



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service
Food and Drug Administration
Central Region

950740

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New Jersey District
Waterview Corporate Center
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Parsippany, NJ 07054

December 14, 2005

WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Shlomo Gabbay, M.D.
Chief Scientific Officer
Chairman of the Board of Directors
Shelhigh, Inc.
650 Liberty Avenue
Union, New Jersey 07083

File #: 06-NWJ-09

Dear Dr. Gabbay:

During inspections of your establishment located in Union, New Jersey, on April 28 through May 16, 2005, and July 21 through August 10, 2005, our Investigators from the Food and Drug Administration (FDA) determined that your firm manufactures Porcine Pulmonic Valve Conduits, Aortic Valve Conduits, Mitral Valve Conduits, Flexible Annuloplasty Rings, Internal Mammary Arteries, and Pericardial Patches. These products are devices as defined by section 201(h) of the Federal Food, Drug, and Cosmetic Act (the Act).

The above-stated inspections revealed that many of your Pulmonic Valve Conduits models NR-4000 series devices are adulterated within the meaning of Section 501(f)(1)(A) of the Act (21 U.S.C. Section 351(f)(1)(A)), in that they are class III devices which are required by regulation promulgated under section 515 to have an approval under such section of an application for premarket approval (PMA) and which are not exempt from section 515 under section 520(g) and for which a PMA or product development protocol was not filed with the Secretary within 90 days of the regulation or for which an application has been filed and has been withdrawn without approval. Specifically, your firm has distributed the following unapproved Pulmonic Valve Conduits models NR-4000 series devices:

1. Curved Sleeve NR-4000PA-C (any size.)

2. Pulmonic Mini NR-4000PA-C (sizes 5 and 6 mm.)
3. NR-4000 (sizes 10, 25 and 27 mm.)
4. NR-4000PA (sizes 25 and 27 mm.)
5. NR-4000PA (any size) shipped prior to approval of this device on September 27, 2000.
6. NR-4000SS (any size) shipped prior to approval of this device on September 27, 2000.
7. NR-4000, NR-4000SS and NR-4000PA (sizes 19, 20, 21, 22, and 23 mm) shipped prior to approval of these devices on November 25, 2003.

The above stated inspections also revealed that your devices are adulterated under 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 conformance with the Current Good Manufacturing Practice (CGMP) requirements for medical devices which are set forth in the Quality System regulation, as specified in Title 21, Code of Federal Regulations (CFR), Part 820. Significant deviations include, but are not limited to, the following:

1. Failure to follow your own written procedures for design control in order to confirm that the changes made to the Pulmonic Valve Conduit were controlled to include validation or where appropriate, verification prior to their implementation, as required by 21 CFR 820.30(i). For example:
 - a. The design validation data ("Clinical Experience with the Shelhigh Pulmonic Valve Conduit, No-React Treated SPVC, January, 2004"), did not include an evaluation of data from 600 implants worldwide.
 - b. The design modifications made to the NR-4000 Pulmonic Valve were not conducted in accordance with your SOP 040028 (Design Control). There was no documentation to show design verification or validation data specifically for the Pulmonic Valve HR-4000 models identified as NR-4000-PA-C ("curved"), NR-4000-PA-C ("mini", sizes 5 or 6 mm) or the [REDACTED] (" [REDACTED] ").
2. Failure to follow your own written procedures for design validation to include a risk analysis for design changes as required by 21 CFR 820.30(g). Specifically, there was no documentation to show that a risk analysis was performed for each change that was made to the Porcine Pulmonic Valve

Conduit design, which included a curved sleeve, mini-pulmonic (5 and 6 mm), and an [REDACTED]. In addition, there was no data to show the estimation of the risks for each hazard. For example, your risk analysis does not identify the possible hazards with the mini-pulmonic (5 and 6 mm) for which the smaller conduit size and [REDACTED] could affect hydrodynamics in an area with significant pressure drop. Furthermore, smaller valves are more easily obstructed and are more quickly outgrown.

3. Failure to adequately verify or validate the corrective and preventive action to ensure that such action is effective and does not adversely affect the finished device as required by 21 CFR 820.100(a)(4). For example:
 - a. Your firm reported mislabeling of products (Lot #010122-SHP) where the corrective actions taken included changes to your computer system, data entry forms, and batch records. Changes to your computer system would require validation activities, which your firm failed to document for this incident.
 - b. Your firm reported that the [REDACTED] overflowed during the night (raw material tissue Lot HA 091801), which resulted in a loss of liquid which resulted in most of the [REDACTED] not being covered with solution. Your corrective actions of changing the [REDACTED] and adding [REDACTED] was not verified or validated in order to ensure that the actions taken did not adversely affect the finished device, and that the corrections were effective.
4. Failure of your Design History File to demonstrate that the design was developed following the approved design plan as required by 21 CFR 820.30(j). Specifically, your design history file for the Shelhigh No-React Porcine Valve Conduit, Model NR-4000, failed to include or reference the records necessary to demonstrate that the design was developed in accordance with the design control requirements of 21 CFR 820.30. For example, there was no documentation in your design control binder (Design History File) for the pulmonic valve conduit to show that design validation, including clinical study data, was performed as of May 16, 2005.
5. Failure to maintain complaint files as required by 21 CFR 820.198(a). Specifically, no complaint files were maintained for the years 2000, 2002, 2003, 2004, and 2005. For example, your firm received oral communication of problems by phone or from physicians during conferences

where these complaints are not reported in your complaint log.

6. Failure to review and evaluate all complaints to determine whether an investigation is necessary as required by 21 CFR 820.198(b). Specifically, your firm has failed to adequately investigate and follow-up on all complaints that were received from physicians by phone or during conferences from 1999 to the present.
7. Failure to establish and maintain procedures to adequately control the environmental conditions, which could reasonably be expected to have an adverse affect on product quality as required by 21 CFR 820.70(c). For example:
 - a. Your firm's sampling of airborne and surface microbes procedure (Document #060018, dated August 2, 2002) failed to explain how and when environmental monitoring of the packaging room [REDACTED] would be performed. In addition, the procedure does not specify the number of air samples that need to be collected (the procedure does no specify the specific sampling sites in each location for manufacturing and final packaging operations).
8. Failure to demonstrate that the device history records for the Pulmonic Valve Conduit Prostheses were manufactured in accordance with the device master records as required by 21 CFR 820.184. For example:
 - a. Your firm failed to document that the inspection and cleaning activities were performed for the [REDACTED] which were used to manufacture the Pulmonic Valve Conduit Prostheses (Serial Nos PE18459-12 (NR-4000SS), PE 19306-13 (NR-4000PA-C, PE18658-18), (NR-4000PA-C), and PE17058-16 (NR-4000PA-SS)).
 - b. Your firm failed to document the initial inspection of the [REDACTED] for the Pulmonic Valve Conduit Prostheses (Serial Nos PE17058-16 (NR-4000PA-SS), and PE19307-18 (NR-4000PA)).
9. Failure to validate a process whose results cannot be fully verified by subsequent inspection and test, as required by 21 CFR 820.75(a). Specifically, the autoclave validation failed to demonstrate that the autoclave process is capable of sterilizing packaging materials and equipment used in final product packaging. For example, your autoclave validation (dated October 25, 2004) documents the [REDACTED] [REDACTED] which is not routinely performed prior to autoclave sterilization.

10. Failure to ensure all personnel are trained to adequately perform their assigned responsibilities, and to document such training, as required by 21 CFR 820.25(b). Specifically, your employees training records do not specify what procedures each employee was trained on, and how their training relates to the procedures that apply to their areas of responsibility.

Furthermore, the inspections as noted above, revealed that your devices are adulterated within the meaning of Section 501(i) of the Act (21 U.S.C. Section 351(i)), and the Investigational Device Exemption Regulation, as specified in 21 CFR Part 812. Specifically, your firm failed to ensure IRB review and approval by FDA, before beginning the study of [REDACTED] device at [REDACTED], as required by 21 CFR Part 812.40.

The inspection conducted July 21 through August 10, 2005, also revealed that your devices are misbranded within the meaning of section 502(t)(2) of the Act (21 U.S.C. Section 352(t)(2)), in that your firm failed to furnish any material or information respecting the devices that is required by or under section 519 of the Act (21 U.S.C. Section 360(i)); the Medical Device Reporting (MDR) Regulation, as specified in 21 CFR Part 803; the Medical Device Tracking Requirements, as specified by 21 CFR Part 821; and the Reports of Corrections and Removals, as specified by 21 CFR Part 806. More specifically, your firm failed to:

1. Develop, maintain and implement an adequate MDR procedure, as required by 21 CFR Part 803.17. For example your firm lacks an adequate system for the effective identification, communication, and evaluation of events that may be subject to medical device reporting.
2. Maintain MDR event files, as required by 21 CFR Part 803.18(b). For example, your firm was notified of four voluntary MDRs for accelerated failure of the device, reported by the Pathology Department of [REDACTED] and your firm has failed document or reference the deliberations and decision making processes used to determine if these device related deaths were or were not MDR reportable events.
3. Adopt an adequate method of tracking for each type of device you distribute, that would enable you to provide FDA with device tracking information, as required by 21 CFR Part 821.25(a) and to keep current records of each tracked device released for distribution as long as such device is in use or in distribution for use, as required by 21 CFR Part 821.25(b). For example, your firm has not been consistently tracking the NR-4000 pulmonic valve conduit implants since its original approval in 1999 (HDE

980007). Your firm's implantation data, 1999 through 2005 for model NR-4000 pulmonic valves, alone and aside from other models, shows [REDACTED] as having been implanted at various U.S. locations. However, the firm's distribution shows [REDACTED] NR-4000 models as having been distributed.

4. Notify FDA and submit Part 806 information in a timely manner after becoming aware of a correction and removal situation with the NR-4000PA-C Mini series conduits, as required by 21 CFR Part 806.10(a). For example, your firm has not recalled the NR-4000 PA-C Mini series conduits in a timely manner as promised at the close of the August 10, 2005, inspection.

Finally, the inspections revealed that your firm has failed to comply with the conditions of approval for the humanitarian device exemption (HDE) for the Shelhigh Pulmonic Valve Conduit, NR-4000, with No React Treatment (H980007), as required by 21 CFR Part 814. More specifically, your firm has failed to comply with the following requirements:

1. 21 CFR Part 814.108 Supplemental applications were not submitted to H980007 for your firm's manufacturing site change to the Union, NJ location.
2. 21 CFR Part 814.126 post-approval requirements and reports were deficient by failing to maintain complete records in accordance with the HDE approval order regarding the Shelhigh Pulmonic Valve Conduit device (H980007) correspondence with IRBs and the agency. For example:
 - a. The most recent annual report submitted to the Agency on January 10, 2004, indicated [REDACTED] total implants world-wide. However, Shelhigh does not have records to show that this number is accurate.
 - b. Shelhigh has failed to collect post implantation data to support clinical experience with H980007 since the initial approval on September 29, 1999. Specifically, Shelhigh lacks documentation of explant data, post implantation outcomes, safety data, MDRs and/or post market studies.
3. 21 CFR Part 814.124(a) Institutional review board (IRB) requirements are deficient by failing to maintain adequate IRB approval documentation under H980007. Shelhigh had approval from one IRB, [REDACTED]. Shelhigh's implantation records show the H980007 device has been implanted in approximately [REDACTED] without evidence of IRB approval at those sites.

Your failure to comply with any post-approval requirement

constitutes a ground for withdrawal of the HDE. Commercial distribution of a device that is not in compliance with these conditions is a violation of the Act.

Federal agencies are advised of the issuance of all Warning Letters about devices so that they may take this information into account when considering the award of contracts. Additionally, no premarket approval applications for Class III devices to which the Quality System regulation deficiencies are reasonably related will be approved until the violations have been corrected. Also, no requests for Certificates to Foreign Governments will be granted until the violations related to the subject devices have been corrected.

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.

FDA's New Jersey District Office and Center for Devices and Radiological Health staff have reviewed your written responses dated June 6, 2005, July 14, 2005, August 30, 2005, and October 24, 2005, to the list of FDA-483 observations issued on May 16, 2005 and August 10, 2005. We have the following comments regarding your responses:

Responses to FDA-483 observations issued May 16, 2005

- Your response to observation one does not identify the actions needed to prevent this incident from reoccurring. Your firm reported that the [REDACTED] overflowed during the night (Lot HA 091801), which resulted in a loss of liquid (most of the [REDACTED] were not covered with solution). Your response does not adequately address why this incident would not affect product quality, and does not ensure that your manufacturing equipment is being properly maintained. You must verify that your correction of changing the [REDACTED] and adding more [REDACTED] did not adversely affect the finished device, and the corrections were effective.
- Your response to the mislabeling of products (Lot # 010122-SHP) does not specify if the changes to your computer system required validation activities. In addition, after the correction there was no evidence of a corrective action to ensure that this problem would not reoccur. Furthermore, there was no preventive action within the quality system documented.

- Your response to observation three was not adequate since this deficiency was once again documented on the FDA-483 issued on August 10, 2005. Your firm continues to not follow your own written procedures for design control in order to confirm that the changes made to the Pulmonic Valve Conduit were controlled to include validation or where appropriate verification prior to their implementation.
- Your response to observation four was not adequate since your risk analysis does not identify all of the possible hazards associated with the design changes to the Pulmonic Valve Conduit, which would include a curved sleeve, mini-pulmonic (5 and 6mm), and an [REDACTED]. These devices described above would not be considered minor changes to the Pulmonic Valve Conduit design.
- Your response to observation five is not adequate since your design history file for the Shelhigh No-React Porcine Pulmonic Valve Conduit, Model NR-4000, failed to include or reference the records necessary to demonstrate that the design was developed in accordance with the design control requirements. The records not included would be the design plan, design reviews, design verification results, design validation (including clinical study data), design transfer, etc.
- Your response to observation seven does not explain why your firm [REDACTED] during your autoclave validation allowing [REDACTED]. This practice of [REDACTED] appears to be not done routinely to sterilize final packaging materials.

Responses to FDA-483 observations issued August 10, 2005

- Your response to observation one is not adequate since the modifications made to the Pulmonic Valve Conduit (NR-4000) were significantly changed or modified (not a minor modification as described in your response) to include a curved sleeve ([REDACTED]), and Mini-pulmonic ([REDACTED]). All of the modifications described above are made from new materials ([REDACTED]), for which the mini-pulmonic contains a [REDACTED] compared to the [REDACTED] of the previous approved device (NR-4000). In addition, you continue to have insufficient data to demonstrate that the design changes made to the original Pulmonic Valve NR-4000 were adequately controlled, verified and/or validated by your firm.

- Your response to observation two is not adequate since there is no corrective and preventive actions within your quality system to ensure your firm will follow your written procedures for design control. There is no assurance that the new revised design control procedure will be followed consistently since no evidence of training was provided to these new procedures.
- Your responses to observations four and five are ongoing issues (no complaints captured for the years 2000, 2002, 2003, 2004, 2005, and no official MDR event file maintained), which have not been corrected. There is no assurance that your revised complaint procedure will be followed by your firm consistently. There was no evidence provided of training to the revised procedures.
- Your responses to observation six and seven did not adequately address your firm's lack of compliance with the device tracking requirements that were a condition of approval for H980007. The response does not include information that demonstrates your firm keeps current tracking information that includes all of the requirements identified under 821.25(a). Additionally, the response does not provide documentation of your tracking procedures and does not ensure the collection and maintenance of device tracking information requirements.
- Your responses to observations eight, nine and ten did not adequately address the lack of compliance with the conditions of approval and post-marketing requirements for H980007. The response does not adequately address how your firm will ensure adequate record keeping, ensure all required information is reported to the FDA, and ensure IRB approval prior to use of the HDE device, is obtained and documented.
- Your response to observation eleven did not adequately address the lack of IRB approval for use of the HUD device H980007. Your firm was unable to produce copies of the initial IRB approval letters for all 9 sites that you stated had IRB approval.
- Your responses to observation twelve, thirteen and fourteen appear to be adequate.

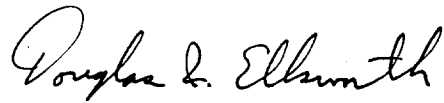
Please notify this office in writing within fifteen (15) working days of receipt of this letter, of the specific steps you have

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taken to correct the noted violations, including an explanation of each step being taken to prevent the recurrence of similar violations. 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.

Your response should be directed to the New Jersey District, FDA, 10 Waterview Blvd., 3rd Floor, Parsippany, New Jersey 07054, Attn: Robert J. Maffei, Compliance Officer

Sincerely yours,



Douglas I. Ellsworth
District Director
New Jersey District