



CBER - 99- 011

Food and Drug Administration  
Rockville MD 20857**WARNING LETTER**

• MAR 2 1999

**CERTIFIED MAIL**  
**RETURN RECEIPT REQUESTED**

Elizabeth A. Cummings  
General Manager  
Biopool International, Inc.  
1230 Wilson Drive  
West Chester, PA 19380

Dear Ms. Cummings:

An inspection of Biopool International, Inc., 1230 Wilson Drive, West Chester, PA, was conducted from December 3, 1998 through December 16, 1998. During the inspection, violations of Section 501(h) of the Federal Food, Drug, and Cosmetic Act and Title 21, Code of Federal Regulations, Subchapter F, Parts 600-680, and Subchapter H, Part 820 were documented as follows:

- I. Failure to implement and record, and verify or validate, corrective and preventive actions to ensure that such actions are effective and do not adversely affect the finished device [21 CFR 820.100 (a)(4) and (a)(5)]. Microbial contamination of at least 13 lots of Reagent Red Blood Cells (RRBC) occurred from September 1997 to July 1998 resulting in ten separate contamination investigations (ICARs). Unresolved issues were forwarded to subsequent investigations and the most recent investigations remain open without implementation of the corrective and preventive actions. For example:
  - a. Investigation and Corrective Action Request (ICAR) #98-12, opened 6/17/98, identifies the following corrective and preventive actions of which none had been implemented at the time of the inspection:
    1. develop effective bulk diluent culturing techniques.
    2. develop effective sterility sampling plan for the deionized (DI) water system.
    3. develop sanitization and filter change procedures for the DI water.
    4. evaluate filtration efficacy for bioburden retention and flow decay.

- b. ICAR # 97-12, opened 10/14/97 and closed 7/14/98, identifies the following corrective and preventive actions of which none had been implemented at the time of the inspection:
  1. Quality Control would develop a more appropriate sterility test method to detect contaminants in the DI water.
  2. the bulk diluent sterility test was to be reviewed and possibly revised.
  3. revise SOP 271.00 \_\_\_\_\_ to include daily disinfection of the \_\_\_\_\_
  
- c. ICAR #98-02 was opened 3/18/98. The closure report, dated 7/15/98 identifies the following corrective and preventive actions. There are no records demonstrating completion of the following actions:
  1. an abbreviated investigational study to determine the effectiveness of the preservatives \_\_\_\_\_ and \_\_\_\_\_ used in red cell products determined that the preservatives were ineffective against *C. acidovorans* and *S. marcesans* which are contaminants found in the RRBCs.
  2. the report states that the autoclave manufacturer \_\_\_\_\_ will visit the firm to discuss validation studies.
  
2. Failure to establish, maintain, and follow procedures for implementing corrective and preventive action, including requirements for investigating the cause of nonconforming product and identifying the action(s) needed to correct and prevent recurrence of nonconformities and other quality problems [21 CFR 820.100] in that unresolved issues and action items are forwarded to subsequent investigations.

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3. Failure to ensure that all inspection, measuring, and test equipment is suitable for its intended purposes and is capable of producing valid results [21 CFR 820.72] in that:
  - a. the \_\_\_\_\_ microbiological sampling, filtration, incubation, and test system for DI water used for the manufacture of licensed Blood Grouping Reagents (BGR), Anti-Human Globulin (AHG), and Reagent Red Blood Cells (RRBC) is not intended to be used to sample and test for USP Purified water.
  
  - b. thermometers used to monitor temperature in incubators and refrigeration units are only calibrated upon receipt.

4. Failure to establish, maintain, and follow procedures to prevent contamination of equipment or product by substances that could reasonably be expected to have an adverse effect on product quality [21 CFR 820.70(e), 660.20(a), and 660.50(a)] in that:
  - a. the DI water system used in the manufacture of BGR, AHG, and RRBCs has not been validated.
  - b. there are no established procedures for installing and conducting filter integrity tests on the DI water system filters.
  - c. the specification for DI water included in SOP 001.35, entitled “Deionized Water Monitoring and Control,” which references the USP standard for Purified Water does not include a specification for Total Organic Carbons.
  - d. sanitizer efficacy studies have not been conducted for the current disinfectants  

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  - e. cleaning validation studies have not been conducted on multi-use equipment including the vial-filling machine, bulk tanks, and pressure cans.
  - f. failure to follow SOP 001.35, entitled “Deionized Water Monitoring and Control,” in that failure investigations were not conducted for out-of-specification results from consecutive monitoring samples collected post-filtration.
  - g. the 

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 used for integrity testing of the in-line sterilization filter for BGR has not been validated.
5. Failure to have a processing method that has been shown to yield consistently a specific, potent final product, free of properties that would affect adversely the intended use of the product throughout its dating period [21 CFR 660.21(a) and 21 CFR 660.51(a)] in that the maximum percentage of reclaimed product allowed into a new bulk lot for BGR and AHG has not been established. Lots which include reclaimed product are not placed on a stability study.
6. Failure to establish, maintain, and follow procedures for process validation in order to ensure that processes have been adequately validated and that the specified requirements continue to be met [21 CFR 820.75] in that:
  - a. container closure integrity tests for BGR, AHG, and RRBC have not been performed.
  - b. validation studies for bacterial retention and product compatibility have not been conducted on sterile filters for bulk BGR and AHG.

- c. there is no documented review of the need for revalidation after replacement of the heat exchanger and door gaskets on the \_\_\_\_\_
7. Failure to develop, conduct, control, and monitor production processes to ensure that a device conforms to its specifications [21 CFR 820.70(a)] in that:
  - a. preservative effectiveness studies for BGR, AHG, and RRBCs have not been performed.
  - b. there is no established maximum hold time for formulated bulk BGR, AHG, and RRBC.
  - c. there is no data to support \_\_\_\_\_ hold times for sterilized vials, stoppers, filling sets, tanks, pressure cans, and filters.
8. Failure to establish, maintain, and follow procedures to adequately control environmental conditions that could reasonably be expected to have an adverse effect on product quality [21 CFR 820.70(c), 660.20(a), and 660.50(a)] in that the environmental monitoring system has not been validated during dynamic conditions.
9. 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 [21 CFR 820.70(g)] in that:
  - a. biological indicators are not placed in dry heat oven sterilization loads which include finished product vials.
  - b. autoclave runs do not always have a positive control and lot numbers of biological indicators are not documented.
  - c. temperature mapping studies have not been conducted for incubators including those used for stability samples and sterility samples.
10. Failure to evaluate and select potential suppliers, contractors, and consultants on the basis of their ability to meet specified requirements, including quality requirements, and to document the evaluation [21 CFR 820.50(a)] in that the quality control materials and suppliers have not been qualified for use.

We acknowledge receipt of your written response of January 15, 1999, to the Form FDA-483 issued at the close of the inspection. We have reviewed your response and find that it is inadequate to address our concerns. In general, while your response provided a basic commitment to correct some of the deviations, we are concerned by the lack of specific time frames in which corrections will be effected. In addition, the response did not provide sufficient documentation to demonstrate that corrections noted as complete have been performed.

We also have the following specific comments on your response, which are numbered to correspond to the observations listed on the Form FDA 483:

1. Please provide the documentation that will be developed by \_\_\_\_\_ that shows corporate management has reviewed the results of the third party audit and the QA monthly reports.
2. Your response does not indicate that corrective actions will be implemented. In addition, please provide documentation when these actions are completed.
- 3b. Please provide a target date for the validation of the autoclave.
5. Your response states that you will continue to use the \_\_\_\_\_ to monitor DI water. This system appears to be inadequate for its intended use. \_\_\_\_\_ was telephoned and told your employee, \_\_\_\_\_ that the \_\_\_\_\_ was not intended to be used to sample and test for USP Purified Water. Please provide your rationale to continue to use this system.
17. Please provide SOP 500.02 which is referenced in your response.
19. Your response states that container closure integrity testing will be performed by \_\_\_\_\_. This time frame appears to be excessive. Please provide your rationale for this extended timeframe.
20. Your response states that preservative effectiveness testing will be performed by \_\_\_\_\_. Taking into account the unresolved RRBC contamination investigations, this time frame appears to be excessive. Please provide your rationale for this extended timeframe and describe any interim measures that will be taken to ensure that the licensed products will be free of contamination.
34. Please provide a target date for the validation of the autoclave.
42. Your response is inadequate. Since the results of the mixing process cannot be fully verified by subsequent inspection, mixing speeds should be established through validation studies.

Neither the above violations nor the observations noted on the Form FDA 483 presented to your firm at the conclusion of the inspection are intended to be an all-inclusive list of deficiencies at your establishment. It is your responsibility to ensure adherence to each requirement of the Federal Food, Drug, and Cosmetic Act and the applicable regulations and standards. The specific violations noted in this letter and the Form FDA 483 may be symptomatic of serious underlying problems in your establishment's manufacturing and quality systems. You are responsible for investigating and determining the causes of the violations identified by FDA. If the causes are determined to be systems problems, you must promptly initiate permanent corrective actions.

You should take prompt action to correct these deviations. Failure to do so may result in regulatory action without further notice. Such action includes license suspension and/or revocation; seizure; injunction; and/or civil penalties. Federal agencies are advised of the issuance of all Warning Letters about drugs and devices so that they may take this information into account when considering the award of contracts. In addition, no license applications or supplements for devices to which the deficiencies are reasonably related will be approved until the violations have been corrected.

You should respond to FDA in writing within 15 working days of receipt of this letter of the specific steps you have taken to correct the noted violations and to prevent their recurrence. Corrective actions addressed in your previous letter may be referenced in response to this letter, as appropriate. If corrective actions cannot be completed within 15 working days, state the reason for the delay and the time within which the corrections will be completed. FDA will verify your implementation of promised corrective action during the next inspection of your facility. Your reply should be sent to the Food and Drug Administration, Center for Biologics Evaluation and Research, 1401 Rockville Pike, Suite 200 N, Rockville, Maryland 20852-1448, Attention: Division of Case Management, HFM-610. If you have any questions regarding this letter, please contact Annette Ragosta at (301) 827-6322.

Sincerely,



Deborah D. Ralston  
Acting Director  
Office of Regional Operations

cc: Michael D. Bick, CEO  
Biopool International, Inc.  
Ventura, CA 93003