



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Los Angeles District

19701 Fairchild
Irvine, California 92612-2506
Telephone (949) 608-2900

WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

February 5, 2007

W/L 08-07

Mr. Michael A. Mussallem
Chairman & CEO
Edwards Life Sciences, LLC
One Edwards Way
Irvine, CA 92614

Dear Mr. Mussallem:

During an inspection of your firm located in Irvine, California, on April 5 through August 10, 2006, investigators from the U.S. Food and Drug Administration (FDA) determined that your firm manufactures the Swan-Ganz Continuous Cardiac Output (CCO) Catheter, Vigilance Monitors, and stents. Under section 201(h) of the Federal Food, Drug, and Cosmetic Act (the Act) [21 U.S.C. § 321(h)], these products are devices because they are intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, or are intended to affect the structure or any function of the body.

This inspection revealed that these devices are adulterated within the meaning of section 501(h) of the Act (21 U.S.C. § 351(h)), in that the methods used in, or the facilities or controls used for, their manufacture, packing, storage, or installation are not in conformity with the Current Good Manufacturing Practice (CGMP) requirements of the Quality System (QS) regulation found at Title 21, Code of Federal Regulations (CFR), Part 820. We received your September 13, 2006, response concerning our investigator's observations that were noted on the Form FDA-483, List of Inspectional Observations issued to you. We also acknowledge receipt of Dr. [REDACTED]'s November 16, 2006, letter, which provided an updated response to the FDA-483 observations. We address these responses below, in relation to each of the noted violations. These violations include, but are not limited to, the following:

1. Failure to establish and maintain adequate procedures to analyze all sources of quality data, to investigate the cause of nonconformities, and to identify corrective and preventive actions (CAPAs), as required by 21 CFR 820.100(a). For example,

- a) There is no documentation that the numerous open complaints from 2000 to the present were analyzed to identify existing and potential nonconforming product, or to determine whether corrective and preventive actions were necessary.
- b) There was no documentation of corrective and preventive action activities regarding the lack of equipment qualifications for a compression tester, vibration control, and four out of five environmental chambers.
- c) A CAPA was opened because your packaging laboratory equipment was not qualified. However, the CAPA was deficient in that you failed to investigate the cause of the nonconformance, identify any necessary corrective and preventive actions, perform a root cause analysis, or validate the corrective action to ensure the action was effective and did not adversely affect the finished device.

According to your response, you have revised SOP [REDACTED] (Quality System Audit Program), which now requires documentation of CAPA activities. The CAPA section stipulates management will provide details regarding root causes to the auditor. The SOP also states CAPA plans must address the impact of nonconformance on product quality, and that final audit reports are to include findings and observations, CAPA plans, and identification of systemic or repeat findings.

Your response also indicates that all equipment qualifications have now been completed. A risk mitigation study found the lack of prior equipment qualification did not affect product quality. You state all other R&D departments are currently evaluating the qualification status of equipment in each laboratory. A re-audit is planned for the fourth quarter of 2006, which will verify corrective actions taken.

Your response to item 1 appears acceptable.

2. Failure to establish and maintain adequate procedures to review, evaluate, and investigate complaints involving the possible failure of a device, as required by 21 CFR 820.198(c). For example,
 - a) During the use of a Swan-Ganz CCO catheter on 12/1/04 (lot # [REDACTED]), the user received the error message, "catheter verification, use bolus mode" ([REDACTED]). The catheter was replaced with a catheter from a different lot and the device functioned as specified, but no further investigation as to the root cause of the device failure was conducted.
 - b) A second complaint ([REDACTED]) for the same catheter and lot number was received for the same problem on the same date. The device was not returned and a complete investigation could not be performed.

- c) Six catheters, separately connected to a Vigilance Monitor, ([REDACTED] #s [REDACTED] through [REDACTED]) at a user facility, experienced thermal filament error messages during use. No investigation or evaluation as to the root cause was conducted on the remaining five catheters.

Your response dated September 13, 2006, and also the follow-up response dated November 16, 2006 is not adequate because the evidence of training and implementation of the revised procedure were not submitted to FDA. The change was supposed to be effective October 1, 2006.

3. Failure to ensure that complaints are processed in a uniform and timely manner, as required by 21 CFR 820.198(a)(1). Numerous complaints remain open dating as far back as the year 2000. For example,
 - a) A complaint for an optical module dated 08/01/05 was returned for evaluation on 08/15/05. The evaluation summary resulted in no fault found. The CER report # [REDACTED] does not report a closed date.
 - b) A complaint for a CCO catheter interface cable dated 11/08/05 was returned for evaluation on 11/21/05. The CER report # [REDACTED] does not show any evaluation summary results or date closed.

Your response indicates all complaints open beyond 60 days between the year 2000 and the present have now been closed. Your response is inadequate, however, because FDA is unable to verify that corrective actions have been implemented and, therefore, that closing all the complaints was effective and appropriate. Furthermore, there is no evidence that personnel have been trained in the new procedure or that the new procedure was implemented.

4. Failure to develop, conduct, control, and monitor production processes to ensure that a device conforms to its specifications, as required by 21 CFR 820.70(a). For example,

Packaging validations for protocol numbers [REDACTED], [REDACTED], [REDACTED], [REDACTED], [REDACTED], and [REDACTED] were performed with non-qualified equipment.

During the inspection, the investigators were provided with a copy of a report that assessed the impact of the calibration method on product quality. The report concluded there was no significant impact. Furthermore, your response indicates your firm has now completed all qualifications for your packaging laboratory equipment. This is supported by Attachment # [REDACTED], Risk Mitigation Summary for Irvine Packaging Engineering Lab.

Your response to item 4 appears acceptable.

5. Failure to establish and maintain adequate procedures and documentation for the design history file, as required by 21 CFR 820.30(j). For example,

A Packaging Engineering Benchmark Study was initiated by your firm in 2004 and completed in 2005. The purpose of the survey was to justify the change from an ASTM pre-conditioning standard to an ambient pre-conditioning procedure, and to reduce sample size. However,

- a) No raw data for the interim report or for the final study results were available for review.
- b) The Vibration Measurement Analysis was missing and not available for review.
- c) No final report for the distribution study was ever issued.

In your response dated September 13, 2006, you stated that you will revise SOP [REDACTED], How to Prepare and Initiate an ECR (Engineering Change Request), to require additional review and approval by engineering management of all changes affecting quality, form, fit, or function. You also stated that training of all employees in the new procedure is expected to be completed by November 2006. Your response is inadequate because the evidence of training and implementation of the revised procedure were not submitted to FDA. Your response dated November 16, 2006 includes an e-mail dated 9/27/06 that indicates a revised SOP exists, and that training was offered in October, but does not adequately show that the training was taken by employees, or that the revised SOP is being implemented.

6. Failure to establish and maintain adequate procedures for changes to a specification, method, or process, or to verify or validate the change under 21 CFR 820.75, as required by 21 CFR 820.70(b). For example,

A change in the procedure for ambient pre-conditioning was made in 1996, but Technical Summary Report (TS # [REDACTED]) describing the change was not written until April 21, 2006.

Your response dated September 13, 2006, includes the revised SOP [REDACTED], How to Prepare and Initiate an ECR, to ensure that such technical reports are prepared in a timely manner. You also agreed to implement a process to ensure closure of any open protocols and stated that you would retrain all employees on the revised procedure by November 1, 2006. Your response is inadequate because adequate evidence of training and implementation of the revised procedure was not submitted to FDA.

7. Failure to establish and maintain adequate procedures for the evaluation, control, and documentation of suppliers, as required by 21 CFR 820.50(a). For example,

Testing, including, but not limited to: vibration test, drop test, and conditioning, for protocol #s [REDACTED], [REDACTED], and [REDACTED] were conducted by a supplier in January and February 2006, but the supplier agreement was not signed until April 12, 2006.

In your response of September 13, 2006, you have submitted revised SOP [REDACTED] (Supplier Approval) and SOP [REDACTED] (Test Protocols and Reports). Also, your November 16, 2006 response included a further revised version of SOP [REDACTED]. The former SOP requires approval of all suppliers whose output could affect product quality. The latter SOP states any suppliers involved in testing must be approved by your firm prior to initiating testing or collecting data. Your responses are inadequate because there is no evidence that personnel have been retrained on the new procedures or that the new procedures have been implemented.

8. Failure to maintain adequate procedures to ensure that sampling methods are adequate for their intended use and to ensure that when changes occur the sampling plans are reviewed and documented, as required by 21 CFR 820.250(b).

For example, the sample sizes used in your package validation study did not follow your procedure for Statistical Techniques ([REDACTED]). This procedure identifies sterile barrier integrity as a critical class and Table [REDACTED] (Attribute Sampling for Validations) specifies that the minimum sample number for critical classes is [REDACTED]. The record shows you will use [REDACTED] samples at [REDACTED] C and [REDACTED] samples at [REDACTED] C, in accordance with SOP [REDACTED], Design Verification for Packaging and Packaging Systems dated 02/02/06.

Your firm provided Technical Summary # [REDACTED] to the investigators on April 21 and May 11, 2006, which indicates a sample size of [REDACTED] at each temperature is consistent with your SOP for Statistical Techniques, [REDACTED]. However, this is contrary to the sample size requirements in the SOP. Your response of September 13, 2006, is inadequate because you have not provided a satisfactory explanation for this inconsistency.

Please explain further the inconsistency between the sample size stipulated in [REDACTED] and in Technical Summary # [REDACTED].

Our inspection also revealed that your Swan Ganz CCO Catheter, Cable and Vigilance Monitor, and LifeStent NT stent delivery system devices are misbranded under section 502(t)(2) of the Act [U.S.C. § 352(t)(2)] in that your firm failed to furnish material or information respecting the device that is required by or under Section 519, [21 U.S.C. § 360i], and 21 CFR Part 803, Medical Device Reporting (MDR) Regulation. Significant deviations include, but are not limited to, the following:

1. Failure to submit an MDR report to FDA within 30 calendar days of becoming aware that a device you market may have caused or contributed to a death or serious injury, as required by 21 CFR 803.50(a)(1).

A patient undergoing cardiac bypass surgery was injured by a CCO thermodilution catheter when its thermal filament malfunctioned causing charring of the atrium. The patient's heart was so badly damaged that he eventually required a heart transplant. No MDR report for this incident was filed within the required 30-calendar day time frame.

Although not an FDA 483 observation, it is clear from Customer Experience Report # [REDACTED] ([REDACTED]) that your firm was aware that the patient's heart was burned and cauterized during surgery and, as a result, required a heart transplant.

Your September 13, 2006, response indicates you have corrected the omission by filing separate MDRs for the Vigilance Monitor, Cable, and Catheter, all 3 of which form the entire monitoring system. Additionally, your Adverse Event Reporting Procedure (SOP [REDACTED]) has been revised to address appropriate filing of future MDRs. Further, the firm's personnel have been trained in the new procedure and the training records have been submitted for FDA review. However, your response is inadequate because there is no documentation that SOP [REDACTED] (revised 9/11/06) has been implemented.

2. Failure to submit an MDR report within 30 days for a device that has malfunctioned and that the device or a similar device would likely cause or contribute to a death or serious injury, if the malfunction were to recur, as required by 21 CFR 803.50(a)(2).
For example:

A LifeStent NT 35 delivery system became stuck in the distal end of the stent ([REDACTED] # [REDACTED]). After [REDACTED] hours, the device was eventually removed; an angiogram revealed it was mangled in the process. The surgeon had to deploy another guide wire to remove the delivery system and prevent further injury. An MDR report for the event was finally filed on August 14, 2006, nearly a year after the event occurred. Adverse Event Reporting Procedure (SOP [REDACTED]) has been revised to address appropriate filing of future MDRs. Further, your firm's personnel have been trained in the new procedure, and the training records have been submitted for FDA review. However, your response dated September 13, 2006, is inadequate because there is no documentation that SOP [REDACTED] (revised 9/11/06) has been implemented.

3. Failure to submit to FDA all information as required in subpart E of 21 CFR Part 803 that is reasonably known to you regarding a device that has caused a serious injury, as required by 21 CFR 803.50(b)(1).

Med Watch Report #6000002-2004-0384, involving the injured heart, was submitted to FDA but indicated the patient's condition was unknown. However, Customer Experience Report ([REDACTED] # [REDACTED]) dated October 11, 2004, reports your firm knew about the event, similar failures and root causes, but did not disclose them in the initial MDR Report.

The revised SOP for Adverse Event Reporting provides a complete and up-to-date procedure for adverse event reporting. For example, section 6.41 states any events that

are determined not to be MDR reportable must contain a second review and the reasons for not reporting must be documented. The SOP also provides that reportable events that result in a patient death, serious injury, or reportable malfunction will need completion of a 3500A (Med Watch) and must be submitted to FDA within 30 calendar days. This meets the requirements of 21 CFR 803.50. You indicate your firm has reviewed all MDRs for the past two years for compliance with SOP1106 and found no other reports that require MDR filing. Further, your personnel have been trained in the new procedure, and the training records have been submitted for FDA review. However, your response dated September 13, 2006, is inadequate because there is no documentation that SOP1106 (revised 9/11/06) has been implemented.

4. Failure to submit a supplemental report to FDA within 1 month of receipt of information that was known to you regarding a serious injury reportable under 21 CFR 803.50, as required by 21 CFR 803.56. For example,
 - a) Your firm failed to submit a supplemental report to FDA for the patient whose heart was burned by the CCO catheter after receiving additional information about the case. The complaint file shows you were aware that the patient required a heart transplant and was "still waiting for a heart" as of October 18, 2004. A supplemental report for MDR #6000002-2004-00384 was not filed until June 6, 2006, (two years after the initial event). No separate report or information with respect to the Cable and Vigilance Monitor was included.
 - b) A similar complaint from [REDACTED] for a CCO catheter that had melted during a procedure on October 9, 2002, was not disclosed in a supplemental report although your firm was aware that a software problem was the root cause of the event.

You have now provided separate MDRs for the cable, Vigilance Monitor, and Catheter, and have revised SOP [REDACTED] (Adverse Event Reporting) to modify the reporting time frames consistent with the regulations. Additionally, you stated that your personnel have been retrained in the new procedure. However, your response dated September 13, 2006, is inadequate because there is no documentation that SOP [REDACTED] (revised 9/11/06) has been implemented.

You should take prompt action to correct the violations addressed in this letter. 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 civil money penalties. In addition, Federal agencies are advised of the issuance of all Warning Letters pertaining to medical devices so that they may consider this information when considering the award of contracts.

Additionally, premarket approval applications for Class III devices to which the Quality System regulation deviations are reasonably related will not be approved until the

violations have been corrected. Requests for Certificates to Foreign Governments will not be granted until the violations related to the subject devices have been corrected.

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 documentation of the corrective actions you have taken. If your planned corrections will occur over time, please include a timetable for implementation of those corrections. 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

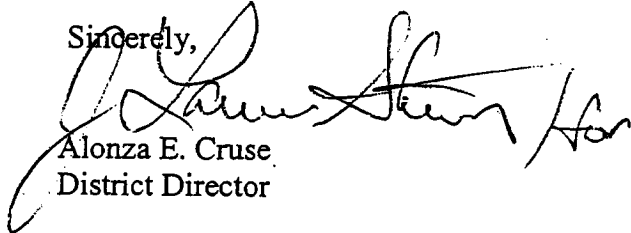
Please direct your written response to the attention of:

Pamela B. Schweikert
Director, Compliance Branch
United States Food and Drug Administration
19701 Fairchild
Los Angeles, California 92612-2506.

If you have any questions about the content of this letter, please contact Robert B. McNab, Compliance Officer at 949-608-[REDACTED]. In order to facilitate and to accommodate your requests for a meeting we are willing to schedule a meeting at the District Office in Irvine, CA in the near future at a mutually agreeable time.

Finally, you should know that this letter is not intended to be an all-inclusive list of the violations at your facility. It is your responsibility to ensure compliance with applicable laws and regulations administered by FDA. The specific violations noted in this letter and in the Inspectional Observations, Form FDA 483 (FDA 483), issued at the closeout of the inspection may be symptomatic of serious problems in your firm's manufacturing and quality assurance systems. You should investigate and determine the causes of the violations, and take prompt actions to correct the violations and to bring your products into compliance.

Sincerely,


Alonza E. Cruse
District Director

cc: Department of Health Services
Attn: Chief, Food & Drug Branch
P.O. Box 997413, MS-7602
Sacramento, CA 95899-7413