DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
555 Winderley Pl., Ste. 200
Maitland, Fl 32751

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VIA FEDERAL EXPRESS

WARNING LETTER

FLA-00-17

December 23, 1999

Rick Ferreira, CEO
Alliance Medical Corporation
3853 E. Weir Avenue
Phoenix, Arizona 85040

Dear Mr. Ferreira:

We are writing to you because on November 17-19, 1999 FDA Investigator R. Kevin Vogel inspected your facility at 254 West Keene Road, Apopka, Florida, and collected information that revealed serious regulatory problems involving your firm's reprocessing of medical devices.

Under the Federal Food, Drug, and Cosmetic Act (the Act), the products that your firm reprocesses are considered to be medical devices that are used to diagnose or treat medical conditions or to affect the structure or function of the body. The law requires that manufacturers, including reprocessors, conform to the Quality System (QS) regulations for medical devices, as specified in Title 21, Code of Federal Regulations (CFR), Part 820.

The inspection revealed that devices that you sort and clean for further reprocessing are adulterated within the meaning of section **501(h)** of the Act, because the methods used in, or the facilities or controls used for, their manufacture, packing, storage, or installation does not conform with the QS regulation. These violations include, but are not limited to the following:

QS Regulation/GMPs

1. Failure to establish and implement a quality policy as required by 21 CFR 820.20. For example, personnel on site had no knowledge that such a policy existed (FDA 483, Item, # 4).

2. Failure to establish and maintain procedures to ensure that device history records are maintained to demonstrate that devices are manufactured in accordance with the device master record as required by 21 CFR 820.184. For example, SOP 003, Appendix A, Initial Cleaning Instructions Rejection List states that used Arthrowands should not be reprocessed. However, on November 13, 1999, three Arthrowands were accepted and forwarded for reprocessing (FDA 483, Item #s 2 & 3).

3. Failure to establish and maintain procedures for implementing corrective and preventive action [21 CFR 820.100], including failure to implement and record changes in methods and procedures needed to correct and prevent identified problems [21 CFR 820.100(a)(5)]. For example, there are no procedures to address change control and corrective and preventive actions (FDA 483, Item #5).

4. Failure to monitor production and process controls to ensure that inspection, measuring, and test equipment is suitable and capable of performing its intended purpose [21 CFR 820.72(a)]. For example, there are no procedures to address the calibration of thermometers and pH meters (FDA 483, Item #5).

5. Failure to adequately train personnel to perform their assigned responsibilities as required by 21 CFR 820.25. For example, employees failed to demonstrate a working knowledge of SOPs and/or other processing instructions (FDA 483, Item #1).

6. Failure to document cleaning and maintenance of the facility and process equipment, as required by 21 CFR 820.70(f) and (g). For example, there is no record to document that the processing room and equipment are cleaned or maintained to ensure that adverse effects on product quality are minimized and that personnel protections are in place (FDA 483, Item #6).

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 awards of contracts. FDA has also notified the Occupational Safety and Health Administration (OSHA) of our findings during the inspection of your facility.

We acknowledge receipt of your firm's response dated December 4, 1999, to the Inspectional Observations (FDA 483) and will evaluate the adequacy of the promised corrections during the next inspection of your facility.

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 penalties.

Any future responses should be sent to Timothy J. Couzins, Compliance Officer, Food and Drug Administration, 555 Winderley Place, Suite 200, Maitland, Florida 32751, (407) 475-4728.

Sincerely,

Douglas D. Tolen

Douglas D. Tolen
Director, Florida District

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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Food and Drug Administration
555 Winderley Pl., Ste. 200
Maitland, Fl 32751

VIA FEDERAL EXPRESS

WARNING LETTER

FLA-00-01

October 14, 1999

Charles A. Masek, Jr.
President & CEO
Vanguard Medical Concepts, Inc.
5307 Great Oaks Dr.
Lakeland, Florida 33815

Dear Mr. Masek:

We are writing to you because on March 29 through April 2, 1999, FDA Investigator Ronald T. Weber collected information that revealed serious regulatory problems involving your firm's practice of reprocessing biopsy forceps.

Under the Federal Food, Drug, and Cosmetic Act (the Act), these products are considered to be medical devices that are used to diagnose or treat medical conditions or to affect the structure or function of the body. The law requires that manufacturers conform to the Quality System (QS) regulations for medical devices, as specified in Title 21, Code of Federal Regulations (CFR), Part 820.

QS REGULATIONS/GMPs

1. Failure to validate the cleaning process with a high degree of assurance as required by 21 CFR 820.75(a). For example:

   a) There is no record of the validation acceptance specifications or records of assay and acceptance for the chemicals used in the validation.

   b) There is no record of the monitoring and control of the chemicals and water used in the validation study.

c) There is no record of the monitoring or control of the mechanical variables: temperature, pressure, and time used in the validation study.

d) There is no record of testing of the VMC-50 or Pressurized Vessel (Big Bertha) to assure the ports produce the same vacuum or pressure, so that the randomization of ports having inoculated forceps used in the study would be valid.

e) The available validation records on the cleaning process have no reference to work done on the sonicator, which is used in processing.

f) There is no record of the monitoring and control of the air used to break the vacuum following the drying of the forceps after cleaning.

Your firm's response dated April 23, 1999 signed by Douglas Stante, Vice President Quality Assurance & Regulatory Affairs, is not adequate because the validation is not complete. The response promises to revalidate the cleaning process by the end of June 1999, using an accepted industry standard procedure and document all parameters. Test results submitted for the vacuum or pressure at the ports of the Pressure and Vacuum cleaning machines showed that there is no significant difference between the ports on either machine. The response states that air used to break the vacuum following drying passes through a 0.2u filter and that testing to establish a baseline for incoming water quality and water quality action levels will be conducted.

2. Failure to adequately validate the sterilization process as required by 21 CFR 820.75. For example:

   a) No information was available or submitted to demonstrate that the sterilization process has no adverse impact on the devices that are processed.

Such demonstration, which is an important part of validation studies, is required for each of the various types of product that are processed at your facility. This demonstration should address

the impact of the sterilization process 1) on the functioning of the device and, 2) on ethylene oxide residue remaining after the process.

b) Information regarding the effectiveness of the process does not demonstrate that the process will consistently and effectively achieve the specified sterility assurance level of 10^{-6}.

Your firm employs a sterilization system manufactured by [redacted], which is not cleared for use in a health care setting.

Your firm's use of this sterilization system is not prohibited because FDA does not regulate sterilizers intended for industrial use. However, the Quality System regulation requires that manufacturers of sterile medical devices demonstrate that their sterilization processes can achieve the desired level of sterility assurance. The equipment and process used by Vanguard for sterilization has the same intended purpose and mechanisms as those used in health care settings for which the Agency found significant deficiencies. The deficiencies found for the use of this equipment in health care settings are also applicable in the industrial setting.

Labeling submitted by [redacted] with its 510(k) premarket notification states that the sterilizer is not intended to sterilize reusable medical devices. This also does not prohibit your firm's use of the system in an industrial setting, but does emphasize the need for validation of the process for these devices.

Your firm's responses dated June 4, 1999 for the Biopsy Forceps were found to be inadequate for the following reasons:

- According to your firm's validation report, the validation of the process was "carried out in accordance with the requirements for validation of an Ethylene Oxide sterilization system as set forth in ANSI/AAMI/ISO 11135-1994" (Sterilization Validation Report, 1998, page 2 of 14). This is not appropriate because the cited standard (ISO 11135) clearly states in its scope that the standard does not cover the

sterilization technology used by your firm (section 1.4 of the standard). The rationale for the validation method set forth in the standard does not apply to this sterilization technology of injecting the gas directly into individual packages.

Your conclusion that the sterilization process will achieve a sterility assurance level (SAL) of 10^{-6} is based on half cycle analysis, as described in ISO 11135. You reference this standard in your sterilization report that half cycle development involves "the determination of the minimum time of exposure to ethylene oxide, with all other process parameters except time remaining constant, at which there are no survivors." (Sterilization Validation Report, 1998, page 2 of 14) The half cycle approach is not applicable in this case because the gas concentration does not remain constant, but is decreasing throughout the exposure period as the gas dissipates out of the bag.

Because of the dissipation of gas out of the bag, the product load is exposed to significantly less EtO gas during the second half of the cycle than during the first half. Your response addressed this situation in Part B of the validation study, which was designed to demonstrate that there is sufficient gas in the bag following the half cycle to provide enough lethality to destroy the biological indicator spores. However, operating conditions in Part B of the study are not the same as in routine processing or in the first half cycle run because a vacuum is not drawn as the gas enters the bag. Conclusions about the effectiveness of the process cannot be drawn from a study with operating conditions that differ from routine processing.

- Your firm identifies "gas concentration, temperature, relative humidity, and exposure time" as "the major factors that affect the inactivation of microorganisms." (Sterilization Validation Report, 1998, page 2 of 14). Yet there are no specifications for, or monitoring of gas concentration or relative humidity in the product load in either the validation study or routine processing of devices.

- Relative humidity is controlled in the environment of the preparation area, but the information submitted did not include any analysis of the relative humidity of the product load just prior to the gas injection. Further, the vacuum drawn in the initial steps of sterilization will affect the humidity in the product load, but there is no assessment of the product humidity during the period of gas exposure.

- Gas concentration in the bag decreases throughout the exposure period. There is no assessment of gas concentration available to the product load during exposure under routine conditions. Also there was no information submitted to show an assessment of the impact of bag size or of load configuration in the aeration chamber on the gas concentration available to product.

- The validation studies have not demonstrated that all parts of the products will be exposed to sterilizing levels of ethylene oxide gas. For example, there is no demonstration that the gas will reach all areas within narrow lumens and long tubes. While biological indicators are placed in what were determined to be the most difficult locations to sterilize within the cabinet and challenge pack, there is no evidence that the firm has considered the most difficult location within the device itself. Since no sterility test of product is performed in the half cycle study, there is no confirmation of sterility in all areas of the device.

- Half cycle studies were not performed for worst case conditions. Although your firm performed the high/low side of sterility testing to demonstrate effectiveness of the process at both ends of the allowable temperature range, similar studies have not been performed over the possible range of ethylene oxide concentration or of relative humidity. Half cycle runs were made in only one size bag even though your firm uses several sizes, without any assessment of worst case size. Further, your firm has not provided data to demonstrate that the load configuration used in half cycle studies represent the worst caseload in the aeration cabinet.

During the half cycle analysis, bags were placed on the floor of the aeration cabinet. This is not the routine placement of bags in the cabinet, when products are placed on carts, which raise the product eight inches above the floor of the cabinet. According to the qualification report for aeration cabinet #4, probes attached to the floor of the aeration chamber "are directly in the path of the heated circulating air" (page 15 of 20). Therefore, during the half cycle studies when product is placed on the floor, the product appears to be located in an area with higher temperatures and more air circulation than in routine production. There is no assessment of the impact of this difference on worst case analysis.

- Bioburden testing (see Appendix D) done in support of the validation studies, appears to be inadequate because no rate of recovery has been determined for the testing. This is a requirement of ISO 11737-1, which you claim to follow.

- The high/low side sterility testing is insufficient to achieve your firm's objective of demonstrating "sterility capability at both extremes within the standard sterilization time." The reason that sterility capability cannot be demonstrated for routine processing with this study is that the study was performed in a different sterilizer with a different load than routine procedures. The conclusions may not be applicable to the chamber and load to be processed routinely. Both factors impact on the effectiveness of the process in achieving sterility. Further, the study proved a 6-log reduction at half cycles for high side temperatures but not in low side temperatures. In neither case, did the study demonstrate an achievement of sterility at the specified level of 10^{-6}. A failure in sterility testing during run 5 of the low side test was unexplained. It is not clear why the half cycle is defined as 15 hours here while it is 12 hours in the validation, part A, study.

- The gas dose confirmation was performed to demonstrate that the amount of gas injected into the pouch is consistent from time to time. The information provided is inadequate to support your firm's claim that this has been demonstrated. The data provided for the study showed that only six samples

were tested and that these were all for the same size bag. There is no statistical rationale provided for the number of samples tested. The conclusions about the amount of gas injected appears to indicate a failure to meet specifications for grams of EtO delivered, as specified in the A-Bio-Vac Operations Manual.

3. Failure to validate the packaging process with a high degree of assurance as required by 21 CFR 820.75(a). For example, there is no record that packaging temperatures and pressure settings used in the validation study were controlled or monitored.

Your firm's response dated April 23, 1998 is not adequate because the testing is not complete. The response states that pre-performance qualification studies on the impulse heat sealers will be conducted to test the sealers at various recorded temperatures to establish an optimal temperature range.

4. Failure to ensure that all equipment used in the manufacturing process meets specified requirements and is appropriately designed, constructed, placed, and installed to facilitate maintenance, adjustment, cleaning, and use as required by 21 CFR 820.70(g). For example:

   a) Installation and operation qualification studies were not conducted on the equipment used in the cleaning process.

   b) Installation and operation qualification studies were not conducted on the equipment used in the packaging process.

Your firm's response dated April 23, 1999 appears to be adequate.

5. 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:

   a) "Production Area Requirements Environmental Controls Number 4005" specifies that the relative humidity in the production area shall be maintained at 30-70% when the manufacturer of the sterilizer recommends that items to be processed be held at 40% RH for a minimum of 4 hours.

b) There are no records of the time devices are exposed to humidity prior to the sterilization process.

c) EtO Sterilization Procedure Number 4120 specifies a temperature range of 95-105°F when the manufacturer of the sterilizer recommends that the sterilization heat/aeration chamber be held at 110°F+/-10%.

Your firm's response dated April 23, 1999 is not adequate because the range chosen is under 40%, the relative humidity recommended by the sterilizer manufacturer. The relative humidity of the manufacturing environment is important because the A-BIO-VAC sterilization system used by Vanguard consists of a pouch and ethylene oxide only—no humidity is added. Also, since the biopsy forceps are dried in a vacuum drying chamber at 140-150°F for 2 hours overnight and surviving organisms would be desiccated the humidification step may be critical to the effectiveness of the sterilization process.

6. Failure to establish and maintain procedures to ensure that Device History Records (DHRs) for each lot are maintained to demonstrate that the device is manufactured in accordance with the DMR and the requirements of the Quality System Regulation as required by 21 CFR 820.184. For example:

   a) The only part of the process that is signed off and dated as released is the sterilization process.

   b) The DHR does not contain sufficient detail to demonstrate that process parameters, e.g., temperature and time for the various decontamination and cleaning processes, and temperature for sterilization process, were met for each step in the manufacturing process.

Your firm's response to Inspectional Observations (FDA 483) dated April 23, 1999 appears to be adequate.

7. Failure to assure that finished devices are not released for distribution until: (1) the activities required in the DMR are completed; (2) the associated data and documentation are reviewed; (3) the release is authorized by the signature of a

designated individual(s); and (4) the authorization is dated as required by 21 CFR 820.80(d). For example, the only part of the process that is signed off and dated as released is the sterilization process.

Your firm's response dated April 23, 1999 appears to be adequate. The response included a draft "Final Product Procedure" which requires production to ensure that all steps of the process on the Job Control Sheet (JCS) are dated and signed and requires Director of Quality to verify each JCS before release.

8. Failure to ensure that validated processes are performed by qualified individuals as required by 21 CFR 820.75(b)(1). For example, the person most responsible for process validation has not received adequate training in this area.

Your firm's response dated April 23, 1999 to FDA 483 Item #4 is not adequate because a copy of the training records was not submitted. The response stated that an individual had been contracted to provide a 3-day training program on process validation to 12 Vanguard employees, including the employee most responsible for process validation.

The specific violations noted in this letter and in the FDA 483 issued to you at the closeout 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 FDA. If the causes are determined to be systems problems, you must promptly initiate permanent corrective actions.

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 awards of contracts. Additionally, no premarket submissions for devices to which QS regulation deficiencies are reasonably related will be cleared until the violations have been corrected. Also, no requests for Certificates for Products for Export will be approved 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 penalties.

Please notify this office in writing within fifteen (15) working days of receipt of this letter, of any steps you may have taken to correct the noted violations, including (1) the time frames within which the corrections will be completed if different from those annotated on the FDA 483, (2) any documentation indicating the corrections have been achieved, and (3) an explanation of each step being taken to identify and make corrections to any underlying systems problems necessary to assure that similar violations will not recur.

Your response should be sent to Timothy J. Couzins, Compliance Officer, Food and Drug Administration, 555 Winderley Place, Suite 200, Maitland, Florida 32751, (407)475-4728.

Sincerely,

Douglas D. Tolen

Douglas D. Tolen
Director, Florida
District

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Atl' District Office
60 8th Street, N.E.
Atlanta, Georgia 30309

July 13, 2001

VIA FEDERAL EXPRESS

Mark Ferreira
President
Alliance Medical Corporation
10232 South 51st Street
Phoenix, Arizona 85944

WARNING LETTER
(01-ATL-61)

Dear Mr. Ferreira:

An inspection of your facility, Paragon Healthcare Corporation, located at 107 Corporate Drive in Spartanburg, South Carolina, was conducted between February 27 and March 9, 2001, by Investigator Claudette D. Brooks. Our investigator found that you continue to operate as a third party reprocessor of a variety of products to include electrophysiology catheters, sequential compression devices, and syringes. These products are devices as defined by Section 201(h) of the Federal Food, Drug, and Cosmetic Act (the Act).

Our investigator documented several significant deviations from the Quality System Regulation (QSR) as set forth in Title 21 of the Code of Federal Regulations (21 CFR), Part 820. These deviations cause the devices you reprocess and distribute to be adulterated within the meaning of Section 501(h) of the Act. These deviations from the QSR include:

1. Failure to establish and maintain a design history file for each type of device that contains or references the records necessary to demonstrate that the design was developed in accordance with the approved design plan and the requirements of the design control provisions of the Quality System regulation, as required by 21 CFR 820.30(j). For example:

   a. Paragon Healthcare Corporation (Paragon) did not have studies or data for a variety of "open-unused" devices; i.e., sutures, grafts, drapes, drains, and gowns. No supporting data could be provided to establish that ethylene oxide sterilization had no adverse effect on the product functionality or packaging materials.

b. Paragon failed to perform risk assessments and design reviews when new devices were selected for reprocessing, and failed to maintain design history files on these devices.

2. Failure to maintain device master records which include, or refer to, the location of quality assurance procedures and specifications, packaging and labeling specifications, and maintenance procedures and methods, as required by 21 CFR 820.181. For example, Paragon had not established procedures and specifications for "open-unused devices" reprocessed by the subcontractor, to include receipt, relabeling, release, distribution, and maintenance of device history records by the subcontractor.

3. Failure to establish and maintain procedures to ensure that device history records for each batch, lot, or unit are maintained to demonstrate that the device is manufactured in accordance with the device master record and the requirements of the Quality System regulation, as required by 21 CFR 820.184. For example, two reprocessed lots were chosen at random for review, #010245 [redacted] grafts) and #000185 (sutures). No sterility test results or product labeling were available for review. The only record on file was the shipping invoice. Processing records, to include sterility testing, had to be retrieved from your contract processor. There was no documentation that anyone at Paragon had reviewed the processing information prior to releasing these devices to your customers.

4. Failure to establish and maintain procedures for validating the device design to ensure that devices conform to defined user needs and intended uses, as required by 21 CFR 820.30(g). For example:

   a. Paragon failed to adequately perform design validation, in that you have not determined the negative consequences of multiple reprocessing and have not established a maximum number of reprocessing operations for cardiovascular catheters. A maximum number is not established in any formalized procedure and you could provide no documentation to demonstrate that a limit on the number of reprocessing operations has been established. Our investigator was told that the maximum number of reprocessing operations is decided collaboratively with each customer. A review of customer specifications revealed catheters to be reprocessed between [redacted] times.

   b. Paragon did not follow the established procedures for evaluating product design when additional devices were selected for reprocessing. Your Product Design procedure required that a meeting be held with Marketing, Operations, and Quality to consider the addition of new products. Tourniquet cuffs were added in January 2000 and there was no indication that the above meeting was held and that all required personnel had appropriate input. No risk assessment was performed and no reviews were conducted other than a Validation Equivalency. Other devices were added for reprocessing that did not go through the design control evaluation.

5. Failure to establish and maintain procedures for receiving, reviewing, and evaluating complaints, as required by 21 CFR 820.198. For example, Paragon had failed to implement appropriate complaint handling procedures. Complaints were not being investigated to identify existing or potential causes of nonconforming product or other quality problems. Of the eight complaints selected for review, five lacked evidence of a detailed investigation (#C0089, C0112, C0141, C0132, and C0179).

6. Failure to establish and maintain procedures for implementing corrective and preventive action (CAPA), to include procedures for investigating the causes of nonconformities relating to product, processes, and the quality system; identifying the action needed to correct and prevent recurrence of nonconforming product and other quality problems; and verifying or validating the CAPA, as required by 21 CFR 820.100. For example, there is no evidence of a detailed investigation, or documentation of action taken to prevent recurrence of nonconforming product, for complaints such as the failure of catheter to ablate, electrical failure, catheter breakage during use, and incorrect labeling.

7. Failure to base sampling plans on a valid statistical rationale, as required by 21 CFR 820.250. For example, Paragon had not defined or established a statistical rationale for the number of devices inspected by QA prior to pre-sterilization or post-sterilization release. The investigator noted that the observation was corrected in that a new procedure was prepared, however, there was no verification of the implementation of this new procedure. Verification of the entire corrective action will need to be assessed during the next inspection.

8. Failure to establish and maintain procedures for acceptance activities, as required by 21 CFR 820.80(a). For example, Paragon had not established procedures for placing customer devices on hold status although at least [redacted] EP catheters are on hold. Receiving procedures did not define the handling of unapproved/unsuitable customer products. The investigator noted that the observation was corrected in that a new procedure was prepared, however, there was no verification of the implementation of this new procedure. Verification of the entire corrective action will need to be assessed 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. At the close of the inspection, the FDA 483 (Inspectional Observations) was issued to and discussed with Deanna Phillips, Quality Systems Manager. A copy of the FDA 483 is enclosed for your review. The specific violations noted in this letter and in the FDA 483 could be symptomatic of underlying problems in your firm's quality assurance systems. You are responsible for investigating and determining the causes of the violations identified by the FDA. If the causes are determined to be systems problems, you must promptly initiate permanent corrective actions. We acknowledge that some corrections were initiated to the investigator's observations during, and subsequent to, the inspection.

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. You should take prompt action to correct these deviations. Failure to promptly correct these deviations may result in regulatory actions being initiated by the FDA without further notice. These actions include, but are not limited to, seizure, injunction, and/or civil penalties.

Please notify this office in writing within fifteen (15) days of receipt of this letter, of the specific steps you have taken to correct the noted violations, including an explanation of each step being taken to identify and make corrections to any underlying systems problems necessary to assure that similar violations will not recur. 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 to this letter should be sent to Philip S. Campbell, Compliance Officer, at the address noted in the letterhead.

Sincerely yours,

Ballard H. Graham, Director
Atlanta District

Enclosure

cc: Deanna Phillips, Quality Systems Manager
Paragon Healthcare Corp.
107 Corporate Drive
Spartanburg, South Carolina 29303