DEPARTMENT OF HEALTH & HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION CENTER FOR DRUG EVALUATION AND RESEARCH

Division of Manufacturing and Product Quality, HFD-320
7520 Standish Place
Rockville, Maryland 20855-2737

TELEPHONE: (301) 594-0095
FAX: (301) 594-2202

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WARNING LETTER

Glaxo Wellcome
Harmire Road
Barnard Castle, Durham County
DL12 8DT, United Kingdom

Dear Dr.

This is regarding an inspection of your pharmaceutical manufacturing facility in Barnard Castle, United Kingdom, by Investigator Thomas J. Arista and Chemist Robert D. Tollefsen of the United States Food and Drug Administration, during the period of December 1 - 16, 1997. The inspection revealed significant deviations from U.S. current good manufacturing practice (CGMP) regulations in the manufacture of sterile and non-sterile pharmaceutical finished products. The deviations were presented to on an Inspectional Observations form FDA-483 at the close of the inspection. These CGMP deviations cause your pharmaceutical products to be adulterated within the meaning of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act.

We have reviewed your January 22, 1998 response to the FDA-483 observations. We note that many corrections were implemented or will soon be implemented. We met with you and representatives of your firm on February 27, 1998, to clarify some of the written responses and your action plan and commitments. The commitments made during this meeting appear adequate, if satisfactorily completed, to bring the facility into compliance with CGMP; however, the following issues concerning your firm's current state of compliance remain of concern:

1. Inadequate retrospective validation of the network computer system used for overall Quality Assurance/Quality Control operations, and for the control and release of raw materials, in-process materials, and finished products. For example:

   a. There were no original planning or systems design documents included in the validation materials for the programs.

b. There were no structural and functional designs included in the validation materials for the programs.

c. Only a small fraction of each program's code underwent detailed review.

d. Sections of code lacked annotations (e.g., the meaning of variables), and contained "dead" or unused code.

e. There were inconsistencies in the review of the validation documentation.

f. There was inadequate software version control.

Your response indicates that your firm is looking forward to replacing the system rather validating the existing system. The new system is expected to be in place and validated prior to The first phase of installation and qualification of the new system, affecting production, QA, and warehousing, is to be completed in The new system should not be used until it is satisfactorily validated. The current system is unacceptable for current use because of the deficiencies listed above. During the telephone conference on March 18, 1998, you agree to submit a plan to bring the system into compliance with validation requirements. We agreed to review this corrective action plan.

2. There was no revalidation of the system following revisions to the software to demonstrate that the sterilization cycle remains capable of the same 6 log reduction as demonstrated before the revision (1992 validation study).

The routine validations did not use appropriate validation conditions, such as concentration and temperature thermocouple locations, to demonstrate that the revisions have not adversely affected the system.

Your response failed to demonstrate that the routine heat distribution studies are an appropriate substitute for revalidation of the system. As discussed during the meeting of February 26, 1998, revalidation is expected be completed by April 1998, and the validation report will be submitted to FDA.

3. Inadequate process validation of the process. The formula has homogeneity variability related to superpotency at the top layer of the bulk suspension. The process validation did not adequately address the extent and variability of the superpotency to provide a consistent process and ensure uniform product potency.

Your response indicates that you have conducted bulk suspension surface studies and revalidated the process to confirm that the portion of the bulk batch subject to superpotency is consistent and controlled during the filling process. As agreed to during the meeting of February 26, 1998, this data will be provided to FDA for review.

4. Inadequate maintenance of the depyrogenation tunnel equipment in the ampule manufacturing operations; for example:

   a. The frequency of integrity checks performed on filters has not been demonstrated to be adequate for filters located in the heating zone of the depyrogenation tunnel.

   b. The depyrogenation fan speed was not calibrated to ensure fans are operating at the required set speed.

   Your response says that in addition to the annual integrity test, a second test on filters associated with depyrogenation tunnels will be performed after months. The response did not demonstrate that the month frequency is adequate to ensure the filters are not compromised by the extreme depyogenation temperatures. As discussed in the February 26, 1998, meeting, a study to determine the appropriate time frame for replacement of these filters will be conducted and an appropriate test frequency will be implemented.

   Your response said that the calibrated differential pressure system gives assurance that appropriate quantities of air are supplied, and that fan speed is a non-critical parameter, and will be removed from calibration requirements. The response did not provide the correlation between the differential pressure and the fan speed in order to demonstrate that it is a non-critical parameter. In the February 26, 1998, meeting your firm committed to calibrate/validate fan speed by April 1998.

5. Failure of the QC Unit to properly maintain records. The performance qualification records in support of a process change for were misplaced and could not be located.

   Your response indicates that an investigation has been performed and although the subject records have not been located, other records support the adequacy of the qualification. You also indicated that corrections to avoid losing records have been implemented. Please provide a copy of these procedures and security measures implemented to avoid losing production and testing records.

6. Inadequate environmental monitoring of the aerosol dispensed medication production environment. The

monitoring program has not demonstrated that the established environmental specifications are being met under operational conditions.

a. Non-viable particulate monitoring is not performed under dynamic conditions in the filling area.

b. Non-viable monitoring is conducted per year for the area, and per year for the area (static conditions).

c. Viable air monitoring is conducted per month (dynamic conditions).

d. Surface microbiological monitoring is conducted per month.

Your response maintains that the air quality monitoring is adequate because the subject products are non-sterile and have no particulate specifications. The response stated that non-viable monitoring (static) would be increased to per month for and per quarter for We believe that established environmental classifications should be demonstrated under static and operational conditions and at appropriate frequencies. Inadequate manufacturing methods and safeguards against contamination at other facilities have not prevented undesirable microbial contamination of non-sterile inhalation solutions for nebulization. Microbial contamination of these products may result in serious health consequences due to opportunistic pathogens entering the lungs, or to the possible inactivation of the drug product by these microorganisms.

As discussed during the meeting on February 26, 1998 you will review what classifications are achievable in the filling areas and submit a commitment which will provide assurance of adequate air quality for the manufacture of these products.

The CGMP deviations identified above are not to be considered an all-inclusive list of the deficiencies at your facility. FDA inspections are audits which are not intended to determine all deviations from CGMPs that exist at a firm. We recommend that you evaluate your facility on an overall basis for CGMP compliance. It is the responsibility of your firm to assure compliance with U.S. standards for current good manufacturing practices for pharmaceutical manufacturers.

As discussed during the February 26, 1998 meeting, please submit the requested information regarding the outstanding issues discussed above, and continue to notify this office as the specific steps discussed during the meeting are completed. Until FDA has confirmed that these deficiencies have been corrected and your firm is in CGMP compliance, we will not recommend approval of new applications listing your firm as a

supplier of sterile, aerosol and tablet drug products. Failure to complete the corrections discussed may result in further regulatory action.

Please contact Edwin Melendez, Compliance Officer, at the address shown above, or by telephone at (301) 594-2454, if you have any questions regarding this letter. Also, please reference within your written response.

Sincerely,

Joseph C. Famulare
Director
Division of Manufacturing and Product
Quality, HFD-320

CC:

Glaxo Wellcome Inc.
1011 N Arendell Avenue
P.O. Box 1217
Zebulon, North Carolina, 27597