



DEPARTMENT OF HEALTH & HUMAN SERVICES

745  
Public Health Service  
Food and Drug Administration  
San Francisco District  
1431 Harbor Bay Parkway  
Alameda, California 94502  
Telephone (510) 337-6700

WARNING LETTER

CERTIFIED MAIL  
RETURN RECEIPT REQUESTED

November 25, 1997

Our ref: 2917681

Scott Garrett  
Chief Executive Officer  
Dade Behring, Incorporated  
1717 Deerfield Road  
P.O. Box 778  
Deerfield, IL 60015

Dear Mr. Garrett:

During an inspection of your firm located in Cupertino and San Jose, California, on October 14 through 17, 1997, our investigators determined that it manufactures a variety of diagnostic products, including Cyclosporine Specific Assay. These products are devices as defined by Section 201(h) of the Federal Food, Drug, and Cosmetic Act (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, packing, storage, or installation are not in conformance with the Current Good Manufacturing Practice (CGMP) Quality System Regulation for Medical Devices, as specified in Title 21, *Code of Federal Regulations* (CFR), Part 820, as follows:

1. Corrective and preventive actions have not been implemented [21 CFR 820.100(a)(5)], verified, or validated [21 CFR 820.100(a)(4)]. Particularly, problems with preservatives in a component led to a recall of three lots of Chlamydia test kits due to excessive bioburden levels. The corrective action was flagged as priority A; your firm's procedures state that priority A actions are "critical, safety or regulatory in nature" and "are resolved as soon as possible." This corrective action has been open since December 1996.

Additionally, a corrective action request to improve preservatives for stock concentrates of enzyme conjugates has been open since February 1997.

2. Processes that cannot be fully verified by subsequent inspection and test have not been validated with a high degree of assurance [21 CFR 820.75(a)]. Key processes listed in the process validation master plan have not been validated. For example, lyophilization has not been validated, and there have been lyophilization failures. Also, one of the validation studies your firm has completed does not provide a high degree of assurance; the validation of mixing solids into solutions did not demonstrate the robustness of the processes in that only a single batch was tested for each condition.
3. All complaints are not processed in a uniform and timely manner [820.198(a)(1)]. In the period from January 1996 to the present, there are 203 open complaints. Additionally, complaints from sources outside the United States are not routinely forwarded to the manufacturing location [21 CFR 820.198(a)(1) and (f)].
4. The sampling plan for testing the reliability of the performance characteristics (e.g., stability studies) has no statistical basis [21 CFR 820.250(b)]; there is one unit tested per attribute. Additionally, the investigators found that test spikes used for these studies had not been qualified against an accepted reference calibrator [21 CFR 809.10(a)(5)].

It was also noted during the inspection that the analytical sensitivity of the method used for validation of the cleaning of the filling machine (used to fill calibrators) has not been challenged to the  $\mu\text{g/ml}$  acceptance level set in your cleaning validation report. It is noted that this observation also was made during an inspection in April 1996 .

We have received your firm's response dated November 14 to our inspectional observations. We acknowledge your firm's progress, particularly in the area of process validation. Nevertheless, we are concerned with the length of time -- until April 1998 -- your firm is proposing to complete process validation. Your response also does not provide a commitment for the length of time required to improve the preservative system.

The above identified deviations are not intended to be an all inclusive list of deficiencies at your facility. It is your responsibility to assure that your establishment is in compliance with all requirements of the federal regulations.

You should take prompt measures to correct these deviations. Failure to correct these deviations promptly may result in regulatory action without further notice. Such action includes seizure and injunction.

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 pre-market applications for Class III devices to which the GMP 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.

Within 15 working days of receipt of this letter, please notify this office in writing of the specific steps you have taken to correct the noted violations and to prevent their recurrence. 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 reply should be sent to the Food and Drug Administration, San Francisco District, 1431 Harbor Bay Parkway, Alameda, CA 94502, Attention: Philip R. Lindeman.

Sincerely,

*Charles D Moss*  
*Acting District Director*

*for*

Patricia C. Ziobro  
District Director  
San Francisco District

cc:

