DEPARTMENT OF HEALTH & HUMAN SERVICES

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Food and Drug Administration
Rockville MD 20857

AUG 16 2004

CBER-04-015

WARNING LETTER

FEDEX

David Watson
Executive Vice President
Aventis Pasteur SA
2 Avenue Pont Pasteur
F-69 007 Lyon Cedex 07
France

Dear Mr. Watson:

The Food and Drug Administration (FDA) conducted inspections of Aventis Pasteur SA located at 1541 Avenue Marcel Merieux, F679280 Marcy L'etoile, Lyon, France, between March 9 to March 18, 2004, and April 26 to April 30, 2004. During the inspections, FDA investigators documented deviations from current good manufacturing practice, including the applicable standards and requirements of Subchapter C Parts 210 and 211, and Subchapter F Parts 600-680 of Title 21, Code of Federal Regulations, (21CFR). Failure to comply with current good manufacturing practice renders products adulterated under Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act). The deviations noted on the Forms FDA 483, Inspectional Observations, issued at the conclusion of the inspections, include, but are not limited to the following:

1. Failure of the quality control unit to review production records to assure that no errors have occurred or, if errors have occurred, that they have been fully investigated. [21 CFR 211.22 and 211.192] For example

   a) The review by the quality control unit of [redacted] batches of Rabies vaccine manufactured between July 2002 and July 2003 did not identify the error that

occurred where you failed to segregate batch processing equipment in that the [redacted] filter integrity tester was being transported back and forth from the live virus area to the inactivated virus area. You acknowledged in communications with FDA that this was a "breach of GMP."

b) Numerous lots of Thymoglobulin did not meet specifications for capping defects during filling and capping operations for which you are the contract manufacturer. Nevertheless, the quality control unit did not thoroughly investigate these defects.

c) The quality control unit did not ensure that the particulates in lots of Haemophilius b Conjugate Vaccine were thoroughly investigated. The investigation was limited to the laboratory and did not include input from other departments, including manufacturing, to determine whether particulates were coming from another source.

d) Review of batch production records for lots X0480-2 and W1386-2 was not adequate because the quality control unit did not identify label accountability errors and the errors. These errors were not investigated.

e) The quality control unit does not ensure that environmental monitoring excursions are thoroughly investigated. For example, the investigations for class [redacted] area environmental monitoring excursions did not include the identification of the organisms for nonconformance investigations 2003-05499 and 2003-003090.

f) The quality control unit does not ensure that WFI excursions for some areas are thoroughly investigated. Examples include the microbial excursion of too numerous to count organisms on port [redacted] in [redacted] in April 2002, and the action level excursions for total organic carbon (TOC) in [redacted] in September 2003 and February 2004.

g) Numerous lots of Haemophilus b Conjugate Vaccine and Rabies vaccine that failed [redacted] testing after [redacted] were released after the inspection of [redacted] additional vials of each lot. The investigation did not provide a rationale for release on the basis of inspection of the additional [redacted] vials. Some examples include Heamophilius b conjugate lots X0803, X0452, X0410, X0409 and Rabies Vaccine lots X0254 and X0115.

2. Failure to establish an adequate quality control unit having the responsibility and authority to approve or reject in-process materials and drug products, and the authority to assure no errors have occurred or, if errors have occurred, that they have been fully investigated. [21 CFR 211.22(a)]. The quality control unit did not have oversight into Water for Injection (WFI) microbial excursions at various ports at [redacted]

3. Failure to keep equipment and supplies used in work on or otherwise exposed to any pathogenic or potentially pathogenic agent separated from equipment and supplies

used in the manufacture of products to the extent necessary to prevent cross-contamination [21CFR 600.11(e)(5)], in that equipment was moved from the virally active area into the virally inactive area, providing an opportunity for cross-contamination.

We acknowledge receipt of your written responses dated April 19, 2004, and May 27, 2004, which address the inspectional observations on the Forms FDA 483 issued at the close of the inspections. Corrective actions addressed in these responses may be referenced in your response to this letter, as appropriate; however, we believe that your responses did not provide sufficient detail to allow us to fully assess the adequacy of the corrective actions. Our evaluation of your responses follows, and is numbered to correspond to the items listed on the Forms FDA 483:

Items # 1-20
Regarding the implementation of corrective actions, your response dated April 19, 2004, states that there are gaps that remain in the full implementation of your corrective actions and that you need to [redacted]. As evidenced by the list of inspectional observations issued on March 18, 2004, and April 30, 2004, we agree with your statements. Please be advised that prompt corrective action to all deviations is expected. Your response did not identify steps to be taken to implement and assure adequate effective corrective and preventive actions within appropriate and responsive timeframes.

Item #1
Your response dated April 19, 2004, states that a [redacted] group was created in [redacted] and that the deficiencies identified during the March 2004 inspection were largely before the complete implementation of the [redacted]. This is not acceptable. Please be advised that systems should be in place, even during the time of implementation, to assure adequate and effective corrective and preventive actions. Please provide a detailed description of your [redacted] group and the procedures in place to ensure that adequate steps are taken for the evaluation of product impact, deviation investigations, and adequate and effective correction and preventive actions.

Your response dated May 27, 2004, states that the site quality systems are being reviewed so that the processes and methods used for the review and investigation of non-conformances are more clearly defined and subjected to a fully systematic approach. Please provide a detailed explanation of the revisions, the steps taken to assure adequate and effective corrective and preventive actions, and the timeframes for implementation.

Neither this letter nor the list of inspectional observations (Form FDA 483) is meant to be an all-inclusive list of deficiencies that may exist at your facility. It is your responsibility as management to assure that your establishment is in compliance with all requirements of the federal regulations. Federal agencies are advised of the issuance of all Warning Letters about drugs so that they may take this information into account when considering the award of contracts.

Please notify us in writing, within 15 working days of receipt of this letter, of any steps you have taken or will take to correct the noted violations and to prevent their recurrence.

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. Failure to correct these deviations promptly may result in regulatory action without further notice. Such actions include license suspension and/or revocation. Your reply should be sent to James S. Cohen, J.D., Acting Director, Office of Compliance and Biologics Quality, U.S. Food and Drug Administration, Center for Biologics Evaluation and Research, HFM-600, 1401 Rockville Pike, Suite 200 N, Rockville, Maryland 20852-1448. If you have any questions regarding this letter, please contact Ms. Mary Malarkey, Director, Division of Case Management, at (301) 827-6201.

Sincerely,

David K. Elder
Director
Office of Enforcement

cc: David C. Williams
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