implanted based upon compassionate use. Please note that if there is a patient or small group of patients who do not meet the requirements for inclusion in the clinical investigation and for which there is no alternative treatment but for whom the treating physician believes the device may provide a benefit in treating and/or diagnosing their disease or condition you should contact the Investigational Device Exemption staff at 301-594-1190 before allowing use of a device on a "compassionate" basis. In addition you can reference the following Internet site: [www.fda.gov/cdrh/devadvice/ide/early.shtml](http://www.fda.gov/cdrh/devadvice/ide/early.shtml).

This letter is not intended to be an all-inclusive list of deficiencies at your facility. As the sponsor, it is your responsibility to ensure that investigations that you participate in are conducted in accordance with each requirement of the Act and regulations. Mr. Alonso indicates that Encore Medical has developed corrective measures and implemented new systems and procedures to ensure these deviations are not repeated in the future.

You should take prompt action to correct these deviations. Failure to promptly correct these deviations 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 civil money penalties.

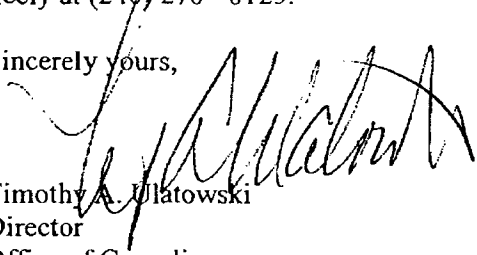
Please notify this office in writing within fifteen (15) working days from the date you receive this letter, of the specific steps you have taken to correct the noted violations, including an explanation of how you plan to prevent these violations, or similar violations, from occurring again. Include all documentation of the corrective action you have taken. If you plan to make any corrections in the future, include those plans with your response to this letter as well. If corrective action cannot be completed within 15 working days, state the reason for the delay and the time within which the corrections will be completed.

You should direct your response to the Food and Drug Administration, Center for Devices and Radiological Health, Office of Compliance, Division of Enforcement B, Orthopedic, Physical Medicine, and Anesthesiology Devices Branch, HFZ-343, 2098 Gaither Road, Rockville, Maryland 20850. Attention: William MacFarland, Branch Chief.

A copy of this letter has been sent to the Food and Drug Administration, FDA's Dallas District Office, 4040 North Central Expressway, Suite 300, Dallas, Texas 75204. We request that a copy of your response also be sent to FDA's Dallas District Office.

If you have more specific questions concerning how FDA marketing requirements affect your particular device, please feel free to contact Mr. William MacFarland at (240) 276 - 0120. For any questions concerning bioresearch monitoring and conduct of a clinical study you may contact Mr. Levering Keely at (240) 276 - 0125.

Sincerely yours,



Timothy A. Ulatowski  
Director  
Office of Compliance  
Center for Devices and Radiological Health