



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

578

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

AUG 28 1997

WARNING LETTER**CERTIFIED MAIL**
RETURN RECEIPT REQUESTED

Irene Clement
Responsible Head
Connaught Laboratories Limited
1755 Steeles Avenue, West
North York, Ontario
Canada M2R 3T4

Dear Ms. Clement:

During an inspection of your facility located at 1755 Steeles Avenue, West, North York, Ontario, Canada M2R 3T4, from April 21 to May 2, 1997, our investigators identified the following violations of Section 501 (a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), and Title 21, Code of Federal Regulations (21 CFR), Part 211:

1. Failure of the quality control unit to maintain a written record of investigations including conclusions and follow up of any unexplained discrepancy or failure of a batch or its components to meet any of its specifications [21 CFR 211.192] in that there is no evidence that microbial load evaluation (MLE) results from [REDACTED], which exceed established limits on October 2, 1996, October 9, 1996, and November 19, 1996 (Original Sample), have been investigated. The building [REDACTED] MLE Summary report, the memorandum dated August 30, 1996, regarding the MLE failure from building [REDACTED] and the memorandum dated December 19, 1996, concerning test deviation report [REDACTED] do not address whether these samples were part of the investigation or why test deviation reports were not initiated.
2. Failure of the quality control unit to review production records to assure that no errors have occurred, or if errors have occurred, that they have been fully investigated [21 CFR 211.22(a)]. For example:
 - a. There is no evidence that corrective action for environmental excursions listed on Environmental Incident Notification/Response Form [REDACTED] and [REDACTED]

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have been completed or that the actions have been effective or appropriate. In addition, the forms have not been signed or dated by production personnel or Quality Assurance (QA).

- b. The section of the Water System Incident Notification/Response Form detailing actions taken and corrective measures to prevent recurrence has not been completed. In addition, the forms have not been signed or dated by production personnel or Quality Assurance. The incident report was generated to address missed MLE samples in
3. Failure to maintain equipment for adequate control over air pressure, microorganisms, humidity, and temperature as necessary for the manufacture, processing, packing, or holding of a drug product [21 CFR 211.46(b)] in that the limits established for humidity and temperature in for bacterial vaccines have been exceeded for every lot manufactured from January to April 1997.
4. Failure to assure an adequate system for cleaning and disinfecting aseptic processing areas and equipment [21 CFR 211.42 (c)(10)(v)] in that the effectiveness of the cleaning procedures and the disinfectant(s) used in the Tetanus Production Ultrafiltration area, was not been established.
5. Failure to destroy obsolete and outdated labels, labeling, and other packaging materials [21CFR 211.122(e)] in that cartons of obsolete product inserts for were stored in the warehouse area designated for released material. Inventory records did not indicate that the labeling was obsolete, and the cartons were labeled with a Quality Control (QC) release label.
6. Failure to establish or maintain written procedures for cleaning and maintenance of equipment [21CFR 211.67(b)] in that there is no written procedure describing routine monitoring of clean steam.
7. Failure to maintain separate or defined areas or such other control systems for operations as necessary to prevent contamination or mixups, and maintain equipment for adequate control over air pressure, microorganisms, humidity, and temperature as necessary for the manufacture, processing, packing, or holding of a drug product [21CFR 211.42(c) and 211.46(b)] in that the air pressure differential between rooms does not meet established specifications.
8. Failure to establish and/or follow written procedures for production and process controls designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess [21CFR 211.100]. For example:

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- a. The standard operating procedures (SOP) entitled "SOP For GMP Training Program" was not followed in that two employees in the manufacturing area have not received Good Manufacturing Practice updates within the past 2 years.
 - b. The SOP entitled "Routine Sampling Procedure For Water For Injection (WFI) Systems" does not address the finding of mold in water samples collected.
 - c. There is no written procedure to describe the receipt of incoming environmental samples including verification of samples received with the collection record, method to resolve discrepancies, or explanation of how samples are handled and stored.
 - d. There is no written procedure to describe the control and acceptance of sterility test media.
 - e. There is no SOP to describe the reporting procedure for sterility test failures.
 - f. There is no procedure to describe (1) how samples are traced through harvesting and extraction to final Gas Chromatography (GC) identification and (2) recording of information in logs books such as the harvesting record, GC log book, and Post GC Run log book.
9. Failure to document that each significant step in the manufacture, processing, packing, or holding of the batch was accomplished [21CFR 211.188(b)]. For example:
- a. There was no signature or date on the [REDACTED] which had a substitution of a filter housing T-1 for a disposable filter.
 - b. There was only one signature for tank [REDACTED] weighing record for the [REDACTED] Attachment 2 [REDACTED]
10. Failure to assure that the equipment used in the manufacture, processing, packing, or holding of a drug product is of appropriate design [21CFR 211.63] in that the effectiveness of the [REDACTED], which is used for measuring physical specifications for glass vials and ampules, has not been established. In addition, there is no evidence that installation qualification has been performed for the Projector.
11. Failure to exercise appropriate controls over computer or related systems to assure that changes in master production and control records or other records are instituted only by

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authorized personnel [21 CFR 211.68(b)] in that there are no procedures for control of the software including procedures to control inappropriate or incorrect changes to the specifications for the '

12. Failure to maintain written procedures for cleaning and maintenance of equipment including the protection of clean equipment from contamination prior to use [21CFR 211.67 (b)(5)] in that Purified Protein Derivative [REDACTED], which had been returned from the filling area for cleaning, was placed in an area with clean tanks. There was no indication that the status of this tank was different from other tanks that were cleaned and ready for re-use.
13. Failure to store components, drug product containers, and closures under quarantine until they have been tested or examined, as appropriate, and released [21CFR 211.82(b)] in that pre-shipment samples of various media were not precluded from use in production before appropriate testing was completed. Neither the box of media samples nor the bottles inside the box were labeled to indicate that the contents were not to be used in production. The box, marked "Media Powder Samples," was stored in room [REDACTED] a cold storage area for chemicals in [REDACTED].
14. 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 there was no number or other identification on the water for injection point of use in [REDACTED] (ampule wash area).

We acknowledge receipt of your May 23, 1997, written response which addresses the inspectional observations on the FDA Form-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. The following represent our comments regarding your response.

FDA 483 item # 3b

Your response indicates that a test deviation report was not generated as a result of an MLE due to the presence of mold because SOP #IES-007 entitled "[REDACTED]" does not require a test deviation report for MLE samples containing mold. Mold in water samples is uncommon and may indicate a serious problem. We recommend that the SOP be revised to address mold detected in water samples.

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

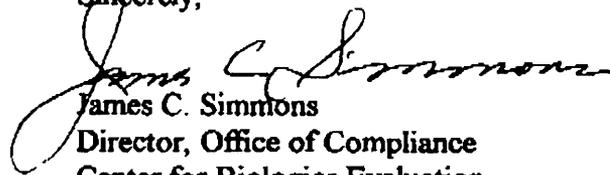
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You should take prompt action to correct these deviations. Failure to promptly correct these deviations may result in regulatory action without further notice. Such action includes seizure and/or injunction, license suspension and/or revocation.

You should notify this office in writing, within 15 working days of receipt of this letter, of specific steps you have taken or will take to correct or prevent these deviations. 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.

Your reply should be sent to the following address: U.S. Food and Drug Administration; Center for Biologics Evaluation and Research; HFM-600; 1401 Rockville Pike, Suite 200N; Rockville, MD 20852-1448.

Sincerely,


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