Inspections, Compliance, Enforcement, and Criminal Investigations

Allergy Laboratories, Inc. 10/4/13

Department of Health and Human Services

Public Health Service
Food and Drug Administration
Office of Regulatory Affairs
12420 Parklawn Drive
ELEM-2152
Rockville, MD 20857
Telephone: (301) 796-2720
FAX: (301) 827-4090

SEP 04, 2013

WARNING LETTER

OOWL-13-01

UPS EXPRESS MAIL

Rebecca (nmi) Johnson
President
Allergy Laboratories, Inc.
1005 SW 2nd Street
Oklahoma City, OK 73109

Dear Ms. Johnson:

The Food and Drug Administration (FDA) conducted an inspection of Allergy Laboratories, Inc., located at 1005 SW 2nd Street, Oklahoma City, Oklahoma, between April 16 and April 26, 2013. During the inspection, FDA investigators documented deviations from current good manufacturing practice (CGMP) requirements in the manufacture of your licensed biological drug products and intermediates and your pharmaceutical drug products. Deviations from CGMP include the applicable requirements of Section 501 (a)(2)(B) of the Federal Food, Drug and Cosmetic Act (FD&C Act), the requirements of your biologics license application approved under Section 351 of the Public Health Service Act (PHS Act), and Title 21, Code of Federal Regulations (21 CFR) Parts 210, 211, and 600. At the close of the inspection, FDA issued a Form FDA 483, Inspectional Observations, which described a number of significant objectionable conditions relating to your firm's compliance with CGMP. Significant deviations observed during the inspection include, but were not limited to, the following:

CGMP DEFICIENCIES CONCERNING DRUG PRODUCTS

1. 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:

a. Your Standard Operation Procedure (SOP) QC-026.00 entitled "**(b)(4)**" states that positive test results must be fully evaluated. Since 11/5/12, your firm has experienced sterility failures for **(b)(4)** product lots. Of those **(b)(4)** lots, only five were subject to an investigation. These investigations were incomplete and inadequate in that:

i. Test equipment was not adequately evaluated due to the lack of documentation to demonstrate that the equipment was prepared and autoclaved appropriately.

ii. Environmental monitoring (EM) samples taken from manufacturing and sterility test operators were found to be positive during the time of the sterility failures, however, the isolates were not sent out for identification.

Additionally, all **(b)(4)** lots have since been retested and released.

b. PAC-021-081312 was opened on 8/10/12 due to the out of tolerance temperature recorder of the **(b)(4)** Oven. The recorder was found to be displaying readings 25°C higher than the referenced temperature which resulted in vial depyrogenation below **(b)(4)**. Your Standard Operation Procedure (SOP) 3020.08 entitled "**(b)(4)**" requires that the oven cycle run for **(b)(4)** hours at a minimum of **(b)(4)**. The investigation determined that the reading errors were due to a bent chart pen and corrective actions included chart pen repair and probe recalibration. Approximately **(b)(4)** lots of aseptically filled drug products were manufactured using the vials processed in this oven and were released for distribution. You conducted a product assessment; however, it only included products manufactured from July 2010 to July 2012. Your assessment should have included products manufactured from July 2009 to July 2012, which represents the time frame between the last two calibration dates of the temperature recorder.

c. Your SOP QC-053.00 entitled "**(b)(4)**" requires that investigations of environmental alert and action level excursions include assurances that an investigation and corrective and preventive actions are completed. However, environmental notices show no evidence of an investigation being conducted and fail to address or document corrective and preventive action. Examples include, but are not limited to:

i. EN# 027-012513, initiated on 1/25/13, documents an active air excursion during the filling of **(b)(4)** Lot# **(b)(4)**. Review of the document revealed an organism was identified but no evidence that the source of the contamination was investigated. The document also noted that a corrective action was required but there was no documentation as to what corrective action was implemented. In addition, preventive actions were not addressed.

ii. EN# 020-011713, initiated on 1/17/13, documents an active air excursion during the manufacture of sterile empty vials (SEV) Lot# **(b)(4)**. All lots passed sterility testing and an organism was identified but there is no evidence that the source of the contamination was investigated, preventative actions were not addressed, and no documentation which identifies or shows implementation of the noted required corrective action.

iii. EN# 018-011713 documents an excursion on an operator's right finger which occurred on Fill Line **(b)(4)** during the production of **(b)(4)** Lot # **(b)(4)**. The organism was identified, but there was no documentation of a corrective or preventive action despite additional excursions noted on the same day in both the gowning and de-gowning rooms, as well as evidence of excursions inside the vial production area.

d. EN# 004-010813, initiated on 1/8/13, documents an out of limit Class 100 surface sample of the Stopper Bowl after filling of SEV Lot# **(b)(4)** on Filling Line **(b)(4)**. The investigation lacked a root cause analysis and failed to evaluate the linkage of two other environmental monitoring excursions, one of which documented an organism from the same family on the floor near the capping machine on Filling Line **(b)(4)** on the same day.

e. EN# 010-011113, initiated on 1/11/13 for an action limit within Filling Line **(b)(4)**, which is a Class 100 area from the stopper bowl after filling of SEV Lot# **(b)(4)**. A video review revealed that the operator opened the RODAC plate early and looked down into the bowl upon sampling. Based on the review, the root cause was deemed to be sampling error. Your firm failed to evaluate the linkage of this incident to additional personnel monitoring results and additional surface monitoring samples working in the class 100 area during manufacturing of this lot. Additionally, no corrective or preventive actions were identified.

f. Environmental monitoring records revealed at least one excursion occurred during manual vial loading in ten of ten records reviewed for aseptically filled drug products

and/or Sterile Empty Vials (SEVs). No actions have been taken to address this non-viable particulate monitoring excursion and all but one of the affected lots have been released.

g. PAC-013-071712 was initiated on 10/31/12 to investigate excursion level particulate counts related to allergenic extract sterilization in the **(b)(4)**. The non-viable particulate excursions were not adequately investigated. Your firm failed to document the review of critical operations; preventive actions have not been initiated; and no due date for completion was established.

2. Failure to establish and follow appropriate written procedures designed to prevent microbiological contamination of drug products purporting to be sterile, including validation of all aseptic processes [21 CFR 211 .113(b)] as follows:

a. You failed to follow your environmental monitoring procedures. For example:

i. Your SOP QC-006.00 entitled "**(b)(4)**" requires that active viable air monitoring in the Class 100 Fill Suite of the Building **(b)(4)** Vial Production Areas and the **(b)(4)** Vial Filling Room **(b)(4)** near the filling machine during Sterile Empty Vial (SEV) production, at the area **(b)(4)** the filling machine during the aseptic connections set-up for liquid-filled vials, and **(b)(4)** other locations, respectively. Additionally, the SOP states that sampling is required in the Allergenic Extract Production Areas at **(b)(4)** different locations at **(b)(4)** during filling operations. However, actual monitoring is only **(b)(4)** location on Filling **(b)(4)** and Filling **(b)(4)**, as well as in the Allergenic Extract Areas.

ii. Your SOP QC-4005.16 entitled "**(b)(4)**" requires sampling to occur on Filling line **(b)(4)** and **(b)(4)** at **(b)(4)** sites at the conclusion of sterile filling or at other designated locations daily. However, only **(b)(4)** critical surfaces are monitored on equipment after filling operations.

iii. Your SOP QC-024.00 entitled "**(b)(4)**" states that operators must clean their garments after personnel monitoring and that no objects should be touched within the Class 100 area while agar is present on their gloved hands from the sampling. However, operators were observed handling items within the Class 100 area without cleaning their hands or removing their outer glove, as well as failing to clean their garments prior to leaving the area.

b. There is no established SOP for the detection and counting of microorganisms on RODAC nutrient agar plates for environmental and personnel monitoring.

c. Your Validation Report VP-023.01 entitled "**(b)(4)**" does not adequately document that the sterilizing filters used for aseptically manufactured allergenic extracts and diluents were adequately validated. Validation of microbial retention was not performed with actual product and there is no documentation supporting validation without use of the actual product. In addition, critical parameters such as filtration pressure and flow rate were not documented during microbial retention and extract filters tested failed the bubble point specification but were reported passing.

d. Operators were observed touching empty vials with unsterilized forceps, holding hands over open empty vials, and performing filling activities with exposed areas of the face.

e. Monitoring is not conducted on sterilized stoppers stored in open bags near a depyrogenation oven nor on goggles used in the allergenic extract areas which are not sterilized prior to use.

f. Depyrogenated vials contained in **(b)(4)** covered trays are stored in a Class 10,000 room for up to two weeks. Inspection of **(b)(4)** integrity is not performed prior to filling and nor are the trays monitored after use.

3. Failure to routinely calibrate, inspect, or check automatic, mechanical, or electronic equipment according to a written program designed to assure proper performance [21 CFR 211.68(a)]. For example:

a. A guide rail was observed to be held to a **(b)(4)** Labeler by rubber bands. In

addition, this line also possessed a cardboard and foam vial tub.

b. Leaking was observed from the 2/6 filling pistons on the **(b)(4)** during aseptic filling.

4. Failure to assure that drug product containers or closures are not reactive and additive so as to alter the safety, identity, strength, quality, and purity of the drug beyond the official or established requirements [21 CFR 211.94 and 600.11 (h)]. Specifically, leachable and extractable studies have not been conducted on **(b)(4)** and **(b)(4)** stoppers used with allergenic extract final products.

5. Failure to document each significant step in the manufacture, processing, packing, or holding of the batch in the batch production and control records [21 CFR 211.188(b)]. In particular, filter pressure and flow rate are not documented in batch records, nor have limits been established or specified in SOPs for **(b)(4)** injections during sterile filtration. Additionally, sterile filtration pressure is not documented in allergenic extract batch records.

REVIEW OF YOUR INSPECTIONAL RESPONSE

We acknowledge receipt of your written response dated May 17, 2013, which addresses the inspectional observations on the Form FDA 483 issued at the close of the inspection of your firm. Corrective actions addressed in your letter may be referenced in your response to the Warning Letter. We have reviewed your response and have the following comments. Please be reminded that these comments are not all inclusive. The items are numbered to correspond to the observations listed on the Form FDA 483.

Form FDA 483 Observation 11

Your response indicated that your firm will discontinue the use of sterility testing vials for the preparation of allergenic extract treatments sets, refills, and custom extracts, but lacked a description of the new sterility testing method for these products. Please provide documentation demonstrating and supporting this new practice.

Form FDA 483 Observation 13

Your response states that your firm will conduct a review of retention sample records to evaluate cloudiness trending of allergenic extracts and then set appearance release specifications. We agree with your assessment that a review is necessary; however release specification changes should be submitted as a prior approval supplement for CBER approval prior to implementation.

Form FDA 483 Observation 16

Your response identified that a time limit of **(b)(4)** will be established for ambient temperature exposure of the allergenic extracts during filling, inspection, labeling, and packaging. However, this is an arbitrary date which is inconsistent with the 10 days used for the stability study conducted by your firm and described in your response. Please provide the documentation which justifies the **(b)(4)** ambient temperature time limit.

Form FDA 483 Observation 22

We acknowledge your commitment to revise your practice and perform 100% visual inspectiorn of terminally sterilized products filled on Line **(b)(4)** after the vials have been sterilized. Further, we acknowledge that a review of the vial inspection process will need to be performed to identify critical steps in the vial inspection process which may require a process change. Discussions with your client may be necessary. A due date was not provided at the time of submission of your response as you needed to consult with your client. Please provide an update as to where you are in the process, to include whether you have consulted with your client and if so when, and a status as to your completed and/or proposed corrective actions.

The deficiencies described in the Form FDA 483 issued at the close of each inspection referenced above and this letter are an indication of your quality control units not fulfilling their responsibility to assure the identity, strength, quality, and purity of your licensed biological drug products and intermediates. These serious deficiencies from the applicable regulations and standards described above, when viewed collectively, represent the extensive failure of your firm to maintain control over the manufacturing process, including 1) release of product, 2) monitoring of the process, 3) appropriate response to a failure in the process, and 4) process controls. These critical aspects of the operation are objectionable and accordingly, the Agency lacks confidence in your firm's ability to manufacture pure, potent, safe and effective products.

FDA expects Allergy Laboratories, Inc., to undertake a comprehensive assessment of all of its manufacturing operations to ensure that all products conform to FDA requirements. Please describe in detail how Allergy Laboratories, Inc. will attain CGMP compliance with regard to the above observations. Please include in that description how you will use all relevant information to conduct thorough investigations to ensure that adequate steps are taken to evaluate whether deviations impact product and to implement effective corrective and preventive actions.

Neither this letter, nor the observations listed on the Form FDA 483 presented at the conclusion of the inspection, are intended to be an all-inclusive list of deviations that may exist at your facilities. We remind you that it is the responsibility of Allergy Laboratories, Inc. to ensure that your establishment is incompliance with the provisions of the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, all applicable federal laws and regulations, and the standards in your license. Federal agencies are advised of the issuance of all Warning Letters about biological and pharmaceutical products so that they may take this information into account when considering the award of contracts.

If, as a result of receiving this warning letter or for other reasons, you are considering a decision that could reduce the number of finished drug products or active pharmaceutical ingredients produced by your manufacturing facility, FDA requests that you contect COER's Drug Shortages Program immediately, as you begin your internal discussions, at drugshortages@fda.hhs.gov so that we can work with you on the most effective way to bring your operations into compliance with the law. Contacting the Drug Shortages Program also allows you to meet any obligations you may have to report discontinuances in the manufacture of your drug under 21 U.S.C. 356C(a)(1), and allows FDA to consider, as soon as possible, what actions, if any, may be needed to avoid shortages and protect the health of patients who depend on your products. [In appropriate cases, you may be able to take corrective action without interrupting supply, or to shorten any interruption, thereby avoiding or limiting drug shortages.]

Please notify this office in writing, within 15 working days of receipt of this letter, of any additional steps you have taken or will take to correct the noted violations and to prevent their recurrence. Include any documentation necessary to show that corrective action has been achieved. 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 action may include license suspension and/or revocation, seizure or injunction.

Any questions regarding this letter you may call Julie D. Bringger, Compliance officer at 904-281-1924 extension 104. Your reply should also be sent to Mrs. Bringger at the following address: U.S. Food and Drug Administration, 6800 Southpoint Parkway, Suite 100, Jacksonville, FL, 32216.

Sincerely,
/S/
Alonza Cruse, Acting Director
Office of Medical Products and Tobacco
Operations

Page Last Updated: 12/03/2013
Note: If you need help accessing information in different file formats, see Instructions for Downloading Viewers and Players.

Links on this page: