Inspections, Compliance, Enforcement, and Criminal Investigations

ABL - Antibiotics Do Brasil

Department of Health and Human Services

Public Health Service
Food and Drug Administration
CENTER FOR DRUG EVALUATION AND RESEARCH
Division of Manufacturing and Product Quality
International Compliance Team, HFD-325
10903 New Hampshire Avenue
Silver Spring, Maryland 20993

Warning Letter

Via FedEx

July 24, 2009

WL: 320-09-08

Mr. Jose Loureiro Cardoso
President, General Manager
Antibioticos do Brasil Uda.
Rod. Gal. Milton Tavares de Souza (SP 332) Km. 135
13150-000, Cosmopolis, Sao Paulo, Brazil

Dear Mr. Cardoso:

This is regarding an inspection of your human and animal drug manufacturing facility in Sao Paulo, Brazil, by Investigator Megan Haggerty and Analyst Jennifer M. Gogley, during the period of October 27 to November 6, 2008. The inspection revealed significant deviations from

U.S. current good manufacturing practice (CGMP) regulations (Title 21, Code of Federal Regulations, Parts 210 and 211) in the manufacture of both sterile active pharmaceutical ingredients (APIs) and finished dosage products. The CGMP deviations were listed on an Inspectional Observation (FDA-483) form issued to you at the close of the inspection.

These CGMP deviations cause your sterile APIs and drug products to be adulterated within the meaning of section 501 (a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (the Act) [21 U.S.C. § 351(a)(2)(B)]. Section 501(a)(2)(B) of the Act requires that all drugs be manufactured, processed, packed, and held according to current good manufacturing practice. Failure to comply with COMP constitutes a failure to comply with the requirements of the Act.

We have reviewed your response letters to the FDA-483 observations dated December 30, 2008, March 13, 2009, and April 17, 2009; along with electronic mail containing corrective action updates that were dated April 27, 2009, May 4, 2009, and May 29, 2009. We note that some corrections have been completed, or will soon be

implemented. However, your response fails to adequately address some deficiencies. Specific violations include, but are not limited to:

Complaint Files

1. Failure to thoroughly investigate unexplained discrepancies of batches of a drug or any of its components that failed to meet its specifications. [21 CFR 211.192]

a. The investigation of a complaint into the sterility failure for **(b)(4)** API batches, **(b)(4)**, was inadequate in that it failed to provide evidence of the origin of the contamination that may have led to the sterility failure of these **(b)(4)** batches manufactured on the same line used for the U.S. products. Your complaint investigation failed to request and evaluate the complainant's (customer) sterility failure investigation, and retrospectively test the 14 retain samples of the **(b)(4)** batches manufactured in the campaign run. In addition, your investigation did not consider that the sample bags sent to your customers (which are **(b)(4)** for sterility) have never been sterility tested as part of your vendor qualification for these bags.

Although you indicate in your December 30, 2008, response that your customer conducted its own investigation into the failure, such investigation was not submitted as part of your response to the FDA-483 observations. You state that your investigation included a documentation review of the **(b)(4)** batches in the campaign, and retesting of lots **(b)(4)** through **(b)(4)** batch before and after the lots subject to the complaint) which passed the sterility retest. Your corrective actions to procedures now require that all lots of a campaign must be analyzed as part of an investigation. However, you do not commit to retest retain samples of the remaining **(b)(4)** lots.

Your firm should carefully evaluate the performance of the sterility test to preclude any practice that allows for possible sample contamination. When microbial growth is observed the lot should be considered non-sterile. Additionally, a thorough investigation should be conducted. An initial positive test would be invalid only in an instance in which microbial growth can be unequivocally attributed to laboratory error. Only if conclusive and documented evidence clearly shows that the contamination occurred as part of testing, should a new test be performed. When available evidence is inconclusive, batches should be rejected as not conforming to sterility requirements. After considering all relevant factors concerning the manufacture of the product and testing of the samples, the comprehensive written investigation should include specific conclusions and identify corrective actions.

In your response to this letter, please provide us with a copy of the investigation's persuasive evidence of the origin of the contamination considering at least the below factors:

- Identification (speciation) of the organism in the sterility test
- Record of laboratory tests and deviations
- Monitoring of production area environment
- Monitoring of personnel
- Product pre-sterilization bioburden
- Process steps that are vulnerable to contamination
- Production record review
- Manufacturing history

b. A complaint was received for a poor spike connection between the **(b)(4)** system and the Cefepime for Injection, batch **(b)(4)** stopper and vial. There was no adequate justification for why retains were not assessed as part of the investigation.

The proposed corrective action included in your December 30, 2008, response only partially addresses the observation. Although you indicate that the procedures were revised to include a note requiring that retain samples be assessed as part of an investigation, there is no indication that a retrospective evaluation of the retain samples was conducted. Your firm received this complaint on August 18, 2008, but failed to retrospectively evaluate the retain samples of those lots manufactured as part of the same campaign. You indicate that a sample from the complainant was requested by ABL, but not received due to customs clearance issues with the Brazilian authorities. However, your response did not provide documentation that you had attempted to obtain the **(b)(4)** portion of the product, which is manufactured by another company. You indicate that no deviation occurred during the production of your product. Although the **(b)(4)** system is not handled by your facility, your firm should determine whether your product contributed to the spike connection deficiency. This is a sterile product, therefore, the connection between the two components is critical and your firm should make every effort to correct this deficiency. In your response to this letter, provide the information discussed as deficient in this paragraph.

Quality System

2. The quality control unit does not adequately exercise its responsibility to approve or reject procedures impacting the quality and purity of drug products. [21 CFR 211.22(c)]

The quality control unit allowed the practice of using autoclave tape on the **(b)(4)** filling machine and operator's gloves. On multiple occasions during the inspection, the FDA investigators observed autoclave tape on the gloves of the **(b)(4)** (class **(b)(4)**) filling operators and filling machine. This deviation was noted while representatives from the quality control unit were present.

Your December 30, 2008, response for Observations 20 and 21 of the FDA-483 failed to address why the quality control unit did not question, and allowed the use of, autoclave tape on the filling machine and the operator's gloves.

Furthermore, we are concerned that questionable **(b)(4)** technique practices cited on the current FDA-483 are similar to deviations cited on the previous FDA-483 issued to you on November 1, 2005. For example, the previous 2005 inspection resulted in the issuance of a twenty-seven item FDA-483, which included similar questionable **(b)(4)** technique practices (FDA-483 Observations 16, 17, & 18).

The current FDA-483 observations also cite your quality control unit for failing to exert its QC and QA responsibilities. We recognize the commitments to improve the quality organization in your response. However, your response failed to address global corrections to prevent recurrence.

Laboratory Control System

3. Laboratory controls do not include the establishment of scientifically sound and appropriate test procedures designed to assure that drug products conform to appropriate standards of identity, strength, quality and purity. [21 CFR 211.160(b)]

Validation of the sterility test method failed to specify or document the amount of **(b)(4)** used to reconstitute the following parenteral antibiotic powders: **(b)(4)**, Cefoxitin (1g, 2g, and 109), Cefazolin (500 mg, 1g, and 109), Cefepime (1g and 2g), and **(b)(4)**.

The reconstitution liquid (**(b)(4)**) assists with the inactivation of the antibacterial properties of the drug products; therefore, the quantity of the reconstitution fluid is important and should be documented to show that a validated amount is being used during routine testing of the finished products, in order to avoid false negative results.

Your response of December 30, 2008, is incomplete in that it fails to address the lack of a documented reconstitution fluid for the following parenteral antibiotic powders: Cefazolin (10g) **(b)(4)** and Cefoxitin (1g, 2g, and 10g). Your response only included the material specification sheets for these products. Although you indicate that the reconstitution volume is described, and that the total contents of the reconstituted product are **(b)(4)** during routine analysis, your response does not demonstrate that the correct amount of fluid was used during the sterility validation studies for Cefazolin (0g), **(b)(4)**, and **(b)(4)**

Please include in your response to this letter, a copy of the validation protocol specifying the amount of fluid to be used [as you did for Cefepime (1g & 2g); Ceftazidime (1g, 2g, & 6g), and Cefazolin (500mg & 1g)], or demonstrate that the protocol refers to the laboratory procedure that was effective at the time of the validation, indicating the amount of fluid to use for reconstitution. Further, the material specifications revised in 2008, and submitted in your initial response, lack the original effective dates. Thus, if you cannot provide evidence that the reconstituted fluid was described in the protocol, or in a document directly referenced in the protocol, you should consider repeating the sterility validation for Cefazolin (10g), **(b)(4)** and Cefoxitin (1g, 2g, & 10g).

Material System

4. Each lot of a drug product container/closure that is liable to microbiological contamination, and that is objectionable in view of its intended use, is not subjected to microbiological tests before use. [21 CFR 211.84(d)(6)]

There is no procedure for sterility testing **(b)(4)** bags upon receipt, used as the immediate container for the following sterile APIs: **(b)(4)**

following sterile APIs: **(b)(4)**
Cefepime, Ceftriaxone, **(b)(4)** and Cefoxitin. ABL has never tested the **(b)(4)** bags for sterility.

Your December 30, 2008, response states that you are performing method validation of the sterility test conducted for the purchased **(b)(4)**. You also indicate that the **(b)(4)** process of the **(b)(4)** was validated by your supplier, and that your quality unit releases for use based on your supplier's Certificate of Analysis (CoA). Your response fails to note that the referenced **(b)(4)** validation for the **(b)(4)** bags was not performed for ABL. It was performed and reviewed by your supplier **(b)(4)**.

We also noted that ABL has not reviewed and approved the **(b)(4)** validation data and final report. The periodic monitoring of the bags for sterility performed by **(b)(4)** is inadequate. ABL should review the **(b)(4)** validation, assess the bioburden data from **(b)(4)** (the contract **(b)(4)**,and conduct sterility testing of each lot. Once satisfactory data is obtained and if high supplier reliability is substantiated, reduced testing may be justified on the basis of a CoA.

A drug product produced by **(b)(4)** processing can become contaminated through the use of one or more components and container/closure systems that are contaminated with microorganisms or endotoxins. It is important to characterize the microbial content (e.g., bioburden, endotoxin) of each component/container/closure system that could be contaminated, and establish appropriate acceptance limits.

Request for additional information

Your April 27, 2009, response provided a protocol to validate the bioburden test performed prior to the **(b)(4)** step to achieve sterility during the manufacturing of Cefoxitin, Cefepime, **(b)(4)** and Ceftriaxone APIs. Your response indicates that you are performing method validation for bioburden testing of the FDA regulated products mentioned above, and that you hope to complete the validation report by May 2009. Please include a copy of the validation report upon completion.

Your March 13,2009, response included the validation report for the Zanasi MD300 powder filler with **(b)(4)** process runs for Cefepime 2g150 ml vials, and included additional machine parameters such as: number of dosing (number of powder fill cavity discharges into each vial), disks graduation, machine discharge pressure, machine vacuum, dosing disks per diameter, and minimum speed. However, the response lacks a parameter for maximum machine run speed. Establishing a maximum speed parameter for equipment operations can be important from a microbial and fill weight perspective. For example, an uncontrolled filling speed can result in an increase of unnecessary interventions due to line stoppages, and can represent a challenge to the required fill weights. In your response to this letter, include the justification and supportive data for not considering the maximum speed as a critical parameter.

Your April 17, 2009, response provided the preliminary report for **(b)(4)** process simulation (Media Fill batch **(b)(4)** runs for the sterile manufacturing of APIs. Your response showed an increase in the amount of **(b)(4)** to yield **(b)(4)** from the **(b)(4)** of **(b)(4)** previously used. Our initial concern was that the media fill lacked a scientific rationale for the volume of **(b)(4)** used to demonstrate that the came into contact with all product contact surfaces. Your response did not provide evidence; photographic, video or calculations, to demonstrate product coverage of the **(b)(4)** or the that connects the **(b)(4)** to the **(b)(4)** and which come into contact with the **(b)(4)**. According to the investigators, the **(b)(4)** and the **(b)(4)** are cleaned between campaigns and, therefore, are able to be disassembled, allowing access for photographs or video which would demonstrate product coverage. Your response of April 17, 2009, does not provide any justification to support either the use of the prior amount of **(b)(4)** or the new **(b)(4)** amount. In your response to this letter, please provide your rationale or evidence to demonstrate **(b)(4)** coverage of equipment product contact surfaces.

The CGMP deviations identified above, or on the FDA-483 issued to your firm, are not to be considered an all-inclusive list of the deficiencies at your facility. FDA inspections are audits, which are not intended to determine all deviations from CGMP that exist at a firm. If you wish to continue to ship your products to the United States,

it is your firm's responsibility to ensure compliance with all U.S. standards for current good manufacturing practice.

Until all corrections have been completed, and FDA can confirm your firm's compliance with CGMP, the Center for Drug Evaluation and Research (CDER) and the Center for Veterinary Medicine (CVM) will recommend disapproval of any new applications or supplements listing your firm as a manufacturer of finished dosage forms and active pharmaceutical ingredients. In addition, shipment of articles manufactured at Antibioticos do Brasil Ltda into the U.S. may be subject to refusal of admission pursuant to Section 801(a)(3) of the FD&C 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 FD&C Act [21 U.S.C § 351(a)(2)(B)].

Please respond to this letter within thirty days of receipt. Identify your response with FEI #3002806919. Please contact Edwin Melendez, Compliance Officer, at the address and telephone number shown below if you have any questions related to the human drugs, need further information, or for further proposals regarding this letter.

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Center for Drug Evaluation and Research
Division of Manufacturing and Product Quality
International Compliance Branch
White Oak, Building 51
10903 New Hampshire Avenue
Silver Spring, Maryland 20993
Tel: (301) 796-3284
FAX: (301) 301-847-8742

If you have any questions related to animal drugs, please contact Lydia Rosas-Marty, Compliance Officer, at the following address and telephone number:

U.S. Food & Drug Administration
Center for Veterinary Medicine (CVM)
Office of Surveillance and Compliance
Division of Compliance
Enforcement & Regulatory Policy Team (HFV-232)
7519 Standish Place
Rockville, Maryland 20855
Tel: (240) 276-9232
FAX: (240) 276-9241

To schedule are-inspection of your facility, after corrections have been completed and your firm is in compliance with CGMP requirements, send your request to: Director, Division of Field Investigations, HFC-130, Room 13-74, 5600 Fishers Lane, Rockville, MD 20857. You may also contact that office by telephone at (301) 827-5655, or by fax at (301) 443-6919.

Sincerely,

/S/
Richard L. Friedman, M.S.
Director
Division of Manufacturing and Product Quality
Office of Compliance
Center for Drug Evaluation and Research

/S/

Neal Bataller, ME, DVM
Director
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