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CBER-99- 002

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

WARNING LETTER

OCT 6 1999

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Larry Thieme
Vice President, World Wide Quality Assurance
Allergan, Inc.
2525 Dupont Drive
P.O. Box 19534
Irvine, CA 92713-9534
U.S. License Number 1145

Dear Mr. Thieme:

The Food and Drug Administration (hereinafter FDA or the agency) conducted an inspection of Allergan Botox Limited, located at Castlebar Road, Westport, County Mayo, Ireland, between July 13 and July 17, 1998. 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 (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 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)(3)] in that the sample size for endotoxin testing of BOTOX ® consists of _____ from a lot size of approximately _____ the sample size has not been demonstrated to be representative of the lot size.
2. 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, not all corrective actions that were developed in response to environmental excursions in

filling room — during filling on March 9, 1998, were implemented in that the same organisms (_____) were isolated in the aseptic core and in the sterility test suite from May through July 1998.

3. Failure to establish and/or follow appropriate written procedures designed to prevent microbial contamination of drug products purported to be sterile [21 CFR 211.113(b)] in that:
 - a. The media fill protocol #RVB811 does not provide specific instructions for performance of media fill interventions nor does it provide instructions for remedial actions in the event of a failure;
 - b. The media fill protocol #RVB811 allows for invalidation of media filled vials post incubation if vials are cracked or incorrectly stoppered without inspection of the vials prior to incubation;
 - c. Water for Injection (WFI) is not sampled in the same manner as it is used in production;
 - d. There are no written procedures for qualification and requalification of personnel working in the aseptic core.
4. Failure to establish an adequate system for cleaning and disinfecting the room and equipment to produce aseptic conditions [21 CFR 211.42(c)(10)(v) and 600.11(b)] in that non-sterilizable equipment and work surfaces in the aseptic core are sanitized with _____ which was shown by Allergan Botox Limited's data to be ineffective against spore forming organisms.
5. Failure to establish an adequate system for maintaining equipment used to control the aseptic process [21 CFR 211.42(c) (10)(vi) and 600.11(b)] in that there is no cleaning/sanitization validation for the non sterilizable vibratory bowl (stopper hopper) in the aseptic filling suite. In addition, the vibratory bowl is not included in the routine environmental monitoring program.
6. Failure to establish appropriate laboratory testing to determine satisfactory conformance to final specifications for each batch of drug product, including identity and strength of each active ingredient prior to release [21 CFR 211.165] in that:
 - a. Standard Operating Procedure (SOP) BV1019, entitled "Visual Inspection of BOTOX Product", does not specify limits for critical, major and minor defects which, when exceeded, would trigger an investigation, and does not instruct operators to place rejected vials in the specific bins;

- b. Analysis Procedure - In House 12IR, entitled "Bacterial Endotoxin Testing (—)", does not provide sufficient detail regarding retesting and does not provide for an investigation in the event that the retest produces results that conflict with the initial test;
 - c. Analysis Procedure - Contract Laboratory 12IR, entitled "Potency Test", does not contain a specification for an acceptable retest on out-of-specification results for stability sample retests for potency.
7. Failure to store labels and other labeling materials for each drug product separately with suitable identification and in a storage area limited to authorized personnel [21 CFR 122(d)] in that package inserts for BOTOX ® are stored in a manner which does not preclude unauthorized access.
 8. Failure to visually examine at least once a year sample lots or batches selected by acceptable statistical procedures for evidence of deterioration [21 CFR 211.170(b)] in that SOP BV4070, entitled "Control of Batch Retains", does not provide for an annual visual examination of retain samples and recording of the results.
 9. 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].
For example:
 - a. SOP BV3033, entitled "Preparation and Control of Disinfecting Solutions", was not followed in that the disinfecting solutions were prepared by indications in the disinfecting log book rather than according to the manufacturers instructions;
 - b. SOP BV4068, entitled "Environmental Monitoring of Personnel in the Allergan BOTOX Plant", is inadequate in that it does not provide for corrective action unless consecutive out-of -specification results are obtained.

We acknowledge receipt of your August 25, 1998, written response which addresses 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

According to SOP BV1030 entitled "Transfer of Equipment/Components to Botox Core Via Transfer Room — Section 4.6, all other objects and equipment should be sanitized using (—) when practical and possible to do so. As the presence of spore formers was attributed to

items being brought in for environmental monitoring purposes from the laboratories, it is our view that the wording in the SOP should be more definitive, i.e., items will be wiped down with _____ . In addition, your response does not address the additional spore former isolated in the aseptic core on June 26, 1998, and the numerous problems with spore formers in the sterility test suite which resulted in sterility test problems.

FDA 483 item #2

The SOP BV4172 entitled "Qualification of Personnel to Work in Aseptic Filling at the Allergan Botox", appears adequate for qualification, however, it does not address the requirement for requalification in that aseptic filling personnel participate in at least _____ .

FDA 483 item #4

Your response is inadequate in that it is unclear where, physically, the bowl will be monitored as part of the routine monitoring program or where it was monitored during the initial qualification. In addition, formal cleaning validation studies should be performed and routine monitoring of possible worst case sites detected during such studies should be instituted. Please be advised that media fills are not a substitute for validation of sanitization and/or sterilization of filling equipment.

FDA 483 item #7

We acknowledge your commitment to further restrict access to the package inserts by placing a physical barrier around the area where the inserts are stored. Please provide a description of the physical barrier in place.

FDA 483 item #10

Your response states Allergan has removed from SOP BV4106 the requirement to perform _____ testing. However, since the SOP pertains to other products, please comment on whether your decision for removing the osmolality testing requirement encompassed these other products.

FDA 483 item #11a

The Analysis Procedure - In House 12IR, entitled "Bacterial Endotoxin Testing (_____)", appears adequate for retesting, however, it does not address the requirement for an investigation prior to retesting.

FDA 483 item #15

We acknowledge your commitment to validating the _____ expiry for the _____ .

Neither this letter nor the list of inspectional observations is meant to be an all-inclusive list of deficiencies at your facility. It is your responsibility to assure that your facility is in compliance with all the provisions of the FD&C 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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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 include seizure, injunction, license suspension, and/or revocation.

Your reply should be sent to the Food and Drug Administration, Center for Biologics Evaluation and Research, 1401 Rockville Pike, Suite 200 N, Rockville, Maryland 20852-1448, Attention: Division of Case Management, HFM-610.

Sincerely,



Elaine Knowles Cole
Acting Director
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research

cc: Victor Wilkie
Director of Operations
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