



DEC - 8 1997

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

WARNING LETTER

CBER-98-009

CERTIFIED MAIL - RETURN RECEIPT REQUESTED

Dr. Rainer Pabst
Vice President of Industrial Operations
Centeon Pharma GmbH
Postfach 1230
D-35002 Marburg
Germany

Dear Dr. Pabst:

An inspection of Centeon Pharma GmbH, located at Emil-von-Behring Strasse 76, Marburg, Germany, was conducted from August 11 to 15, 1997. While we recognize that this facility has been closed since May 1997, for extensive renovations, the inspection focused on the manufacture of Antihemophilic Factor (Human) (Humate-P™) between January and May 1997. During the inspection, violations of Sections 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and Title 21, Code of Federal Regulations (21 CFR), Parts 211 and 600 were documented as follows:

1. Failure to report to the Director, Center for Biologics Evaluation and Research, important proposed changes in manufacturing methods as required by 21 CFR 601.12, in that the methodology for the hepatitis B surface antigen assay and the residual moisture assay was changed without notifying the agency.
2. Failure to establish and follow appropriate written procedures designed to prevent microbiological contamination of drug products purporting to be sterile and to assure that such procedures include validation of any sterilization process [21 CFR 211.113(b)] in that:
 - a. manual interventions performed by the filling operators during media fill operations are not routinely documented;
 - b. between January and May 1997, microbial monitoring results for the pasteurization water exceeded the action limit of 100 CFU/ml on a number of occasions, however, there was no identification of the contaminants recovered ;

- c. media fill bottles are not inverted so that all interior surfaces of the containers are exposed to the microbial growth medium;
 - d. there is no established procedure for periodic requalification of operators who perform media fills;
 - e. there are no posted gowning instructions in the gowning areas for the sterile filling suite.
3. Failure to maintain laboratory controls that include the establishment of scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that components, drug product containers, closures, in-process materials, labeling, and drug products conform to appropriate standards of identity, strength, quality, and purity [21 CFR 211.160(b)]. For example:
- a. prior to the current inspection, the dry heat ovens had not been revalidated since 1983, to demonstrate that the depyrogenation ovens can remove or reduce known levels of endotoxin;
 - b. prior to the current inspection, the steam sterilization validations for the lyophilizers did not include heat distribution studies to establish and confirm the coldest spot;
 - c. during validation of the sterilization cycles and equipment load patterns of the autoclaves in 1994 and 1996, only a single biological indicator was used;
 - d. there is no analysis performed to assure the required microbial concentration of the biological indicators;
 - e. the biological indicators are not stored in accordance with the manufacturers' requirements for temperature and relative humidity.
4. Failure to document each significant step in the manufacture, processing, packing, or holding of the batch [21 CFR 211.188(b)], in that the batch record for Humate P™ lot 012661 did not include documentation of the removal of [~] vials by the quality control unit. (b)(4)
5. Failure to document any test or examination performed on components, drug product containers, closures, and labeling [21 CFR 211.184(b)], in that the heat sensitive recording chart paper used to record the internal temperature of plasma during transit from [~~~~] to Germany was illegible.
6. Failure to maintain separate or defined areas or such other control systems for operations as necessary to prevent contamination or mixups [21 CFR 211.42(c)], in that:

- a. one of the non-viable particle monitoring probes in front of the lyophilizer is positioned such that when the lyophilizer doors are open the monitoring probe is obstructed;
 - b. the pressure differentials between classified areas [~~~~~] and non-classified areas are not monitored to ensure that acceptable levels of positive pressure relative to the surrounding areas are maintained;
 - c. there are no written procedures that describe actions to be taken by the security guards during an alarm condition concerning air pressure differentials or when there is a malfunction of the lyophilizers on weekends or when the facility is not otherwise staffed;
7. Failure to assure an adequate system for cleaning and disinfecting aseptic processing areas and equipment [21 CFR 211.42(c)(10)(iv) and (v)], in that:
- a. the cleaning solution used to disinfect stainless steel work surfaces is not sporicidal;
 - b. solutions used for cleaning aseptic manufacturing areas are not sterilized prior to use;
 - c. personnel monitoring of individuals working within the aseptic filling areas consists only of contact finger plates.
8. Failure to establish and follow written procedures for the receipt, identification, storage, handling, sampling, testing and approval or rejection of components and drug product containers and closures [21 CFR 211.80], in that:
- a. there are no established procedures for monitoring the expiration dates of raw materials to assure rotation so that the oldest approved stock is used first;
 - b. the quarantine sampling area [~~~~] has no ventilation or sampling hood to prevent contamination of the raw materials;
 - c. there are no established procedures for obtaining quality control samples of raw materials intended for identity testing.

(b)(4)

(b)(4)

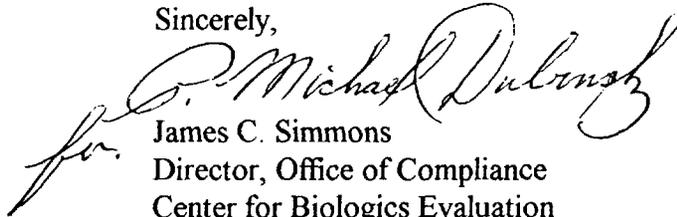
Neither this letter nor the list of inspectional observations is meant to be an all-inclusive list of deviations at your facility. It is your responsibility as management to ensure that your facility is in compliance with the provisions of the Federal Food, Drug, and Cosmetic Act and all applicable regulations and standards. 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.

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We acknowledge receipt of your response dated August 29, 1997, to the Form FDA 483 issued at the close of the inspection. The promised corrective actions appear to adequately address the observations. FDA's review of your response, however, has not yet been completed and your corrective actions may be addressed under separate cover by the agency. Your August 29, 1997 response may be referenced in your response to this letter. Please submit in writing, within 15 working days of receipt of this letter, your responses to the violations identified in this letter. Failure to promptly correct these deviations may result in regulatory action, such as seizure, injunction, license suspension and/or revocation, without further notice.

Your reply should be sent to the Food and Drug Administration, Center for Biologics Evaluation and Research, 1401 Rockville Pike, Suite 200N, Rockville, Maryland 20852-1448, Attention: Division of Case Management, HFM-610. If you have any questions regarding this letter, please contact Anita Richardson at (301) 827-6201.

Sincerely,

A handwritten signature in cursive script, appearing to read "G. Michael Dulongh". The signature is written in black ink and is positioned above the typed name and title.

for. James C. Simmons
Director, Office of Compliance
Center for Biologics Evaluation
and Research