DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration

Center for Biologics Evaluation and Research
1401 Rockville Pike
Rockville MD 20852-1448

SEP 19 2007

CBER-07-011

WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Henri A. Termeer
Chairman, President and CEO
Genzyme Corporation
500 Kendall Street
Cambridge, MA 02142
USA

Dear Mr. Termeer:

The Food and Drug Administration (FDA) conducted an inspection of Genzyme Polyclonals S.A.S. located at 1541 Avenue Marcel F-69280 Marcy L'etoile, Lyon, France between June 6 and June 19, 2007. During the inspection, the FDA investigator documented significant deviations from current good manufacturing practice (CGMP) in the manufacture of Thymoglobulin Formulated Bulk lots (bulk lots). These deviations from CGMP include deviations from the applicable requirements of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), as well as requirements of your biologics license application approved under section 351(a) of the Public Health Service Act (PHS Act) and Title 21, Code of Federal Regulations (21 CFR) Part 601.

At the close of the inspection, FDA issued a Form FDA 483, Inspectional Observations, which described a number of significant deviations in the manufacture of your Thymoglobulin Bulk lots that are used to formulate your Thymoglobulin [Anti-thymocyte Globulin (rabbit)] product. Specific areas of concern include, but are not limited to:

PRODUCTION AND PROCESS CONTROLS

1. At least three [redacted] manufactured in 2006 exceeded your endotoxin action limit of [redacted] EU/ml. Three [redacted] that exceeded the endotoxin action limit were blended with [redacted] that did not exceed your action limit and were used in the formulation of final product lots TH173 and TH174 that were shipped to and distributed in the United States.

2. On several occasions you continued to use components and intermediates that failed your in-process limit for bioburden and presence of pathogenic microorganisms and you did not conduct sufficiently comprehensive investigations of these failures. For example, a Too Numerous to Count (TNTC) bioburden result with the presence of *Pseudomonas fluorescens* was obtained for [redacted] lot [redacted] Additionally, a bioburden result of >200 CFU/ml with the presence of *Enterobacter cloacae* was obtained for [redacted] lot [redacted] after the [redacted] step.

   We also note that it is unclear what your "TNTC" designation represents in terms of bioburden. Because of this, it is also unclear how your assay is used to determine whether or not certain limits have been exceeded. For example, as stated in deviation report N2006-210, you have established an action limit of [redacted] and [redacted] for [redacted] yet you described TNTC at this step as [redacted] Please provide additional information regarding your use and application of the TNTC designation.

   We acknowledge that the final Thymoglobulin product resulting from the bulk lots and intermediates referenced in items 1 and 2 met all specifications. However, based on FDA's experience, there is a high probability that the observed CGMP deviations, if not corrected, would substantially increase the risk of future product failures. Of particular concern is that you continued to use components and intermediates that did not meet your internal in-process limits and you did not fully investigate these deviations and implement appropriate corrective and preventive actions. Adequate process control and correcting and preventing deficiencies in the process before they result in product failures are underlying principles of CGMP.

3. You failed to control the Purified Water System used in the manufacture of bulk lots. For example;
   a) From July 19, 2005 to July 27, 2005, purified water monitoring results exceeded the action limit of [redacted] for distribution points [redacted] and [redacted] of highly purified water loop [redacted]
   b) On May 5, 2004 and October 26, 2006, purified water monitoring results exceeded the action limit of [redacted] in that pathogenic organisms *Burkholderia cepacia* and *Enterobacter cloacae* were isolated from various sampling points.

INVESTIGATION OF FAILURES

4. Your investigation into the deaths of two [redacted] during safety and potency tests [redacted] and the associated lack of investigation regarding Adverse Events THYM11145 and THYM11146 are inadequate. The relationship between the [redacted] deaths and the Adverse Event reports, which all implicated Thymoglobulin bulk lot #06TMG0080, should have triggered a comprehensive, in-depth investigation into all areas of the production process including manufacturing records and any associated deviations that occurred.

BUILDINGS AND FACILITIES

5. Your disinfectant effectiveness study # FR039-01 dated September 20, 2004, is incomplete. The study did not evaluate the effectiveness of the disinfectants in use on fungi and spore forming microorganisms. Spore forming microorganisms have been routinely isolated in your manufacturing facility and accounted for 17% of total isolates in 2004 and 2005; 14% in 2006 and 7% in 2007, at the time of the inspection. We note that this is a repeat observation from our 2004 inspection.

The deficiencies described in this letter are indicative of your quality control unit not fulfilling its responsibility to assure the quality and purity of your components/in-process materials. Please describe in detail how Genzyme will attain CGMP compliance with regard to bulk lot production and process controls. Please include in that description how Genzyme will use all the relevant information to conduct thorough investigations, to ensure that adequate steps are taken to evaluate whether deviations impact product, and to implement effective corrective and preventive actions.

We acknowledge receipt of your written response dated July 30, 2007 which addresses the inspectional observations on the Form FDA 483 issued at the close of the inspection. We have reviewed the contents of your response. Corrective actions addressed in your letter may be referenced in your response to this letter; however, we believe that your response did not provide sufficient detail to fully assess the adequacy of the corrective actions. Our comments and request for further information regarding corrective action are detailed below. The items correspond to the observations listed in the Form FDA 483.

FDA 483 observation # 1

Your response indicates that rabbit pyrogen testing is performed on [redacted] finished vial lot as required by the product release specifications for Thymoglobulin. We agree that [redacted] finished product testing is required as part of CGMP. However, in-process controls are also needed to further monitor the performance of the manufacturing process and to ensure that it remains within validated limits. When such limits are exceeded, it is an indication that the process is not in a state of control and a full investigation is warranted to determine appropriate corrective and preventive actions.

You stated in your overall response that "it is not always possible to have the final endotoxin results available prior to the initiation of the next process step." Please provide further details as to how your commitments will allow detection of endotoxin in a more timely manner and whether or not this will require process changes.

FDA483 observations # 4/8

Please provide a copy of your Water System Summary Report as well as any conclusions and associated timelines for implementing any improvements identified during your assessment.

FDA 483 observation # 5, 6, 7

While we acknowledge the details of the investigations outlined in your response, we believe that more in-depth investigations, including batch record review and a review of associated adverse events (AE), were warranted. Please provide details as to how you plan to address the inadequacies in your AE investigations in the future.

FDA 483 observations #9/10

Your responses indicate that you will conduct an additional study to evaluate the effectiveness of your disinfectants, as well as perform cleaning validation of the [redacted] laminar flow hood. Please be advised that the completion date of Q1/2008 for these activities appears excessive. We remind you that the failure to adequately evaluate your disinfectants is a repeat observation from our 2004 inspection. We recommend that you re-evaluate your proposed timeframe for completion of both studies.

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 the provisions of the FD&C Act, PHS Act, and applicable federal regulations. Federal agencies are advised of the issuance of all Warning Letters about drugs so that they take this information into account when considering the award of contracts.

You should take prompt action to correct these deviations. Failure to promptly correct these deviations may result in FDA initiating regulatory action without further notice. Such action may include license suspension and/or revocation.

Please notify us in writing, within 15 working days of receipt of this letter, of any additional steps you have taken or will take to correct the noted violations and to prevent their recurrence. Include any documentation necessary to show that correction has been achieved. 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.

Your reply should be sent to me at the U.S. Food and Drug Administration, Center for Biologics Evaluation and Research, HFM-600, 1401 Rockville Pike, Suite 200N, Rockville, Maryland 20851-1448. Additionally, we acknowledge your request for a meeting. In order to facilitate your meeting request, please contact Robert McElwain at (301) 827-6196 to discuss an appropriate time for the meeting or if you have any questions regarding this matter.

Sincerely,

Mary A. Malarkey

Mary A. Malarkey
Director
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research

Cc: Mark Bamforth
Senior Vice President
Corporate Operations and Pharmaceuticals
Genzyme Corporation
500 Kendall Street
Cambridge, MA 02142
USA

Henry Darnell
VP Quality
Genzyme Polyclonals
C4-C5 Buildings
1541, avenue Marcel Merieux
69280 Marcy L'Etoile, France