Inspections, Compliance, Enforcement, and Criminal Investigations

Arrow International, Inc. 10-Oct-07

Department of Health and Human Services

Public Health Service
Food and Drug
Administration

PHILADELPHIA DISTRICT
900 U.S. Customhouse
2nd end Chestnut Streets
Philadelphia, PA 19106

Telephone: 215-597-4390

CORPORATE WARNING LETTER
08-PM-01

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

October 10, 2007

Philip B. Fleck, Interim President and Chief Executive Officer
Arrow International, Inc.
2400 Bernville Road
Reading, Pennsylvania 19605

Dear Mr. Fleck:

During inspections of your facilities located in Everett, MA, on January 17 through February 13, 2007, and Asheboro, NC, on January 8 through February 13, 2007, investigators from the United States Food and Drug Administration (FDA) determined that your firm manufactures various devices, including Intra-Aortic Balloon (IAB) catheters, catheters intended for hemodialysis, central venous, cardiovascular, percutaneous, and epidural uses, and other devices. 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.

These FDA inspections revealed significant regulatory problems involving the devices

manufactured by your firm. It is imperative that you understand the serious nature of the deficiencies and the urgent need to promptly implement corrective actions that will effectively remedy the problems found. As you are aware, FDA issued to your corporation three (3) Warning Letters in 2005 relating to deficiencies we identified during inspections at three (3) separate Arrow International facilities. The first Warning Letter was issued on June 3, 2005, to your Mount Holly, NJ, facility. The second Warning Letter was issued on June 16, 2005, to your Reading, PA, facility. The third Warning Letter was issued on August 3, 2005, to your San Antonio, TX, facility, which we now understand is no longer in operation. The Warning Letters identified systemic deviations from the Current Good Manufacturing Practice (CGMP) requirements set forth in FDA's Quality System (QS) regulation found at Title 21, Code of Federal Regulations (21 CFR), part 820.

Carl Anderson, past Chief Executive Officer for Arrow International, Inc. participated in a regulatory meeting with FDA's New Jersey District Office on November 29, 2006, to discuss continuing violations documented during FDA's inspection of your Mount Holly, NJ, facility in September 2006.

The purpose of this letter is to make sure you are aware of the serious nature of the problems we found during the facility inspections and to remind you of your responsibility to assure that all of your facilities establish and maintain a quality system that complies with the Act and all pertinent regulations. Although your corporation has made some attempts to correct the identified deficiencies, these efforts to date have been inadequate as evidenced by the continuing violations at your facilities. If we continue to observe similar problems at the same or other Arrow International facilities, you will not receive any further warnings from our office prior to us taking regulatory action against your firm.

The above-referenced inspections revealed that your firm's 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 CGMP requirements of the QS regulation at 21 CFR part 820. Specifically,the deficiencies found include the following, among others:

1. Failure to establish and maintain procedures for investigating the cause of nonconformities relating to product, processes, and the quality system, as required by 21 CFR 820.100(d)(2). For example, the Asheboro, NC, facility did not review the corrective action taken in response to reported sterilizer cycle deficiencies to ensure that appropriate action was taken. Unscheduled sterilizer maintenance was not evaluated to ensure repairs were timely and correct. Non-conformance **[redacted]** was written in response to a temperature over exposure of 48.1 degrees Celsius for 10 minutes on August 14, 2006 in cycle **[redacted]** in Sterilizer **[redacted].** The relay switch that controlled the steam valve on the sterilizer was replaced. No test runs were performed. Subsequently, cycle **[redacted]** was aborted due to high temperature during the exposure phase of **[redacted]** degrees Celsius. The main stem valve was found defective and replaced. Your Asheboro, NC, facility failed to ensure the initial action taken corrected the problem.

2. Failure to establish and maintain procedures for identifying all of the actions needed to correct and prevent the recurrence of nonconforming product and other quality problems,as required by 21 CFR 820.100(a)(3). For example, the Asheboro, NC, facility did not implement corrective and preventive actions for the following:

a. Management did not implement corrective action for previously-identified deficiencies between the **[redacted]** and **[redacted**] computer systems. Specifications and part numbers were incorrectly transferred when the facility went from the **[redacted]** computer system to the **[redacted**] computer system. Your Asheboro, NC, facility had 604 non-conformances relating to graphic, specifications, and inspection criteria which more issued between May 1, 2006 and December 29, 2006. This facility submitted a CAPA Project Request for action to the Arrow corporate CAPA board in October 2006. However, the project request was denied in December 2006 and sent back to the Asheboro, NC, facility without any corrective action being taken at the corporate level.

b. The Asheboro, NC, facility initiated CAPA **[redacted]** for loose Y-connectors coming off the trays before or during the packaging processes. The corrective action was referred to Arrow corporate for follow-up; however, no preventive/corrective action was implemented. Additionally, the bioburden program was not updated to include the Central Venous Catheters (CVC)/Dialysis Large Bore Kits as a product family as per corporate memo addressed to **[redacted]** from **[redacted]** dated July 11, 2006.

c. The Asheboro, NC, facility did not perform corrective actions after confirming complaint **[redacted]** dated June 4, 2006, and MDR **[redacted]** in which the user reported both ports of a Cannon hemodialysis catheter fragmented and migrated into a patient's pulmonary artery. The investigation by Arrow corporate concluded that a manufacturing error occurred during plastic welding of the distal legs to the main catheter body. The weld failed and caused serious injury to the patient. The corrective action indicated that the Asheboro, NC, facility was to assess corrective actions. The February 2007 FDA inspection revealed that your Asheboro, NC, facility was not aware of this complaint and that corrective action was needed. As a result, there were no improvements or changes made to the welding process.

d. Your Asheboro, NC, facility received at least four (4) complaints **[redacted]** and **[redacted]** in 2006 which indicated that customers received hemodialysis catheters that were blocked. A manufacturing defect was confirmed in several returned samples. The complaints indicated that corrective action would include a 100% check for tip blockage with a gauging wire. There were no instructions or documentation included in the firm's assembly

procedure **[redacted]** indicating that these corrective actions have been implemented: The current procedure, which was released in October 2005, did not include any updates or revisions to account for the 100% inspection of the catheter tips to check for excessive glue.

3. Failure to establish and maintain procedures for analyzing processes, work operations, concessions, quality audit reports, quality records, service records, complaints, returned product, and other sources of quality data to identify existing and potential causes of nonconforming product, or other quality problems, as required by 21 CFR 820.100(a)(1). For example:

a. At your Asheboro, NC, facility, complaint **[redacted]** indicated that a Device History Record (DHR) review was performed in response to a customer complaint of a blocked hemodialysis catheter. The complaint report indicates that your firm's review of the DHR did not reveal any abnormalities; however, during the February 2007 FDA inspection, no device history records were available for the lot at issue in this complaint (Lot # **[redacted]**) and the FDA Investigator noted that the subject lot number was not a valid number: There were numerous cases of incorrect information in the complaint handling system.

b. The analysis of complaints at your Everett, MA, facility did not include an analysis by the IAB catheter lot number to determine problems with a particular lot. The printouts from the corporate Complaint Management System (CMS) included a field for lot number; however, the lot number was often recorded as either unknown or was listed as the sterilization load number which can include multiple lots of product. The spreadsheet used in-house for data analysis of complaints did not include a field for lot number. At least eight (8) of 24 complaints reviewed listed the sterilization load number in the lot number field although the catheter lot number was determined. At least nine (9) of 24 complaints reviewed listed "Unknown" in the lot number field although the catheter lot number was determined.

4. Failure to establish and maintain procedures for submitting relevant information on identified quality problems, as well as corrective and preventive actions, for management review, as required by 21 CFR 820.100(a)(7). For example, the management reviews at your Asheboro, NC, facility did not include non- conformances and quality data analysis from all sources, in that re-works, re-sterilizations, preventive maintenance corrective actions and returned goods (sources of quality problems) were not addressed in management reviews.

5. Failure to establish and maintain acceptance procedures, where appropriate, to ensure that specified requirements for in-process product are met, as required by 21 CFR 820.80(c). For example:

a. There was no required review of each lot of balloons by the Quality Assurance department prior to using the balloons in IA8 catheter manufacturing at your Everett, MA, facility. The balloons are critical components of the catheters according to your Associate Quality Assurance/Regulatory Affairs (QA/RA) Manager.

b. The DHR for catheter lot **[redacted]** showed 98 balloons were wrapped on October 12, 2006, and that subsequently 99 balloons were heat treated (furl baked) on October 13, 2006. The quality review of the DHR was on October 13, 2006. There was no evidence that the discrepancy in the listed quantities was noted at your Everett, MA, facility.

6. Failure of the management representative to ensure quality system requirements are effectively established and effectively maintained within the organization, as required by 21 CFR 820.20(b)(3)(i). For example, problems were noted with quality assurance, documentation, process controls, complaint handling, data analysis, employee training, and equipment maintenance at your Everett, MA, facility that resulted in the development of the Process Validation Remediation Project Summary (Summary). This Summary described Arrow International's reengineered Quality System which was implemented in August 2006, and applies to all Arrow International manufacturing facilities. On February 8, 2007, the Management Representative stated that he had not seen the Summary prior to February 7, 2007. This Summary was sent to the FDA with a December 18, 2006, cover letter January 10, 2007, the Summary was sent to two employees who reported to the Management Representative at the Everett, MA, facility (the Plant Manager and the Quality Manager of Instrumentation), but apparently had not been provided to the Management Representative himself.

7. Failure to establish and maintain procedures to ensure that all purchased or otherwise received product and services conform to specified requirements, as required by 21 CFR 820.50. For example, your Asheboro, NC, facility receives many components, finished devices, and kits for further packaging and ethylene oxide (EO) sterilization from other Arrow facilities. There was no indication that the Asheboro, NC, facility has procedures to ensure that all materials received from your other facilities (Mt Holly, NJ; Reading, PA, Czech Republic; and Mexico) conform to specified requirements.

8. Failure to develop, conduct, control, and monitor production processes to ensure that a device conforms to its specifications and failure to establish and maintain process control procedures that describe any process controls necessary to ensure conformance to specifications, as required by 21 CFR 820.70(a). For example:

a. For your Asheboro, NC, facility, their established procedure, Operational Procedure for Product Sterilization, indicated that Arrow products can be re-sterilized up to two (2) times with minimal limitations and exceptions. Your firm does not have data and has not conducted testing, especially functionality testing, that shows

the components in Arrow kits can be re-sterilized.

i. Your firm re-sterilized a lot of epidural catheterization kits that contain syringes (Lot [**redacted]** Two (2) complaints were received from the field for condensation in the syringe **[redacted]** and a leaking syringe **[redacted]**. Your Asheboro, NC, facility did not perform functional testing on the re-sterilized kits.

ii. Lot **[redacted**] was re-sterilized. No functional testing was done post-sterilization.

iii. Lot **[redacted]** was re-sterilized. No functional testing was performed post-sterilization.

b. The viscosity measurement was not compared to the Dipping Configuration Matrix for the balloon type, as required by procedure #**[redacted]** "Texin Bladder Dipping Procedure" for your Everett, MA, facility. The matrix was left out of Revision 6 of the updated procedure in December 2006. There was no Dipping Configuration Matrix within the dipping room on January 19, 2007, during the 2007 FDA inspection.

9. Failure to review, evaluate and investigate a complaint involving the possible failure of a device, labeling, or packaging to meet any of its specifications, as required by 21 CFR 820.198(c). For example:

a. The complaint investigations were not carried out to the degree necessary to draw conclusions as to the validity and cause of complaints at your Asheboro, NC, facility. For example,

i. A failure investigation and follow-up have not been initiated in response to a report that a catheter (**[redacted])** migrated from the femoral vein into a patient's pulmonary artery after the catheter body detached at the hub **[redacted]** dated October 10, 2006; **[redacted]** The patient expired as a result of blood pressure and other issues. Complaint records indicated that a comprehensive investigation could not be completed since the sample was not available for review. The hospital system pulled all of the subject lot from ten (10) hospitals and your Asheboro, NC, facility replaced the customer's product at no charge. At the time of inspection, one hundred and twelve (112) unopened kits were in quarantine in the re-packaging area of the firm and could have been used for purposes of evaluating the subject lot.

ii. At least six (6) complaint incidents indicating "patient vessel perforation" with multi lumen Percutaneous Sheath

Introducer kits were documented on August 26, 2005 for one (1) hospital. Each of the six (6) scenarios were different; however, there was no documented investigation into these incidents or documentation of any follow-up with the hospital.

b. At your Everett, MA, facility at least eight (8) complaint investigation records **[redacted]** showed no review by either Engineering or Research & Development (R&D) although the root causes of the complaints were reported as either unconfirmed or undetermined. In many cases the products at issue in the complaints were returned for evaluation. The initial evaluation, including the decision to have Engineering or R&D review the complaint, in each case was made by the QA Technical Support Specialist.

10. Failure to promptly review, evaluate, and investigate a complaint that represents an event which must be reported to FDA under part 803 and maintained in a separate portion of the complaint files or otherwise clearly identified, as required by 21 CFR 820.198(d). For example, the MDR determinations and complaint evaluations were not promptly reviewed or evaluated for several complaints at your Asheboro, NC, facility, including: (1) **[redacted]**, Spring Wire Guide Deformed, Reported: February 20, 2006, MDR Evaluation: January 9, 2007, Status: Closed June 20, 2006, and (2) **[redacted]** Blocked Catheter, Reported: March 17, 2006, MDR Evaluation: January 9, 2007, Status: Open.

11. Failure to perform design validation under defined operating conditions on initial production units, lots, or batches, or their equivalents and to ensure that devices conform to defined user needs and intended uses and include testing of production units under actual or simulated use conditions, as required by 21 CFR 820.30(g). For example:

a. Validation was not conducted prior to implementing Engineering Change Order (ECO) **[redacted]** in August 2003 at your Everett, MA, facility. **[redacted]** added the **[redacted]** Procedure to the LWS (Light Wave Sensor) or Fiber Optic Sensor catheters. Performance testing was conducted on only three (3) catheters and five (5) sensors. As a result of higher yield losses (due to low pressure readings found during manufacturing after the **[redacted]**. Process was removed from the manufacturing process for LWS catheters in October 2004.

b. There were no manufacturing design validation records for the balloons or catheters used to verify the new 35cc balloon size introduced in 2004 at your Everett, MA, facility. The Product Design Verification Report, **[redacted],** was approved in August 2004.

12. Failure to establish procedures for identifying training needs, ensure that all personnel are trained to adequately perform their assigned responsibilities,

and document training, as required by 21 CFR 820.25(b). For example:

a. Training records for a sterilizer operator and packager were requested at your Asheboro, NC, facility during the 2007 FDA inspection. Out of five (5) training records requested for the sterilizer operator, only two (2) were available. Two (2) training records were requested for the packager and only one (1) record was available.

b. A number of documents were collected demonstrating that employees were not adequately trained, at your Everett, MA, facility:

i. The IAB Manufacturing Technician who prepared dipping solutions for balloons and cleans the mixing tanks, said there was no procedure for cleaning the mixing tanks for the dipping solution. Process Specification **[redacted]** "Urethane Solution-Mixing" did in fact include instructions for cleaning the dip circuit between polyurethane mixes.

ii. An IAB Manufacturing Technician who was hired in April of 2001 did not receive GMP training until 2006.

iii. Affected employees were not trained on Procedure **[redacted]** "Environmental" Monitoring Viable Counts Revision 8, which was effective from February 2003 until July 2003.

iv. All seven (7) employee training records reviewed had incomplete training requirements. According to procedure #CHR-001. "Training Administration, Documentation, and Recordkeeping Procedure," your firm has 30 days to complete the training. One training requirement was over six (6) months late.

13. Failure to establish, procedures for and conduct quality audits to assure that the quality system is in compliance with the established quality system requirements and to determine the effectiveness of the quality system, including reaudits of deficient matters, as required by 21 CFR 820.22. For example:

a. Your Asheboro, NC, facility did not perform quality audits with sufficient frequency to identify and correct deficiencies within the quality system as evidenced by the multiple observations noted during the February 2007 FDA inspection.

b. Your Asheboro, NC, facility did not re-audit deficient areas identified during quality audits and did not monitor corrective action for effectiveness. The established procedure, Internal Audit System, indicated non-conformances were entered into the non-conformance system and then, the audit was closed. There

was no verification of corrective action, preventive measures, or of a re-audit of the deficient areas.

14. Failure to validate computer software for its intended use according to an established protocol when computers or automated data processing systems are used as part of production or the quality system; as required by 21 CFR 820.70(i). For example:

a. Your Everett, MA, facility had a validation deficiency that was identified during the February 2007 FDA inspection. The Post Sterilization Functional Release Testing **[redacted]** software **[redacted]** was not validated which has been in use since October 2002. The **[redacted]** Testing software is used to conduct post-sterilization functional testing of the IAB catheters.

b. For yours, Asheboro, NC, facility, the **[redacted]** Training Database software validation used to document employee training was deficient in that the test scripts were not available to show the execution of the software validation protocol. It appears that at least five (5) tests specified in the. approved protocol were not performed.

15. Failure to establish and maintain procedures to ensure that sampling methods are adequate for their intended use, to ensure,that when changes occur the sampling plans are reviewed, and that sampling plans are written based on a valid statistical rationale, as required by 21 CFR 820.250(b): For example:

a. Your Asheboro, NC, facility did not have a robust endotoxin testing program for Central Venous Catheters (CVC) kits; CVC/Dialysis Large-bore ChlorPrep Drape Chlorhexidine (CDC) kits, epidural kits, and Percutaneous Sheath Introducer kits which are all labeled "non-pyrogenic." Of approximately 30 sterilizer loads per week, only three (3) 10 tests were performed on a weekly basis. Statistical techniques were not used for control purposes where statistical techniques were applicable.

b. For your Everett, MA, facility, post-sterilization functional testing after the rework of catheter **[redacted]** was not conducted on a sample from the same lot, but rather on a sample from a different catheter lot in the same sterilization load. That test resulted in the functional release of product from lot **[redacted]** which was subsequently shipped to customers. Lot **[redacted]** had been reworked due to a previous failed post-sterilization functional check that identified a hole in the catheter.

16. Failure to establish and maintain procedures to control all documents, as required by 21 CFR 820.40. For example, the following deficiencies were identified for your Everett, MA, facility.

a. The released updated revision #2 of procedure **[redacted]**

"Drying Procedure for **[redacted]** Pellets" actually contained a different procedure (Urethane Mixing Solution, SOP **[redacted]**. This was not noted by any of the six (6) approving officials on December 19-20, 2006, or during employee training on the updated procedure on January 9, 2007.

b. The released updated revision #6 of procedure **[redacted]** Texin Bladder Dipping Procedure" was missing the Dipping Configuration Matrix which was included in the red-lined version in the Engineering Change Order. This was not noted by any of the six (6) approving officials on December 19-20, 2006, or during the employee training on the updated procedure on January 5 and 9, 2007.

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. Also, 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, 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 action 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.

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 483s, issued at the closeout of the referenced inspections 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.

Response to FDA 483 Observations

We acknowledge the receipt of the responses from Arrow International, Inc., Reading, PA, which address the two Form FDA 483s that were issued to management at the Everett, MA and Asheboro, NC facilities on February 13, 2007. Your firm's first response, dated March 7, 2007, was signed by Carl G. Anderson, Jr., former Chairman and CEO. The second response, dated June 27, 2007, was signed by you. We have reviewed these responses and the commitment to take corrective action that was made

by Your firm during the November 2006 regulatory meeting. However, your firm's efforts to date have failed to achieve the necessary systemic approach to comprehensively address the noted violations. In your corporate responses dated, March 7 and June 27, 2007, your firm describes your corporate wide "Project Operational Excellence" program, initiated at Arrow International in January 2005, in which your firm created a new Quality Management System for all of your manufacturing facilities, including the Everett, MA, and Asheboro, NC, facilities. The responses also indicated that the "...implementation of the new Quality Management System is complete and has been operating since September 2006." However; during the inspections at your Everett, MA, and Asheboro, NC, facilities we observed significant violations from the Quality System regulation, as described above.

Complaint Handling

We understand from your responses that you will be modifying the complaint handling SOP and providing updates to the handling and investigation of complaint reports. You stated that an improved complaint database called **[redacted]** is on schedule for implementation on October 27, 2007. In your Everett, MA, June 27, 2007, response you stated that your review of the April and May 2007 complaints identified a 50% failure rate based mostly on clerical errors. This significant failure rate occurred even after you revised the SOP and retrained the personnel. Your corrective actions to date appear ineffective in addressing the complaint handling issues and will require immediate action.

Training

Your corporate response indicates that training databases are being improved, a project team is being formed, and a "project plan is being developed to continually improve the corporate training system." In most of your responses, you either created procedures or revised existing procedures to include training with deadline dates. We would like immediate assurance that your personnel are trained and competent to perform their duties. As such, you need to address your training issues immediately. Your response should include a description of the steps you are taking, corporate-wide, to address these serious training violations.

Sterilization

Your Asheboro, NC facility referenced compliance standard ISO **[redacted]** for sterilization operations in the June 27, 2007 response. This standard indicates the minimum parameters that should be monitored and the list includes, "Time, temperature, and pressure changes in the chamber and evidence that the gaseous sterilant has been added to the chamber." This is something that is ordinarily established during validation, which was not completed for your Asheboro, NC facility. Additionally, it was unclear in your response if endotoxin testing would be performed on each lot of product for each sterilization load. The USP requires endotoxin testing on each sterilizer load if you are claiming the products are non-pyrogenic. In the corporate June 27, 2007, response to validating the **[redacted]** software, you indicated the **[redacted]** software was tested and updated but did not indicate that the system was validated.

Quality management problems, corrective action and preventive action, complaint handling, and training issues were previously brought to your firm's attention in two (2) Warning Letters that were issued on June 16, 2005, and August 3, 2005. Additionally, your corporate-wide "Project Operational Excellence" program has had more than two (2) years to implement an effective CAPA program that would review, evaluate, correct, and prevent this type of problem from recurring. These recurring, serious deficiencies with your corporate quality management operations are significant. Changes made to your corporate quality system as detailed in your recent responses to these FDA 483s have failed to adequately correct these systemic quality problems, and assure that an effective quality system is currently in place. As such, we will need to verify implementation of your promised corrections, proposed plans, and revised/new procedures through reinspections. We are aware that your proposed plans arid revised/new procedures covered many areas of the Quality System, including document controls, management, DHRs, audits, production/process controls, and validation. The violations included in this Warning Letter and discussed above are significant deficiencies that warrant your immediate attention to assure an effective quality system.

Your response to this letter and any questions you may have should be sent to William J. Forman, Compliance Officer, Food and Drug Administration, 2nd & Chestnut Streets, Room 900, Philadelphia, Pennsylvania 19106.

Sincerely yours,

/S/

Thomas D. Gardine
District Director Director.
Philadelphia District Office

/S/

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