



d19246

CBER-98- 021

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

WARNING LETTER

JUL 10 1998

CERTIFIED MAIL - RETURN RECEIPT REQUESTED

Martin R. Page
Senior Vice President
Worldwide Regulatory Affairs and Quality Assurance
Centocor, Inc.
200 Great Valley Parkway
Malvern, PA 19355-1307

Dear Mr. Page:

The Food and Drug Administration (hereinafter "FDA or "the agency") conducted a combined biennial and pre-license inspection of Centocor, B.V., located at Einsteinweg 101, P.O. Box 251, 2300 AG Leiden, The Netherlands, between April 20 and May 1, 1998. During the inspection, FDA investigators documented violations of Sections 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and numerous significant 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 (21 CFR). The deviations noted on the Form FDA 483, Inspectional Observations, issued at the conclusion of the inspection include, but are not limited to the following:

1. Failure to establish and follow appropriate written procedures designed to prevent objectionable microorganisms in drug products purporting to be sterile and to assure that such procedures include validation of any sterilization processes [21 CFR 211.113(b)] in that:
 - a. _____

 - b. During _____ chromatography purification of Abciximab, in-process product was observed dripping from a triclamp on the bottom of the holding tank;
 - c. The current gowning practices do not provide an effective method of segregation to prevent the possibility of cross contamination in that, there is _____ hallway in which personnel working in both critical and controlled areas have _____ access. Further, personnel who don additional gowning to work in certain Class

— areas are permitted to exit and re-enter into the Class — area without changing gowning attire;

- d. During sterile media fill operations, not all glass vials that are filled with growth media are incubated to detect microbiological growth. For example, vials with the incorrect volume of growth media, vials with incorrectly seated rubber stoppers, and vials with defective metal crimps are discarded;
- e. Sterile media fill vials are not incubated at an optimum temperature to promote mold growth, despite the identification of mold contaminants recovered from manufacturing areas during routine environmental monitoring;
- f. The Sterile Connecting Device used to join tubing in the manufacturing processes for — and Abciximab has not been validated to ensure sterility.

2. Failure to establish and/or follow control procedures to monitor the output and to validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product, and to test and approve, or reject in-process material at the commencement or completion of significant stages of the production process [21 CFR 211.110]. For example:

a. _____

b. Clarification of the fermentor harvest for — and Abciximab has not been adequately validated in that the effect on — cell fragmentation of operating the — micron filter at the maximum pressure limit of — PSI has not been established and documented;

c. _____

d. The flow rate across the — column, used in the purification process for Abciximab, was changed following replacement with a column of a different size and manufacturer, without validation.

3. Failure to establish and/or follow adequate written procedures for production and process control designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess and to assure that such procedures, including any changes, are drafted, reviewed, and approved by the appropriate

organizational units and reviewed and approved by quality control [21 CFR 211.100] in that:

- a. At least _____ lots of Abciximab intermediates were manufactured using one or more chromatography media that had exceeded the replacement criteria stated in standard operating procedure (SOP) 069S "_____". _____ of these lots of Abciximab intermediates were released and used to formulate final product Abciximab;
- b. SOP 032M, "_____" is inadequate in that, the storage conditions specified for the working cell banks are inconsistent with those described in the _____ SOP 032M calls for storage in a _____ freezer, whereas the BLA specifies storage at _____
- c. There is no written procedure for periodic review and evaluation of cumulative performance data collected for chromatography resins used in the manufacture of Abciximab and _____
- d. SOP 019G, "_____" was not followed in that, operators were observed leaning over the glass vials during media fill operations, which created a physical barrier obstructing the HEPA filter's unidirectional air flow over the opened vials. Additionally, contrary to the SOP, operators were observed performing work less than 20 cm from the boundary of the down flow LAF Hood;
- e. SOP 019G does not require documentation of all steps in manufacturing, including documentation that the metal tools used to make equipment adjustments or alignments in the aseptic filling area, are cleaned or decontaminated with _____ ethanol;
- f. There is no written procedure to describe the placement of thermocouples and biological indicators used during the _____ sterilization validation runs for the _____ and _____ autoclaves;
- g. SOP 021J, "_____" is inadequate in that it does not require review of environmental monitoring data when the identification of the microbial contaminants are listed as "pending". At the time of the inspection, approximately _____ isolates recovered from the Class _____ and Class _____ filling areas had not been identified and were therefore not included in the review;
- h. Growth promotion qualification of the media used for environmental monitoring does not include a challenge with mold isolates;
- i. There is no written policy or procedure for retention of records.

4. Failure to thoroughly investigate any unexplained discrepancy in drug product production and control records or the failure of a batch or any of its components to meet any of its specifications [21 CFR 211.192] in that, the early elution of Abciximab during a purification step was noted in the manufacture of _____ separate lots between December 1995, and December 1997. All lots were released, however, and a comprehensive evaluation of the recurring problem was not performed until January 1998. Further, the resulting corrective action plan has not been completed to date.
5. Failure to clean, maintain and sanitize equipment, utensils, and supplies at appropriate intervals to prevent malfunctions or contamination that would alter the safety, identity, strength, quality, or purity of the drug product, to establish or maintain written procedures for cleaning and maintenance of equipment, and to maintain records [21 CFR 211.67 and 600.12]. For example:
 - a. The agent used to disinfect the pre-culture incubators, _____, was not shown to be effective against the mold, _____ which was isolated most frequently from the incubators;
 - b. A dry crust of white material was observed around a valve gasket on _____ device in room _____,
 - c. There are no records that document which of the approximately _____ HEPA filters in the manufacturing areas has been patched;
 - d. The error messages printed by the autoclaves are not maintained as permanent records;
 - e. There is no record to document that the _____ biological indicators are stored at the recommended temperature and relative humidity required by the manufacturer.
6. Failure to test or examine representative samples of each lot of components, drug product containers, and closures [21 CFR 211.84] in that, appropriate tests for strength, quality and purity are not performed by the firm for some components used in the manufacture of _____ and Abciximab, including all chromatography resins and _____
7. Failure to maintain buildings used in the manufacture, processing, packing or holding of a drug product in a clean and sanitary condition and failure to establish written procedures describing the cleaning schedules, methods, equipment, and materials to be used in cleaning buildings and facilities [21 CFR 211.56(a) and (b) and 600.11(a)] in that,
 - a. Immediately over the crimping station there was a light fixture panel that contained dirt, dust, and a water stain on the interior surface;

- b. There is no written procedure to describe the yearly cleaning of the light fixtures in classified manufacturing areas.
8. Failure to exercise appropriate controls over and to routinely calibrate, inspect, or check for accuracy automatic, mechanical, or electronic equipment used in the manufacture, processing, packaging, and holding of a drug product according to a written program designed to assure performance [21 CFR 211.68] in that:
 - a. The maximum allowable number of thermocouplers that can fail during the steam sterilization validation runs has not been established;
 - b. The dry heat oven used to depyrogenate glass test tubes which are used for LAL testing to detect the presence of bacterial endotoxins has not been validated;
 - c. The temperature monitoring device on the ——— microbial identification system has not been calibrated to a reference standard to assure the accuracy of the incubation temperature.
9. Failure to establish laboratory controls that include 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, the Centocor specification for endotoxin of the culture media ingredient, —————, exceeds the maximum acceptance limit of the material supplier.

We acknowledge receipt of your written responses dated May 26, 1998, and June 11, 1998, which address the inspectional observations on the Form FDA 483 issued at the close of the inspection. We have reviewed the contents of your responses and we have a number of comments addressing the adequacy of your corrective actions. Our comments and requests for further information regarding corrective action and clarification are detailed below. The items correspond to the observations listed on the Form FDA 483:

FDA 483 item #1

In your response, you propose a comprehensive revalidation of the Abciximab purification process. This response is incomplete because it does not address: 1) the cause of the deviation, 2) steps that will be or have already been taken to remove chromatography media that have exceeded the established replacement criteria from routine production, and 3) the time frame for completion of the revalidation plan. Additionally, we advise that you submit the revalidation protocol and a complete report for inclusion in the Abciximab product license application (PLA).

FDA 483 item #2

Please indicate how frequently the routine trend analysis will be performed.

FDA 483 item #5

Please submit the process validation report _____ that is targeted for completion by mid July 1998.

FDA 483 item #6

According to SOP 012J, validation of the supplier's test results can be accomplished solely by _____. SOP 012J does not appear to specify that the _____ are repeated by Centocor or an external testing laboratory at any time. Please review SOP 012J and your entire vendor certification program to assure compliance with 21 CFR 211.84(d).

FDA 483 item #7.b.

Your response is inadequate in that it does not address the effect of the leak on the in-process product that was present in the tank (Abciximab concentrated and clarified _____ lot 28-0067), nor does it specify whether the equipment was removed from production and repaired. It is our view that the leak placed the material at risk for in-process contamination, as it provided a potential egress for adventitious agents.

FDA 483 item #9

Please indicate whether any additional controls have been instituted for monitoring in-transit frozen bulk material. Additionally, please state whether SOPs have been developed that include actions to be taken in the event of future temperature excursions during shipment of frozen bulk material.

FDA 483 item #10.a.

Please clarify the method used in your calculations for the data in _____. Your response indicates that the mean plus three standard deviations of the data is calculated as _____ however, our calculation yielded a mean plus three standard deviations to equal _____ (mean of _____ and standard deviation of _____).

FDA 483 item #13

Your response is inadequate in that it does not provide any method of segregation to prevent the possibility of cross contamination between "crude" and "refined" operations. While we acknowledge that a renovation and expansion of the Leiden facility is underway, you have not offered interim measures to prevent cross contamination.

FDA 483 items #16 and #18

You have stated that during the media fill process you will continue to remove vials with the incorrect volume, rubber stoppers that are incorrectly seated, or bad crimps, without evaluating those vials as part of the aseptic process. It is our view that this response is unacceptable. While the agency does not expect incubation of those media filled containers that have visible cracks, breakage, or loss of seal integrity, the FDA expects all media filled vials that are filled in a classified, aseptic production area that has been designed, qualified and appropriately validated to be incubated and evaluated as part of the aseptic process.

FDA 483 item #26

Your response is inadequate because the outline of your new SOP does not include validation using thermocouplers and biological indicators placed in loaded autoclaves to evaluate performance during a typical run. Additionally, an assessment of steam penetration inside the autoclaves should be made.

FDA 483 item #37.d.

You indicate that the maximum time period for the drained culture vessel to set prior to initiation of the cleaning procedure will be set at _____; however, the validation studies appear to have had a maximum time of _____. Please explain your rationale for setting the maximum time period for allowing the drained vessel to set prior to initiation of cleaning at _____. In addition, please submit your revised SOPs that relate to cleaning of the culture vessels.

FDA 483 item #38

Please submit to FDA the validation report # _____. Additionally, we request that you review your cleaning SOPs to ensure that the _____ contact time and concentration is greater than or equal to the validated contact time and concentration in the validation report.

FDA 483 item #46.b.

Your response is unclear in that you do not indicate whether other endotoxin-producing species of _____ have been incorporated into the alert criteria in QSM 050-620 and

SOP 02Q. Please provide clarification.

FDA 483 item #60

We acknowledge your decision to purchase qualified depyrogenated glass test tubes instead of depyrogenating test tubes in-house using a dry heat oven. Please be advised that validation of the dry heat oven would be required if, at some time in the future you decide to resume use of the equipment for sterilization or depyrogenation of process related materials.

FDA 483 item #95

You state in your response that _____

FDA 483 item #96

FDA 483 item #97

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.

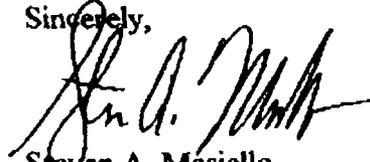
Please notify this office, in writing, within 15 working days of receipt of this letter of any steps

Page 9 - Martin R. Page

you have taken to correct the noted violations and to prevent their recurrence. If corrective action 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, such as seizure, injunction, license suspension and/or revocation, without further notice.

Your reply should be sent to me at 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.

Sincerely,



Steven A. Masiello
Acting Director
Office of Compliance and Biologics Quality
Center for Biologics Evaluation
and Research

cc: David P. Holveck
Chief Executive Officer
Centocor, Inc.
200 Great Valley Parkway
Malvern, PA 19355-1307

cc: John H. Parker, Ph.D.
Vice President, Corporate Quality Assurance
Centocor, Inc.
200 Great Valley Parkway
Malvern, PA 19355-1307

cc: Annie Rietveld
Director, Quality Assurance
Centocor, B.V.
Einsteinweg 101, P.O. Box 251
2300 AG Leiden, The Netherlands