



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service  
Mid-Atlantic Region

9/9/97  
CJF

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Telephone (201) 331-2909

Food and Drug Administration  
Waterview Corporate Center  
10 Waterview Blvd., 3rd Floor  
Parsippany, NJ 07054

August 11, 1997

**WARNING LETTER**

Mr. David DeFrangé  
Responsible Head  
Ortho Diagnostic Systems, Inc.  
1001 US Hwy 202  
Raritan, New Jersey 08869-0606

**File No: 97-NWJ-45**

Dear Mr. DeFrangé:

On June 4 - 19, 1997, Investigators from this office and the Center for Biologics Research and Evaluation (CBER) conducted an inspection of your manufacturing facility located at 1001 US Hwy 202, Raritan, New Jersey. This inspection covered RhoGAM and MICRhoGAM, which are drugs as defined by Section 201 (g) of the Federal Food, Drug and Cosmetic Act (the Act).

The above-stated inspection revealed that these drugs are adulterated with the meaning of Section 501 (a)(2)(B) of the Act, in that the methods used in, or the facilities or controls used in manufacturing, processing, packaging or holding, are not in conformance with Good Manufacturing Practices (GMPs) for Drug and Biologic Products, as specified in Title 21, Code of Federal Regulations (CFR), Parts 210 & 211 and 600 - 680, as follows:

Reclamation procedure

1) The manufacturing process for RhoGAM and MICRhoGAM using reclaimed material obtained from QA packaging rejects and bulk residue, has not been validated with regard to the difference in source material and additional product manipulation.

Environmental Monitoring

2) Environmental monitoring activities were found to be deficient, for example:

a) Action limits were exceeded during microbial sampling on two separate occasions, of the magnetic stirrer and the Capper in the sterile filling room. Sampling to determine the effectiveness of corrective actions were not completed within the timeframes required per SOP.

**RELEASE**

REVIEWED BY Murphy WOTZ 8/12/97  
C.O. DATE

In addition, the deviation report was not reviewed and considered closed until requested during the inspection, which was 9 and 11 months after the events occurred.

b) The Environmental Monitoring Program SOP requires monitoring of equipment only after room disinfection and does not consider the effect of equipment and/or product manipulation during operation.

c) Employees working in aseptic filling and filtration are responsible for taking their own personnel monitoring samples, which are not collected on a random basis.

#### Media Fills

3) When a media fill failure was attributed to human sourced contamination, introduced during filtration, the responsible individual was not retrained for two months following the event.

4) The SOP for Aseptic Filling Qualifications requires that "worst case" scenarios in Media Filling be identified. This has yet to be established.

5) There is no system to ensure that all employees working in sterile filling operations have been certified and qualified. For example, an employee working in the sterile filling areas had not participated in media fills since 1995. Environmental trending data indicated this employee had exceeded action limits more times than other employees.

#### Quality Assurance Program

6) The Quality Assurance Program was found deficient in several areas, for example:

a) RhoGAM Lot RHL272A1 was reworked after personnel monitoring tests yielded an out-of-specification result, however there was no documentation of review and approval by Quality Assurance of the reprocessing.

b) There was no documented investigation or deviation notice completed for RhoGAM Lot RHL259A, in which a non-sterile .22 micron filters was changed due to clogging, during filling operation. Clogging appears to occur in 15% of all production lots, yet these events are not

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documented regarding the cause and/or subsequent corrective actions.

#### Vendor Qualification

7) Vendors have not been adequately qualified for example:

a) Growth promotion testing is not performed on media purchased from an outside vendor to verify the supplier's Certificate of Analysis.

b) Sterile syringes purchased from an outside vendor have yet to be independently tested and qualified.

The above list is not intended to be all-inclusive of deficiencies at your facility. It is your responsibility to ensure that the drug products you manufacture are in compliance with the Act and the regulations promulgated under it. In addition, this letter does not include deficiencies noted during the pre-license inspection conducted between June 23 and 27, 1997, the results of which continue to be reviewed by FDA. Federal agencies are routinely advised of Warning Letters issued so that they may take this information into account when considering the award of contracts. You should take prompt action to correct these deficiencies. Failure to implement corrective measures may result in regulatory action, including license suspension/revocation, seizure and/or injunction, without further notice.

We are in receipt of your written responses, dated June 30, 1997 and July 17, 1997 to the FDA483 List of Inspectional Observations. We acknowledge your decision to discontinue the reclamation process, as of June 23, which resolves Observations 1-4. However, should you propose to resume using reclaimed material in the future, we expect that your firm will prospectively validate this process and receive approval of a license supplement from CBER prior to resumption of reprocessing activities.

The development of a study to determine the cause for filter clogging in response to Observation 5 is not considered a timely response. The larger concern is documenting the event and conditions under which any process variation may occur, in order to conduct an investigation and determine the root cause. These occurrences may indicate a need for revised instructions on setting up filter stacks to prevent air from being trapped, which should not wait for the completion of a study.

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The Deviation System detailed in your response to Observation 6 seems adequate, but will require close monitoring to determine the effectiveness of this system.

Response to Observation 7 appears adequate, but does not address whether additional Specification Advisories have been reviewed and closed out in a more timely manner.

Responses to Observations 8 - 18 appear adequate and are subject to verification upon reinspection.

You should notify this office in writing, within 15 working days or receipt of this letter, of the additional steps you have taken to correct the noted deficiencies, including an explanation of each step being taken to prevent the recurrence of similar conditions. If corrective action cannot be completed within 15 working days, state the reason for the delay and the timeframe within which corrections will be completed. Your reply should be sent to the New Jersey District Office, FDA, 10 Waterview Blvd., 3rd Floor, Parsippany, New Jersey 07054, Attn: Mercedes B. Mota, Compliance Officer.

Sincerely,



DOUGLAS ELLSWORTH  
District Director  
New Jersey District

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

cc: Mr. Gerard Vaillant  
Chairman  
Ortho-Clinical Diagnostics

MBM:np