



11/25/97

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CBER-98-006

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

WARNING LETTER

NOV 20 1997

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Howard R. Six, Ph.D.
Responsible Head
Connaught Laboratories, Inc.
Route 611
Swiftwater, Pennsylvania 18370

Dear Dr. Six :

An inspection of Connaught Laboratories, Inc., located at Route 611, Swiftwater, Pennsylvania, was conducted from September 29 through October 03, 1997. During the inspection, violations of Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act and Title 21, Code of Federal Regulations (21 CFR), Parts 211 and 600 were documented, as follows:

1. Failure to establish separate or defined areas or other control systems for manufacturing and processing operations to prevent contamination or mixups [21 CFR 211.42(c)(10); 211.63; and 600.11] in that:

(b)(4)

a. the physical barriers between the areas of the room determined to be [] and [] do not adequately protect the [] aseptic filling area. For example,

- i. the bottom edge of the plastic curtains in filling line [] is approximately four feet above the horizontal plane of the filling line.
- ii. open, sterile, empty vials on the loading table in filling line [] are approximately one foot inside the vertical plane of the curtained [] the bottom edge of the plastic curtain appears to be four feet above the open, sterile, empty vials.
- iii. syringe filling and capping operations occur in filling line [] trays with filled syringe barrels are placed about four inches from the edge of the capping-side of the table which is approximately on the same vertical plane as the periphery of the HEPA filters above and there is no primary barrier extending below the HEPA filters.

(b)(4)

b. during the tray loading of the lyophilizer in room [] the lyophilizer door extends

(b)(4)

outside the curtained [wavy] area.

2. Failure to establish 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 "static" media fills are not representative of routine aseptic operations manipulations and activities such as the frequency of manual stoppering, break periods, and emptying of stopper bags; the duration of the simulated run; weight check line stoppage; and the loading of trays to the lyophilizer.
3. Failure to thoroughly review any complaint involving the possible failure of a drug product to meet any of its specifications and determine the need for an investigation [21 CFR 211.198 and 211.192] in that:
 - a. approximately 23% of the complaints received from September 1996 to the close of the inspection involved the presence of particulates that were determined to be isolated incidents and required no further action.
 - b. there is no assurance that product complaints are thoroughly investigated since evaluation of retention samples; review of other batches of the same drug product and other drug products that may have been associated with the specific failure; and review of drug product production and control records such as environmental monitoring is not always done.
4. Failure to have adequate acceptance criteria for sampling and testing to assure that batches of drug products meet each appropriate specification and appropriate statistical quality control criteria as a condition for their approval and release in that the statistical quality control criteria do not include appropriate acceptance levels and/or appropriate rejection levels [21 CFR 211.165(d)] as follows:
 - a. there is no specified action level or limit for the filled product container visual inspection performed by the Filling Department.
 - b. the visual inspection action limits (2-10%) specified for the Quality Assurance Inspection audit exceeds the Filling Department inspection criteria (all units with visible particulate are to be discarded) and three inspections must fail before an incident investigation is initiated.
5. Failure to establish written 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 [21 CFR 211.110(a)] in that there is no procedure for the periodic validation of the aseptic bulking/pooling process for Fluzone®.

6. Failure to clean, maintain, and sanitize equipment and utensils to prevent malfunction or contamination that would alter the safety, identity, strength, quality, or purity of the drug product [21 CFR 211.67(a) and 600.11(b)] in that:
 - a. the air vent filters used on the WFI storage tanks in building [] are not integrity tested when replaced. (b)(4)
 - b. the effectiveness of the cleaning method used during the cleaning of the ultra filtration units used in the purification of Tetanus and Diphtheria Toxoids has not been established.
7. Failure to have appropriate written standards or specifications, methods of testing, and, where indicated, methods of cleaning, sterilizing, and processing to remove pyrogenic properties from drug product containers and closures [21 CFR 211.122(a)] in that there is no assurance that the scoop, stock pot, and rotating drum used during the preparation, depyrogenation, and sterilization of final container stoppers are pyrogen and particulate free.
8. Failure to maintain or follow written procedures to protect clean equipment from contamination prior to use [21 CFR 211.67(b)(5)] in that non-hermetically sealed boxes of depyrogenated glass vials are placed in a [] holding area for cooling.
9. Failure to establish and/or follow 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 the quality control unit [21 CFR 211.100] in that the in use written procedure entitled [] [] specifies a [] dilution of pooled bulk product before filling; the approved procedure specifies no dilution of pooled bulk product before filling. (b)(4)
10. Failure to have an adequate written stability testing program including test intervals based on statistical criteria for each attribute examined to assure valid estimates of stability [21 CFR 211.166(a)(1)] in that products with well established shelf life and stability histories are tested only at release and six month after expiration date.
11. Failure to have the appropriate quantity of reserve samples necessary to perform the required tests and to examine the reserve samples visually at least once a year for evidence of deterioration [21 CFR 211.170].
12. Failure to have a procedure designed to evaluate any production, control, or distribution record at least annually to determine the need for changes in drug product specifications or manufacturing or control procedures [21 CFR 211.180(e)].

We acknowledge receipt of your October 24, 1997, written response which addresses the inspectional observations on the Form FDA 483 issued at the close of the inspection. 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 evaluation of your response follows, and is numbered to correspond to the observations listed on the Form FDA 483:

1a-e The plan to conduct air flow pattern studies during static and dynamic periods does not fully address the absence of an appropriate physical barrier between [redacted] and [redacted] zones. Since vertical air flow offers little or no resistance to cross-stream migration, the absence of an appropriate physical barrier allows the opportunity for cross-stream migration into the [redacted] zone. (b)(4)

1f Your response states that "...suitable modifications will be made to allow the lyophilizer door to fully swing under [redacted] conditions." Please provide a description of the modifications.

3 & 6 The proposed holding area modifications and the proposed depyrogenation procedure and validation process for the siliconization bowl will be evaluated when the appropriate documentation is provided.

8a-f The proposed doubling of rate of interventions during a [redacted] units media fill is not representative of worst case number of activities associated with a routine manufacturing [redacted] units lot. Please comment.

(b)(4)

9b The accuracy of aseptic media fill volumes is not critical and is not a factor associated with the objectives of conducting aseptic media fills. The intervention into the aseptic process that is carried out in order to acquire the units used for weight checks must still be simulated a "worst case" number of times during the aseptic media fill. It is not necessary to perform the destructive weight check on media fill units.

12 The change to a final stability test from six months post expiration to stability testing at expiration does not assure that the licensed products maintain proper activity for the duration of its approved shelf life.

17 The proposed annual record review procedure will be evaluated when the appropriate written procedure is provided.

18 The procedure for monitoring the cleaning proficiency will be evaluated when the appropriate written cleaning procedure and monitoring data is provided.

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The above identified deviations are not intended to be an all inclusive list of deficiencies at your facility. 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 awards of contracts. It is your responsibility to exercise control of the establishment in all matters relating to compliance with all pertinent regulations.

Please notify this office, in writing, within 15 working days of receipt of this letter of any additional steps 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 without further notice. These actions include license suspension and/or revocation, and seizure.

Your reply should be sent to the Food and Drug Administration, Center for Biologics Evaluation and Research, Office of Compliance, 1401 Rockville Pike, Suite 200 N, Rockville, Maryland, 20852-1448, Attention: Division of Case Management.

Sincerely,


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