U.S. Department of Health & Human Services

FDA U.S. Food and Drug Administration

Inspections, Compliance, Enforcement, and Criminal Investigations

Aurobindo Pharma Limited 5/20/11

Department of Health and Human Services

Public Health Service
Food and Drug Administration
Silver Spring MD 20993

Warning Letter

VIA UPS MAIL **WL: 320-11-013**

May 20, 2011

Mr. M. Madan Mohan Reddy, Director
Aurobindo Pharma Limited, Units III and VI
Auro House, 313, Bachupally
Quthubullapur (M), RR District
Hyderabad 500 090 A.P., India

Dear Mr. Reddy:

The U.S. Food and Drug Administration (FDA) conducted inspections of Aurobindo Pharma Limited, Unit III (hereinafter referred to as "Unit III"), located at Survey Nos. 313/314, Bachupally, Quthubullapur Mandal, Hyderabad, Andhra Pradesh, India, and Aurobindo Pharma Limited, Unit VI (hereinafter referred to as "Unit VI"), located at Survey Nos. 329/39 & 329/47, Chitkul Village, Patancheru Mandal, Medak Dist, Andhra Pradesh, 502 307, India. The inspection of Unit III took place during September 20 - 24, 2010 (September 2010 inspection). The inspection of Unit VI took place during December 7 - 22, 2010 (December 2010 inspection).

During our inspection of Unit VI, and through Field Alert Reports related to Unit III, FDA identified significant violations of Current Good Manufacturing Practice (CGMP) regulations for Finished Pharmaceuticals, Title 21, Code of Federal Regulations, Parts 210 and 211. In addition, violations of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (the Act) [21 U.S.C. § 351(a)(2)(B)] were documented with respect to APIs. These violations cause your drugs to be adulterated within the meaning of section 501(a)(2)(B) of the Act in that the methods used in, or the facilities or controls used for, their manufacture, processing, packing, or holding do not conform to, or are not operated or administered in conformity with, CGMP.

Unit VI

We have reviewed your January 13, 2011 response to the Form FDA-483 issued at the conclusion of the December 2010 Unit VI inspection, and note that it lacks sufficient corrective actions.

Specific violations observed during the inspection include, but are not limited, to the following:

1. Your firm's laboratory records fail to include complete data derived from all tests necessary to assure compliance with established specifications and standards [21 C.F.R. § 211.194].

For example,

a. On December 13, 2010, the FDA investigator observed a microbiological plate that contained one (1) large colony forming unit (CFU) of mold. However, your firm's laboratory documentation reported 0 CFU for the same microbiological plate.

The inspection found that the laboratory manager had documented "NIL," (i.e. no growth for this plate), while the same laboratory manager confirmed microbial growth in the presence of the investigators. Later during the inspection, the FDA investigator asked to see the original plate and was told that it had been destroyed. On December 21, 2010, your firm prepared a corrective and preventive action (CAPA) stating that the laboratory manager misread the plate count, and that this deficiency was the result of a human error. We are concerned that your firm lacks documentation to support this conclusion and moreover, that the original plate was destroyed during the FDA inspection, as reported.

Your response of January 13, 2011, raises some additional concerns as it includes a photo of the original plate that your firm stated was destroyed and a second photo of a plate that was allegedly misread. Please explain this discrepancy.

We are concerned that this is a repeat violation. During the inspection of Unit VI conducted in May 2007, investigators also reported your failure to document positive results for a microbial plate that was confirmed as containing microbial growth.

b. On December 17, 2010, the investigator noted that many microbial plates containing environmental monitoring and personnel samples, collected on December 12, 2010 during production, were missing from the incubator. Your response confirmed that 33 of 150 (22%) of the personnel monitoring samples were missing and that in one instance, 9 of 10 samples were missing for a single operator.

Your response indicates that no missing plates were reported for the period of January 2009 through November 2010. We have determined that this conclusion is not reliable because neither reconciliation procedures nor data regarding the number of microbial plates used for environmental monitoring and microbiology laboratory samples were available at the time. Please explain how your firm determined the effectiveness of this review of 2009 and 2010 plates, without having a procedure in place for the reconciliation.

Our inspection found that your environmental monitoring data for 2009 and 2010 reported no alert or action level results in the Grade **(b)(4)** areas used to manufacture products intended for the U.S. market. This finding is questionable in that during an FDA visit to your microbiology laboratory on December 13, 2010, twenty-eight (28) plates, collected as part of the environmental monitoring program were found inside an incubator in the microbiology laboratory with visible growth of microorganisms. According to your response to the inspectional observations, many of the microorganisms recovered were identified as "new isolates", which had not been previously recovered in Unit VI.

We are concerned that similar situations were observed by other FDA investigators during previous inspections conducted in November 10 – 17, 2005, and May 7 – 15, 2007. This disproportionate detection of microbial contamination during FDA inspections questions the validity of the data generated by your microbiology laboratory. Accurate and reliable microbial management data is essential to support the aseptic processing operations used during the manufacturing of sterile active pharmaceutical ingredients (API) and finished drug product intended for distribution in the United States.

2. Your firm has not established or followed appropriate written procedures designed to prevent microbiological contamination of drug products purporting to be sterile [21 C.F.R. § 211.113(b)].

For example, during the December 2010 inspection, the investigators found that your SOPs related to your environmental programs failed to adequately identify (e.g., diagrams) the locations where active and passive environmental monitoring samples are to be collected from. The inspection also found that your procedure for environmental sampling does not require that employees be sampled **(b)(4)** time they exit the Class **(b)(4)** clean rooms.

This deficiency increases our concern regarding the reliability of the data generated and your ability to identify the source of your microbial contamination. We expect that SOPs related to Environmental Monitoring include sufficient instructions to ensure that the plates intended to detect microbial growth are appropriately located. These procedures should also include specific instructions for the collection of microbiological samples.

Your firm needs to establish a robust environmental monitoring program capable of generating meaningful data, and that would serve as an early warning system to detect possible environmental contaminants that may impact the sterility of the sterile APIs and finished drug products manufactured at your facility. There is no assurance that your current environmental monitoring program is capable of detecting microbiological contaminants.

In addition to the items listed above, the inspection uncovered additional deficiencies that increase our concerns regarding the validity of the data generated in the microbiology laboratory, and the quality of the sterile API and finished drug products manufactured at your facility. These issues include, but are not limited, to:

- Discrepancies in the procedures and documentation practices related to use of extra plates to replace missing or damaged plates that are collected as part of the environmental monitoring program.
- The device used to handle **(b)(4)** stoppers during the aseptic filling of sterile API is not sampled.
- Failure to follow established procedures for control of all pages in the batch production records.

Unit III

III. Your firm has not thoroughly investigated the failure of a batch or any of its components to meet its specifications whether or not the batch has already been distributed [21 C.F.R. § 211.192].

For example,

Investigations related to Field Alert Reports (FARs) submitted to the agency during 2009 and 2010, regarding your packaging and labeling system are found to be inadequate. Your inability to implement appropriate corrections to prevent future significant problems raises concerns regarding the robustness of your quality system.

On January 19, 2010, a FAR submitted to the agency reported that a **(b)(4)** Tablet was found inside a bottle labeled as containing **(b)(4)** Tablets **(b)(4)** mg. Subsequently, on April 12, 2010, and March 24, 2011, your firm submitted FARs reporting that eleven (11) bottles labeled as containing **(b)(4)** mg were found containing more than 30 **(b)(4)** Tablets **(b)(4)**mg; and that a bottle labeled as containing **(b)(4)** tablets **(b)(4)**mg, was found containing 90 **(b)(4)** Tablets **(b)(4)**mg, respectively.

Your investigation into the April 12, 2010 event attributed the root cause to a human error. You concluded that unlabeled bottles of **(b)(4)** tablets were re-introduced into the packaging line packaged with the **(b)(4)**mg labels. Your investigation regarding the March 24, 2011 event also attributed human error as the root cause of the problem. In this case the label printer manufacturer (PI) and labeling operations at Production Block-**(b)(4)** were also related to the product mix-up problems. We are concerned with your inability to conduct a thorough evaluation of your packaging and labeling systems and identify problems that may lead to subsequent or new incidents of product/labeling mix-ups. It is your responsibility to determine the appropriate corrective actions that will reduce the possibility of future product/labeling mix-up problems.

Your response to this letter should include a detailed action plan describing the changes and improvements made in your packaging and labeling operations that will prevent recurrence of similar or new violations. Also include an evaluation of products packaged during the same campaign and that may also be also be affected by the root cause assigned.

It is important that you take appropriate actions to address the aforementioned violations. Provide your justification for not taking market action against batches that may be affected and distributed in the United States.

The violations cited in this letter are not intended to be an all-inclusive statement of violations that exist at your facilities. You are responsible for investigating and determining the causes of the violations identified above and for preventing their recurrence and the occurrence of other violations. If you wish to continue to ship your products to the United States, it is the responsibility of your firm to ensure compliance with all U.S. standards for CGMP and all applicable U.S. laws and regulations.

Until all corrections have been completed and FDA has confirmed corrections of the violations and your firm's compliance with CGMP, FDA may withhold approval of any new applications or supplements listing your firm as a drug product manufacturer. In addition, failure to correct these violations may result in FDA refusing admission of articles manufactured at Aurobindo Pharma Limited, Unit III, located at Survey Nos. 313/314, Bachupally, Quthubullapur Mandal, Hyderabad, Andhra Pradesh, India, and Aurobindo Pharma Limited, Unit VI, located at Survey Nos. 329/39 & 329/47, Chitkul Village, Patancheru Mandal, Medak Dist, Andhra Pradesh, 502 307, India, into the United States. The articles are subject to refusal of admission pursuant to section 801(a)(3) of the Act [21 U.S.C. § 381(a)(3)], in that, the methods and controls used in their manufacture do not appear to conform to Current Good Manufacturing Practice within the meaning of section 501(a)(2)(B) of the Act [21 U.S.C. § 351(a)(2)(B)].

Within fifteen working days of receipt of this letter, please notify this office in writing of the specific steps that you have taken to correct violations. Include an explanation of each step being taken to prevent the recurrence of violations and copies of supporting documentation. If you cannot complete corrective action within fifteen working days, state the reason for the delay and the date by which you will have completed the correction. Please identify your response with FEI #3004021263 (Unit VI) and FEI #3004021229 (Unit III).

We also recommend that within five days of receipt of this letter you contact Paul Balcer, at paul.balcer@fda.hhs.gov or 301-796-3525, to schedule a regulatory meeting at our office.

If you have questions or concerns regarding this letter, contact Douglas A. Campbell, Compliance Officer, at the below address and telephone number.

U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Division of Manufacturing and Product Quality
International Compliance Branch
White Oak, Building 51 Room 4240
10903 New Hampshire Ave
Silver Spring, MD 20993
Tel: (301) 796-3201
Fax: (301) 847-8741

Sincerely,
/S/
Richard L. Friedman
Director
Division of Manufacturing and Product Quality
Office of Compliance

Center for Drug Evaluation and Research

Links on this page: