



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

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Atlanta District Office
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Atlanta, GA 30309

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June 17, 2002

VIA FEDERAL EXPRESS

Steven G. Anderson
President and CEO
CryoLife, Inc.
1655 Roberts Blvd., NW
Kennesaw, GA 30144

WARNING LETTER
(02-ATL-30)

Dear Mr. Anderson:

During an inspection of your firm located in Kennesaw, GA, conducted March 25 through April 12, 2002, our investigators determined that your firm manufactures and distributes cryopreserved heart valves. This product is a device as defined by section 201(h) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act). Our investigators documented significant deviations from the Quality System Regulation (QSR), as set forth in Title 21 Code of Federal Regulations (21 CFR), Part 820. These deviations cause your devices to be adulterated within the meaning of Section 501(h) of the Act, pursuant to 21 CFR 820.1(c). These deviations include:

1. Failure to fully validate and approve a process whose results cannot be fully verified by subsequent inspection and test, as required by 21 CFR 820.75 (a). For example, review of the validation studies for the [REDACTED] System (a.k.a., [REDACTED]) revealed that you did not use positive and negative controls with the samples, which were tested for the study. Your validation work does not support the reduction of culture incubation from [REDACTED] to [REDACTED] days. No growth promotion testing of the [REDACTED] media bottles and the anaerobic Blood Agar plates was done as part of the study. You did not challenge the [REDACTED] media with a full range of challenge organisms (aerobic and anaerobic) from known traceable sources to show that the media can support the growth over a wide range of challenge organisms. No data was available to support your use of the worst case situation [REDACTED]. Your validation study did not show that you continued to monitor the samples beyond the [REDACTED] days incubation period in the study to assure detection of slow growing organisms or fungi.
2. Failure to use sampling plans, which are based on a documented valid statistical rationale, as required by 21 CFR 820.250 (b). For example, the [REDACTED]-unit sample size

which was used for the final method study to compare culture results of the [REDACTED] system versus the old method [REDACTED] is not based on a documented valid statistical rationale.

3. Failure to revalidate a process conducted in response to changes or process deviations, as required by 21 CFR 820.75 (c). For example, CryoLife did not revalidate when it changed the [REDACTED] anaerobic media bottle from regular media to the anaerobic [REDACTED] bottle on/about 3/15/02. Also, the Tissue Processing Laboratory (TPL) autoclave was not revalidated after a sterilization time change on 4/26/01. Review of processing and maintenance records indicated continuing problems with the TPL autoclave dating back to 1999. Sterilization cycle failures of this autoclave were encountered during September and October of 2001.
4. Failure to adequately inspect or test incoming product to verify conformance of incoming product to specifications, as required by 21 CFR 820.80 (b). For example, your firm had not performed a [REDACTED] growth promotion test utilizing all the challenge organisms shown on the certificates of conformance for the aerobic and anaerobic media. Your firm routinely only uses [REDACTED] selected organisms for growth promotion testing on new lots of media that you receive. Without using a comprehensive list of various organisms for growth promotion, your firm has no assurance that your use of the [REDACTED] challenge organisms is sufficient to demonstrate that each lot of media will enable detection of all the aerobic and anaerobic contaminants that might be present on the heart valves.
5. (a) Failure to fully document process validation activities and results, as required by 21 CFR 820.75 (a). For example, the Anti-Microbial Cocktail Comparison Study (Protocol 990426-1 dated April 1999) lacked documentation of review of all data to support acceptance of the study. Information on study conditions was not documented and several sample processing records (i.e., cardiac tissue samples 461516 and 43609) were not available. This study failed to show data to support your stated specifications of [REDACTED] hours treatment of heart valves in the Anti-Microbial Cocktail. None of the samples in the study were processed and evaluated at the lower and upper limits of treatment processing times permitted by that specification.

(b) Another example of failure to fully document process validation activities is the lack of any testing of the Biological Safety Cabinet [REDACTED] Biological Safety Cabinet [REDACTED] the [REDACTED] Laminar Flow Hood [REDACTED]; and [REDACTED] Laminar Flow Hood [REDACTED] under dynamic or fully operational conditions to assure the air flow functions as needed for aseptic processing conditions during tissue dissection and during packaging/labeling operations. Testing and validation work on these units is not considered complete and/or meaningful without testing under dynamic conditions. Additionally, our investigators noted that the polylined drapes used to prepare the sterile field covered a major section of the perforated front grill thus interfering with the designed airflow of the cabinet.

6. Failure to fully monitor and control the component and device characteristics during production, as required by 21 CFR 820.70 (a) (2). For example, your firm does not monitor or evaluate the bioburden level or microbial load on recovered cadaveric heart valves prior to exposure to antibiotic treatment. Without knowing and monitoring the incoming bioburden level or microbial load on the heart valves, your firm cannot fully assure the consistency and control of your operations.

Our investigators also determined that your firm processes human tissues intended for transplantation. Our investigators documented significant violations of the requirements for human tissue intended for transplantation set forth at Title 21, Code of Federal Regulations (21 CFR), Part 1270, promulgated under the authority of Section 361 of the Public Health Service Act. These violations include:

Failure to prepare, validate, and follow written procedures for prevention of infectious disease contamination and cross-contamination during processing, as required by 21 CFR 1270.31 (d). For example:

1. Written procedures were not validated in that:
 - There was no evaluation that included bacteriostasis and/or fungistasis testing with the current antibiotic/antifungal cocktail(s). Your firm did not have data to ensure that the antibiotic/antifungal cocktail(s) did not interfere with or inhibit the growth of microorganisms in culture media(s) during post-processing culturing of tissues. Your firm has not validated its microbiology testing methods to ensure that residual antibiotic/antifungal cocktail(s) do not result in false-negative microbiological testing results.
 - There were no data to support the use of the processing parameters of [REDACTED] hours for cardiac and orthopedic tissues, and for the use of [REDACTED] hours for vascular tissue.
 - There were no validation studies to justify that the sample sizes obtained for post-processing microbiology quality assurance (QA) testing are adequate and representative of the tissues(s) being processed.
 - There was no information to validate procedures that did not provide for testing of incoming tissues prior to being processed. For example, there are no current studies showing that your firm has knowledge of the average bioburden of tissues received from your suppliers.
2. Written procedures were not followed for specific antibiotic treatment periods where:
 - Tissue was packaged and subsequently released prior to the completion of the specified antibiotic treatment period(s).

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 FD&C Act, Section 361 of the Public Health Service Act, and the federal regulations. The specific violations noted in this letter and in the FDA-483, Inspectional Observations (copy enclosed) issued on 4/12/02 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 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 award of contracts. Additionally, no premarket submission for devices to which the Quality System/good manufacturing practice (GMP) deficiencies are reasonably related will be cleared until the device violations described above have been corrected. Also, no requests for Certificates 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. FDA may take additional regulatory action without further informal notice, including, but not limited to, seizure, injunction, civil penalties, and/or an Order for Retention, Recall and/or Destruction.

Please notify this office, in writing, within fifteen (15) working days of receipt of this letter, of the 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 actions cannot be completed within fifteen (15) working days, state the reason for the delay and the time within which corrections will be completed.

We acknowledge receipt of your May 15, 2002 response letter to the inspectional observations. We have reviewed your response and determined that it is inadequate. Your response does not fully address the issues raised during the inspection. Without the supporting documentation that you promised to send as an appendix, we can not adequately evaluate your response. Where corrective actions were promised in your response, you did not provide written documentation of policies and procedures to verify that corrective actions have been implemented. Once we receive the additional information promised in your letter, as well as any additional information in response to this letter, we will evaluate it. We encourage you to meet with us at the Atlanta District Office to discuss corrective actions in further details.

Your response should be sent to Serene A. Kimel, Compliance Officer at the address noted in the letterhead.

Sincerely,


for Ballard H. Graham, Director
Atlanta District

Enclosure