



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service  
Food and Drug Administration

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San Francisco District  
1431 Harbor Bay Parkway  
Alameda, CA 94502-7070  
Telephone: 510/769-3010

**WARNING LETTER**

**VIA FEDERAL EXPRESS**

Our ref: 2919376

November 16, 1998

William Buxbaum  
President  
Hematronix, Inc.  
1505 Capital Ave.  
Plano, TX 75074

Dear Mr. Buxbaum:

Your firm located at 524 Stone Rd., Benicia, CA was inspected between June 26 and July 16, 1998 by Investigator Sally O. Lum, California Department of Health Services, Food and Drug Branch, under contract with the U. S. Food and Drug Administration (FDA). Investigator Lum, operating under the authority of the Federal Food, Drug, and Cosmetic Act, focused her inspection on the manufacture of whole blood controls and cell indices calibrators for hematological use. These products are medical devices as defined by Section 201(h) of the Act.

The inspection revealed that these devices are adulterated within the meaning of Section 501(h) of the Act, in that the methods used in, or the facilities or controls used for manufacturing, packaging, storage, or installation are not in conformance with either the Good Manufacturing Practice Regulation (GMPs) or the Quality Systems Requirements (QSRs) for medical devices as set forth in Title 21, Code of Federal Regulations (CFR) Part 820. We acknowledge that your firm has sent a letter to this District in response to the inspection. The following list of violations includes our assessment of some of the corrective measures which have been described.

1. You have not established manufacturing procedures which define the production specifications for the suspension fluid of the Centrifig Blood Control reagent. [REDACTED]

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[REDACTED] Investigator Lum was presented with what appears to be a handwritten batch record for the mixing of lot #005ACD. Management officials at the facility inspected consider the formulation to be a closely guarded trade secret and had made the decision to withhold documentation of the specifications. The formula apparently can vary, dependent upon the judgement of the operator. The Quality Systems Requirements require that each manufacturer maintain a device master record which includes, or refers to the locations of, specific information such as specifications, formulation, production processes, quality assurance procedures. [21 CFR 820.181]

Your firm's response letter is inadequate. It included what appears to be a blank manufacturing record for the mixing of the ACD suspension fluid. It is unclear whether this document is intended to represent the device master record or the device history record. Information required under 21 CFR 820.181, such as manufacturing instructions, equipment, labeling and controls, have not been defined in this document.

2. The reverse osmosis and deionized water system has not undergone annual USP testing by a certified analytical laboratory as set forth in your specification sheet Doc. #001.401. This testing was done once, in 1994. [21 CFR 820.70] We note with particular concern that previous inspectional observations regarding revalidation of the water system had neither been addressed nor corrected until the current inspection.

Your firm's response letter describes a retrospective validation of the reverse osmosis water system and sets forth a plan for revalidation and for annual monitoring. This appears adequate; future inspections will confirm full implementation of your plan.

3. Your autoclave validation records are incomplete in that there are omissions of information required by the Quality System Requirements, such as the identity of the equipment being validated (autoclave identification), acceptable ranges of parameters, identity of the person(s) approving the validation, and the person(s) performing the validation. [21 CFR 820.75]

Your firm's response letter includes a document which represents the retrospective validation of the autoclaves. This may be sufficient to demonstrate acceptable performance in the past. Our future inspections will include evaluation of such related parameters as your firm's control of environmental factors which may affect the microbial bioburden and control of the validated process.

4. Your autoclave validation process has not specified a biological indicator organism, nor has it specified an acceptable reduction value (kill rate) for the reagent vessels which are subjected to steam sterilization. [21 CFR 820.75]

The response to this observation is not acceptable at this point in time. The spore strip

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indicator organism, *Bacillus stearothermophilus*, is mentioned in what appears to be an unimplemented raw material specification (RMS #01.0274). The strip identity will need to be incorporated into your prospective validation protocols for the autoclaves, as will your acceptable kill rates. Placement of the strips in the autoclaves during a validation run will need to be specified. A subsequent inspection of your facility will include review of prospective validation plans and a review of the data covering your retrospective validation.

5. The complaint evaluation system which is in place at your firm does not document the status of each specific complaint. Currently complaints are generically discussed during meetings; minutes taken of the meeting reflect a general discussion, but are insufficient in recording the information required in the Quality Systems Requirements. [21 CFR 820.198]

This observation does not appear to have been addressed in your firm's response.

6. Documentation for your validation studies is not maintained with the information required under the Quality Systems Requirements. For instance, the validation of Lot Uniformity Procedural Change failed to identify the person performing the validation, the date of the validation, and the person who reviewed and approved the work. [21 CFR 820.75]

Your firm's response included a third page to this validation study. This additional page had not been provided to Investigator Lum during the inspection. It does bear the signatures of the persons who conducted and reviewed the study. Both signatures are dated on the same day, which we interpret to mean that the study was completed, reviewed, and approved on the same day. We wish to emphasize that signed records should accurately reflect the contemporaneous dates of the signatures.

7. You have failed to establish and maintain procedures for the identification, documentation, validation (or where appropriate, verification), review, and approval of design changes before their implementation. You have a procedure for change requests, but his procedure does not reference design changes. [21 CFR 820.30(1)]

A document submitted with your firm's response, SOP #03.QSP.040, acknowledges the role of the Quality/Regulatory Compliance Manager in evaluating whether a change effects the design of your devices. This document appears to be unimplemented, as no effective date is indicated. During our next inspection of your firm, we will verify that you have fully implemented a mechanism which addresses design changes.

This letter is not intended to be an all-inclusive discussion of deficiencies at your facility or of the adequacy of your firm's response. 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

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FDA483 issued to Mr. Thomas P. Davis, Quality/Regulatory Compliance Manager, may be symptomatic of serious underlying problems in your firm's manufacturing and quality assurance systems. If the causes are determined to be systems problems, you must promptly initiate permanent corrective actions. You are responsible for investigating and determining the causes of the violations.

We have been advised that Mr. Davis has sent to the offices of Senator Diane Feinstein a letter explaining your firm's position on the inspectional observations and outlining corrective measures which were being undertaken. Senator Feinstein has requested that the agency respond to the issues which Mr. Davis has raised. This letter serves to advise you not only of your obligations to satisfy the Act and regulations, but also of this District's determination that Mr. Davis' letter only partially addresses the inspectional concerns.

Mr. Davis has claimed that the regulatory requirements should be waived for a firm as small as the Benicia facility, and which has simplistic manufacturing processes. He further claims that the Quality Systems Requirements were not intended to be overly burdensome on small firms and that the low risk factor involved in your products would suggest lessened obligation to comply. The Quality Systems Requirements do permit manufacturers to establish procedures appropriate to their operations. The violations observed at your firm, however, are significant, regardless of the size of the manufacturing facility, and require that you immediately implement systemic corrective action. The letter to Senator Feinstein contains numerous statements regarding the inspectional outcome, such as, "there are no required actions as a result of this inspection". These statements may reflect a lack of understanding on the part of your firm's managerial staff that the FDA483 observations point to possible violations of the Act and regulations.

You should take prompt action to fully correct these deviations. Failure to do so 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. We acknowledge that corrective measures are already being taken to address some of the observations. We will verify full implementation of these measures during our next inspection of the Benicia facility.

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, requests for Certificates of Exportability and to Foreign Governments will not be cleared until the violations related to the subject devices have been corrected.

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 violations, including an explanation of each step being taken to identify and make corrections to any underlying systems problems as necessary to assure that similar violations will not recur. If corrective actions cannot be completed within 15 working days, state the reason for the delay and the date on which the corrections will be completed.

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Your response should be sent to the following:

Andrea P. Scott  
Compliance Officer  
U. S. Food & Drug Administration  
96 North Third St., Suite 325  
San Jose, CA 95112

Sincerely,



Patricia C. Ziobro  
Director  
San Francisco District

cc: The Honorable Dianne Feinstein  
Thomas B. Davis