



M3321N

CBER-00-011

Food and Drug Administration  
Rockville MD 20857

WARNING LETTER

DEC 23 1999

CERTIFIED MAIL  
RETURN RECEIPT REQUESTED

H. Michael Koplove, Ph.D.  
Vice President of Manufacturing  
Genetics Institute  
One Burtt Road  
Andover, MA 01810

Dear Dr. Koplove:

The Food and Drug Administration (FDA) conducted an inspection of Genetics Institute located at One Burtt Road, Andover, Massachusetts, between September 29 and October 8, 1999. During the inspection, FDA investigators documented violations of Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and deviations from the applicable standards and requirements of Subchapter C Parts 210 and 211, and Subchapter F Parts 600-680, Title 21, Code of Federal Regulations, (21CFR). The deviations noted on the Form FDA 483, Inspectional Observation, issued at the conclusion of the inspection include, but are not limited to the following:

1. Failure to thoroughly investigate any unexplained discrepancy or the failure of a batch or any of its components to meet any of its specifications [21 CFR 211.192]. For example:
  - a. Between the time period of July 1997 and September 1999, mold was found in numerous samples collected from the purified water loops. No investigations were conducted into these findings.
  - b. Between the time period of February 1998 and July 1999, excursions from bioburden specifications were found for at least 25 Water For Injection (WFI) and Purified Water samples. No investigations were conducted into these findings.
2. Failure to maintain and follow an appropriate written testing program designed to assess the stability characteristics of drug products [ 21 CFR 211.166(a)], in that

there was no data available to demonstrate that assays used in the stability testing of bulk Antihemophilic Factor Concentrate (Recombinant) (rAHF) are stability indicating.

3. Failure to establish and follow written procedures for cleaning and maintenance of equipment, including utensils, used in the manufacture, processing, packing, or holding of a drug product [21 CFR 211.67(b)]. For example:
  - a. The routine heat sanitation of the purified water system has not been validated.
  - b. No data was available to demonstrate the bacteriostatic effectiveness of the \_\_\_\_\_ containing storage solution, which is used in the monoclonal antibody (Mab) purification columns during periods of disuse.
  - c. Post use integrity testing was not performed for the \_\_\_\_\_ filters, used during the manufacture of bulk drug substance Coagulation Factor IX (Recombinant).
4. Failure to establish adequate control measures for air filtration systems [21 CFR 211.46] in that there were no specifications for velocity and pressure drop in the certification of the HEPA filters on the HVAC system. Additionally, there is no data to support the specification set for total airflow.
5. Failure to establish scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that components, drug products containers, closures, in-process materials, labeling, and drug product conform to appropriate standards of identity, strength, quality, and purity [21 CFR 211.160 (b)]. For example:
  - a. There were no completed studies to support the current in-house specifications for rinse water conductivity testing.
  - b. Specifications have not been established for all in-process analyses performed on samples collected during the manufacture of Recombinant Human Interlukin 11, Antihemophilic Factor Concentrate (Recombinant), and Coagulation Factor IX.

We acknowledge receipt of your written response dated November 15, 1999, which addresses the inspectional observations on the Form FDA483 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, as appropriate; however, your response did not provide sufficient detail to fully assess the adequacy of the corrective actions. Our comments and requests for further information regarding

corrective action are detailed below. The items correspond to the observations listed on the Form FDA 483:

Item 1

Your response fails to fully address alert and action limit specifications for the purified water and WFI systems. Please be advised that in addition to trending of low levels of microbial growth, including mold, all purified water and WFI water bioburden samples exhibiting results of 1-10 CFU/100mL should be thoroughly investigated. Please comment.

Item 2

Please further explain how the findings of your investigation indicate that the columns were most likely contaminated during system preparation and column commission wash procedures. Please note that the source(s) of the contamination should be identified if possible.

Item 4

We acknowledge your commitment to revise standard operating procedure (SOP) FR003 to clearly define responsibilities and the linkage to other deviation reporting systems. However, please note that your internal Alert Notices and Error or Accident Reports should not be closed until a decision on the disposition of affected lots is made and all corrective actions emanating from that decision are completed.

Item 6

Please note that potency assays are inherently variable. Therefore, additional tests should be validated as stability indicating and should be employed in the stability protocols.

Item 9

Your response is inadequate in that it states that adverse event reports are reviewed by the Medical Monitor who is responsible for determining if the adverse event meets the criteria for a 15 day report after which it is reported to the FDA within 15 days. Please be advised that each adverse experience that is both serious and unexpected shall be reported as soon as possible but in no case later than 15 calendar days of initial receipt of the information.

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 this office 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 promptly correct these deviations may result in regulatory action without further

notice. Such actions includes license suspension, revocation, and seizure. Your reply should be sent to the U.S. Food and Drug Administration, Center for Biologics Evaluation and Research, 1401 Rockville Pike, Suite 200 N, Rockville, Maryland 20852-1448.

If you have any questions regarding this letter, please contact Ms. Cathy Conn, Director, Division of Case Management, at (301) 827-6201.

Sincerely,

A handwritten signature in black ink, appearing to read "Deborah D. Ralston". The signature is fluid and cursive, with the first name being the most prominent.

Deborah D. Ralston

Director

Office of Regional Operations