Antibioticos Do Brasil Ltda 12/8/16

Department of Health and Human Services

Public Health Service
Food and Drug Administration
10903 New Hampshire Ave.
Silver Spring, MD 20993

Via UPS
Return Receipt Requested

Warning Letter 320-17-10

December 8, 2016

Mr. Marco Bosoni
President
Antibioticos do Brasil
Rod. Professor Zeferino Vaz, Km 135-SP 332
Cosmopolis, Sao Paulo 13150-000
Brazil

Dear Mr. Bosoni:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Antibioticos do Brasil, at Rod. Professor Zeferino Vaz, Km 135-SP 332, Cosmopolis, Sao Paulo, from April 18 to 27, 2016.

This warning letter summarizes significant violations of current good manufacturing practice (CGMP) regulations for finished pharmaceuticals. See 21 CFR, parts 210 and 211.

Because your methods, facilities, or controls for manufacturing, processing, packing, or holding do not conform to CGMP, your drug products are adulterated within the meaning of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 351(a)(2)(B).

We reviewed your May 18, 2016, response in detail and acknowledge receipt of your subsequent correspondence.

During our inspection, our investigator observed specific violations including, but not limited to, the following.

1. Your firm failed to use equipment in the manufacture, processing, packing, or holding of drug products that is of appropriate design, adequate size, and suitably located to facilitate operations for its intended use and for its cleaning and maintenance. (21 CFR 211.63)

The **(b)(4)** sterile **(b)(4)** filling line for **(b)(4)** and **(b)(4)** lacks unidirectional airflow in the ISO 5 aseptic filling zone. The **(b)(4)** airflow in the filling zone is not sufficiently robust to protect the sterile injectable product during interventions involving operator entry into the aseptic filling **(b)(4)**. Smoke studies demonstrated that the filling line design permits turbulence above and below open vials. **(b)(4)** closure significantly disrupts airflow. This turbulent air in the aseptic filling zone poses a significant contamination hazard.

2. Your firm failed to establish and follow appropriate written procedures that are designed to prevent microbiological contamination of drug products purporting to be sterile, and that include validation of all aseptic and sterilization processes. (21 CFR 211.113(b))

Your smoke studies do not support your assertion that you maintain unidirectional airflow for all aseptic operations. At times, the smoke volume was too low to accurately demonstrate airflow. You did not inject the smoke in areas that showed the effects of operator interventions on the unidirectional air stream. These smoke studies do not demonstrate that your line is designed to prevent microbiological contamination, or to provide high assurance of product sterility.

In your response, you stated that you are planning additional smoke studies. Your new smoke studies should clearly demonstrate unidirectional air flow under dynamic processing conditions.

It is essential that smoke studies simulate manual interventions performed during actual operations in order to gauge whether the activities disrupt unidirectional airflow.

3. Your firm failed to establish an adequate system for monitoring environmental conditions in aseptic processing areas. (21 CFR 211.42(c)(10)(iv)).

You failed to adequately document environmental monitoring. For example, your records did not establish that during manufacture of **(b)(4)** lot **(b)(4)**, you collected environmental monitoring samples from all locations designated in your environmental monitoring procedure. Records did not clearly reconcile samples you collected with the results you obtained. Also, your procedure instructed operators to record environmental monitoring data only in instances where there are “any results different from zero.” Your environmental monitoring records do not document any zero counts.

CGMP consultant recommended

FDA cited significant CGMP observations in a 2009 Warning Letter (320-09-08) issued to your firm. These recurring problems demonstrate that executive management oversight and control over the manufacture of drugs is inadequate.

Based upon the nature of the violations we identified at your firm, we strongly recommend engaging a consultant qualified to evaluate your operations, and qualified as set forth in 21 CFR section 211.34, to assist your firm in meeting CGMP requirements. Your use of a consultant does not relieve your firm’s obligation to comply with CGMP. Your firm’s management remains responsible for fully resolving all deficiencies and ensuring ongoing CGMP compliance.

Additional guidance on aseptic processing

See FDA’s guidance document, *Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Practice*, to help you meet the CGMP requirements when manufacturing sterile drugs using aseptic processing. It is online at
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070342.pdf (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070342.pdf

Conclusion

Violations cited in this letter are not intended as an all-inclusive list. You are responsible for investigating these violations, for determining the causes, for preventing their recurrence, and for preventing other violations.

If you are considering an action that is likely to lead to a disruption in the supply of drugs produced at your facility, FDA requests that you contact CDER's Drug Shortages Staff immediately, at drugshortages@fda.hhs.gov, so that FDA can work with you on the most effective way to bring your operations into compliance with the law. Contacting the Drug Shortages Staff also allows you to meet any obligations you may have to report discontinuances or interruptions in your drug manufacture under 21 U.S.C. 356C(b) 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.

Until you correct all violations completely and we confirm your compliance with CGMP, FDA may withhold approval of any new applications or supplements listing your firm as a drug manufacturer.

Failure to correct these violations may also result in FDA refusing admission of articles manufactured at Antibioticos do Brasil at Rod. Professor Zeferino Vaz, Km 135-SP 332, Cosmopolis, Sao Paulo, into the United States under section 801(a)(3) of the FD&C Act, 21 U.S.C. 381(a)(3). Under the same authority, articles may be subject to refusal of admission, in that the methods and controls used in their manufacture do not appear to conform to CGMP within the meaning of section 501(a)(2)(B) of the FD&C Act, 21 U.S.C. 351(a)(2)(B).

We request that you contact Nabeel Babaa, by email to Nabeel.Babaa@fda.hhs.gov, within five days of receipt of this letter to schedule a regulatory meeting.

After you receive this letter, respond to this office in writing within 15 working days. Include the following supporting documentation:

- a comprehensive evaluation of the adequacy of your processing line design and control, and assessment of operator aseptic techniques
- robust smoke studies that adequately represent all aseptic interventions, and clearly evaluate airflow during all manual activities that can affect the exposed product and its components
- a comprehensive evaluation of your environmental monitoring process and procedures, including documentation and evaluation of test results
- an interim plan to ensure the quality of drugs that you continue to manufacture and distribute

Also specify what you have done since our inspection to correct your violations and to prevent their recurrence. If you cannot complete corrective actions within 15 working days, state your reasons for delay and your schedule for completion.

Send your electronic reply to **CDER-OC-OMQ-Communications@fda.hhs.gov (mailto:CDER-OC-OMQ-Communications@fda.hhs.gov)** or mail your reply to:

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