



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Purgad.  
CA  
6/7/99

m26750

JUN - 7 1999

Food and Drug Administration  
2098 Gaither Road  
Rockville MD 20850

**WARNING LETTER  
VIA FEDERAL EXPRESS**

Mr. Roy S. Johnson  
President & Executive Vice President  
Diametrics Medical, Inc.  
2658 Patton Road  
St. Paul, Minnesota 55113

Dear Mr. Johnson:

The Office of Compliance (OC) in the Center for Devices and Radiological Health (CDRH) has completed its review of the Establishment Inspection Report (EIR) for the inspection conducted at High Wycombe, Bucks, England on March 23-29, 1999, by our investigator, Victor Spanioli. The above was a Quality System Regulation (QS Reg) inspection for your Class III 510(k) [REDACTED], covering the [REDACTED]. The inspection determined that a second 510(k) concerning the [REDACTED] [REDACTED] was also pending.

At the conclusion of the inspection, Mr. Spanioli issued to you a form FDA-483, Inspectional Observations, listing a number of observations regarding the methods, facilities and controls at that plant. Our review found that those observations represent deviations from the QS Reg of such significance that we are not able to recommend clearance of the [REDACTED] and the [REDACTED] to the Office of Device Evaluation (ODE) until noted corrections to those deviations have been verified during a follow-up inspection. We acknowledge that you have submitted responses, dated 4/9/99, 4/30/99, and 5/7/99, concerning the investigator's observations noted on the form FDA 483.

**Failure to review and evaluate all complaints to determine whether an investigation is necessary, as required by 21 CFR 820.198(b).**

For example, no evaluation has been done to determine if there is any long-term risk (chronic toxicity, carcinogenicity) with respect to sensors that have or may have remained in several patients. Also, Complaint 98-J1766, relating to reflush at the sensor connector, states that another sensor was primed through the prime line with saline and air bubbles backflowed up the graduated insertion tube. The complaint documentation does not discuss the status of this sensor and why failure investigation was not done.

**Failure to process complaints in a uniform and timely manner, as required by 21 CFR 820.198(a)(1).**

For example, Complaint 98-J1793, relating to blood leaking through the sensor, states that the sensor was to be returned for investigation on or about September 4, 1998. Report dated March 23, 1999, states that no investigation was possible because the sensor was not returned. There is no documentation that explains why the sensor was not returned. Also, the investigator listed two complaints that were not investigated in a timely manner.

You addressed all complaint handling processes by amendment to the Product Performance Monitoring procedure. Also, a Complaint Progress Manager has been appointed with the following responsibilities:

- Ensure all complaints are processed in a timely manner
- Ensure consistency in documentation of investigations and actions taken
- Ensure decisions made and conclusions drawn are documented
- Provide reports as required.

Also, a complaint file closure checklist will be created and incorporated as part of the complaint handling procedure to provide the Complaint Progress Manager with a tool to verify that all necessary actions have been taken and documented. Corrective actions were due by 4/30/99.

Your response to the two charges listed above (21 820.198(b), 21 820.98(a)(1)) appears to be adequate. Corrections will be verified during the next inspection.

**Failure to validate with a high degree of assurance where the results of a process cannot be fully verified by subsequent inspection and test, as required by 21 CFR 820.75(a).**

For example, no testing has been done to confirm that sensors will meet biocompatibility and functionality requirements when they are sterilized under worst-case conditions (highest irradiation dose).

Your response to this observation is not adequate because the study has not yet been performed. You have targeted the completion date for May 31, 1999.

**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, prior to a change to the dose in November 1998, the minimum sterilization dose limit for [REDACTED] cannot assure the achievement of the specified sterility assurance level of  $10^{-6}$  because bioburden test results included "TNTC" (too numerous to count) determinations as follows:

- a) [REDACTED] batch 677; Seven of 20 bioburden samples had "TNTC" results.
- b) [REDACTED] batch 682; Nine of 20 bioburden samples had "TNTC" results.
- c) [REDACTED] batch 686; One of 20 bioburden samples had "TNTC" results.
- d) [REDACTED] batch 687; Six of 20 bioburden samples had "TNTC" results.
- e) [REDACTED] batch 689; Seven of 20 bioburden samples had "TNTC" results.

The following corrective actions have been initiated:

- The Microbiologist is currently undertaking re-training to the requirements of ISO 11137 by external experts. Should have been completed by 4/16/99.
- The verification audit process is being formally documented in a DML procedure with a requirement for the Quality & Regulatory Manager and the Technical Director to review the data and approve the audit report prior to acceptance. Should have been completed by 4/16/99.
- The original dose-setting exercise established an acceptable minimum dose of 23.7 kGy. DML set the dose at 25 kGys giving a buffer and added assurance.
- The re-setting exercise established an acceptable minimum dose of 19.6 kGy. DML retained the minimum dose at 25 kGy giving an even greater buffer and assurance.

Your response to this observation appears to be adequate. Corrections will be verified during the next inspection.

**Failure to establish and maintain procedures for implementing corrective action, as required by 21 CFR 820.100(a).**

For example, when bioburden levels have exceeded specified target levels, the corrective actions specified in document 11-043 have not been taken.

You immediately implemented the requirement for cleanroom personnel to wear gloves, wherever practicable, and for Quality and Goods-in personnel to wear gloves during handling of raw materials. Microbiological testing has been conducted at additional assembly stages in production to identify potential for bioburden contamination. The tests will be ongoing until consistent, acceptable levels of bioburden contamination are maintained. Bioburden results following these corrective actions were submitted and indicate lower bioburden levels.

Your response to this observation appears to be adequate. Corrections will be verified during the next inspection.

**Failure to identify the action(s) needed to correct and prevent recurrence of nonconforming product and other quality problems, as required by 21 CFR 820.100(a)(3).**

For example, investigation of Complaint 98-J1832 received on November 3, 1998, could not determine cause of why the [REDACTED] (batch 677) failed to calibrate. No assessment was done to determine if additional testing could identify the failure mode.

As stated in the previous observation, a complaint file closure checklist will be created and incorporated as part of the complaint handling procedure. It will require that failure investigations which are inconclusive will be held open until all other possibilities are investigated and final conclusions drawn. Corrective actions were due by 4/30/99.

Your response to this observation appears to be adequate. Corrections will be verified during the next inspection.

**Failure to establish and maintain procedures to ensure that Device History Records (DHR) for each batch, lot, or unit are maintained to demonstrate that the device is manufactured in accordance with the Device Master Record (DMR) and the requirements of this part, as required by 21 CFR 820.184.**

For example, the original production copy of the manufacturing instructions attached to Concession/Change Control #89721, dated January 18, 1999, is not controlled as part of the DHR. The copy attached to the manufacturing instructions was prepared after January 18, 1999, but bears this date.

The Change Control procedure 01-031 has been modified to require that concessions approved with instructions appended are referenced to the concession, and remain with the DHR when extension to concessions are approved. The additional batches covered by the approval shall be added to the concession note, not the instruction sheet.

Your response to this observation appears to be adequate. Corrections will be verified during the next inspection.

**Failure to establish and maintain procedures for finished device acceptance to ensure that each production run, lot, or batch of finished devices meets acceptance criteria, as required by 21 CFR 820.80(d).**

For example, the procedure for endotoxin testing states that [REDACTED] finished product should have the tonometer solution removed "by immersing sensor fully in low endotoxin water." No testing has been done to verify that this procedure does not remove endotoxin prior to endotoxin determination.

Your response to this observation is not adequate. You need to provide data demonstrating that the rinse solution does not remove endotoxin that might be present on the device.

**Failure to investigate the cause of nonconformities relating to product, processes, and the quality system, as required by 21 CFR 820.100(a)(2).**

For example, sensor outer sheath sub-assembly rejects are not evaluated or documented to determine if the failure mode/rate exceed validation/historical levels. Review of device history records for recent lots found reject rates varying from 1% to 23%.

You have amended the Defect Management procedure to incorporate use of a proforma for the recording of defect investigations with aim of providing the necessary consistent documentary evidence that investigations have taken place. Also, the amended procedure will include trending process defects. You included charts to show that the sub-assemblies identified have been trended to show reject rates per batch and historical data collected from 1/1/99. Corrective actions will be completed by 5/31/99.

Your response to this observation appears to be adequate. Corrections will be verified during the next inspection.

**Failure to document investigation of nonconforming product, as required by 21 CFR 820.90.**

For example, engineering evaluation identified an outer sheath lapweld deformation in [REDACTED] from batch 691. Investigation results for affected lots (sub-assemblies and finished sensor assemblies), such as, screening test procedure used, and corrective action, were not documented.

You will amend your Defect Management process to incorporate a proforma for recording of defect investigations in a single document. The form will include:

- Description and trend of defects
- Summary of investigations including test methods (where relevant)
- Results with batch/lot details
- Corrective action and implementation point
- Reference to Process Validation system (where relevant)

The revised procedure should have been completed by 4/30/99. In the interim, all information resulting from any defect investigations arising will be collated in a single file. In addition, a central database will be established to manage corrective actions company-wide (also applies to observation 6).

Your response to this observation appears to be adequate. Corrections will be verified during the next inspection.

**Failure to inspect, test, or otherwise verify incoming product as conforming to specified requirements, as required by 21 CFR 820.80(b).**

For example, one each of four reels of coated silver wire from batches G17997 and G18192 were rejected in September 1998 because they did not meet the elongation test requirement. No information has been received from the supplier and no internal investigation has been initiated to determine the root cause of this non-conformance.

You stated the reason that one each of four reels of coated silver wire from batches G17997 and G18192 were rejected was due to a problem with the supplier's annealing oven. Repairs were undertaken by the supplier in order to reduce material variability and regain the desired quality for subsequent supplies. You have updated your Material Control procedure to include the requirement for investigation into raw material defects and their corrective actions to be logged into the Corrective and Preventive Action database. You stated that the full documented response from the supplier of the coated silver wire, subject of this observation, is on target for completion by May 31, 1999.

Your response to this observation appears to be adequate. Correction will be verified during the next inspection.

**Failure to establish and maintain the requirements, including quality requirements, that must be met by suppliers, contractors, and consultants, as required by 21 CFR 820.50(d).**

For example, calibration gas and CBAS-Heparin certificates of analysis have not been verified.

You have contacted the two suppliers of the raw materials subject to the observation for retrospective data to perform the interim verification for the specific observation made. You will conduct a review of key suppliers and implement a system whereby such suppliers would be required periodically to provide detailed manufacturing and test data to support certified claims for verification. Corrective actions are due by 5/31/99.

Your response to this observation appears to be adequate. Corrections will be verified during the next inspection.

**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, the sensor heparin coating procedure (04-122) for the H2 (section 4.4.8) and H4 (section 4.4.19) solutions allows for the potential acceptance/use of solutions that may be exposed to temperatures above the specified upper limit of 60 degrees C.

Your heparin coating procedure 04-122 requires the temperature of solutions to be measured within the range 55 degrees C  $\pm$  degrees C and recorded on the Product Assembly cards. As an additional precaution the procedure has been modified to include that in the event that the solution reaches temperatures exceeding 65 degrees C the solutions will be discarded.

Your response to the observation appears to be adequate. Corrections will be verified during the next inspection.

**Failure to establish and maintain procedures to ensure that equipment is routinely calibrated, inspected, checked, and maintained, as required by 21 CFR 820.72(a).**

For example, TrendCare Calibrator gas leak testing specifies a maximum pressure loss of one PSI after ten minutes. The pressure gauge used for this measurement has not been calibrated to verify that it provides this sensitivity. The gauge is marked in five PSI graduations.

You have acquired calibrated gauges, which have the required 1 PSI graduations.

Your response to this observation appears to be adequate. Corrections will be verified during the next inspection.

**MDR Violation:**

**Failure to report within 30 days whenever the manufacturer receives or otherwise becomes aware of information, from any source, that reasonably suggests that a device, or similar device marketed by the manufacture has malfunctioned and such device marketed by the manufacturer would likely to 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, the following MDR reports were not submitted within the 30-day reporting period:

COMPLAINT NO.	DATE COMPLAINT REC'D	DATE SUBMITTED
98-J1766	8/24/98	10/18/98
98-J1793	9/4/98	10/20/98

Page 8 - Mr. Roy S. Johnson

You have modified the language in procedure 01-019 Product Performance Monitoring to state DML employee responsibility for immediate reporting of complaint information. Retraining of sales personnel and parent company staff has been documented via the employee instruction sheet.

Your response to this observation appears to be adequate. Corrections will be verified during the next inspection.

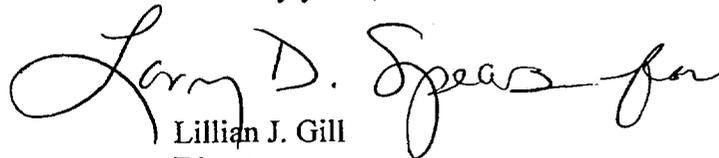
This letter is not intended to be an all-inclusive list of deficiencies at your facility. It is your responsibility to ensure adherence to each requirement of the Act and regulations. The specific violations noted in this letter and in the form FDA-483 issued at the conclusion of the inspection may be symptomatic of serious underlying problems in your firm's manufacturing and quality assurance systems. You are responsible for investigating and determining the causes of the violations identified by the Food and Drug Administration. If the causes are determined to be systems problems, you must promptly initiate permanent corrective actions.

We acknowledge that you have submitted to this office responses concerning our investigator's observations noted on the form FDA-483. Please notify this office in writing within 15 working days of receipt of this letter, of the specific steps you have taken to correct the noted deviations, including an explanation of each step being taken to identify and make corrections to any underlying systems problems necessary to assure that similar deviations will not recur. Please include any and all documentation to show that adequate corrections have been achieved. In the case of future corrections, an estimated date of completion and documentation showing plans for corrections should be included with your response letter. Please address your response to:

Wayne Q. Miller, Consumer Safety Officer  
Office of Compliance  
Division of Enforcement III (HFZ-343)  
Center for Devices and Radiological Health  
2094 Gaither Rd.  
Rockville, MD 20850

If you have any questions, please contact Mr. Miller at the above address or at (301) 594-4659, or fax (301) 594-4672.

Sincerely yours,

A handwritten signature in cursive script that reads "Lillian J. Gill". The signature is written in black ink and is positioned above the typed name and title.

Lillian J. Gill  
Director  
Office of Compliance  
Center for Devices and  
Radiological Health