Inspections, Compliance, Enforcement, and Criminal Investigations

Laboratoire Atlas Inc. 6/25/09

hhsbluebird **Department of Health and Human Services**

Public Health Service
Food and Drug
Administration
Silver Spring, MD 20993

Warning Letter

Via Fed Ex

WL: 320-09-07

June 25, 2009

Mr. Mario Ostiguy
President
Laboratoire Atlas, Inc.
9600 Boul Des Sciences, Ville d'Anjou, Quebec
Canada, H1J3B6

Dear Mr. Ostiguy:

This is regarding a September 2-5, 2008, FDA inspection of your pharmaceutical manufacturer facility in Ville d'Anjou, Canada by Investigator Carla Lundi and Chemist Katherine Szestypalow. The inspection revealed significant deviations from U.S. current good manufacturing practice (CGMP) regulations [Title 21 Code of Federal Regulations (CFR), Parts 210 and 211] in the manufacture of human drug finished products. These deviations were listed on an Inspectional Observations (FDA 483) form issued to you at the conclusion of the inspection.

These CGMP deviations cause your drug products to be adulterated within the meaning of section 501 (a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) [21 U.S.C. 351 (a)(2)(B)]. Section 501(a)(2)(B) of the Act

requires that all drugs, as defined in the Act, be manufactured, processed, packed, and held according to CGMP. Failure to comply with CGMP constitutes a failure to comply with the requirements of the Act. Also, your firm has imported into the United States the (b)(4) product, labeled under the trade name" (b)(4) an (b)(4) that is not sterile and is therefore in violation of 21 CFR 200.50.

We have reviewed your October 24, 2008 response to the FDA-483 observations and note that some corrections appear to have been completed or will soon be implemented. However, your response does not adequately address some of the deficiencies. Specific violations include, but are not limited to:

Misbranded Drug

During the inspection, you stated that your firm does not intend to market any products in the United States. However, our records indicate that your firm shipped (b)(4) liters of (b)(4) (lot# (b)(4) Expiration Date 05/2011) into the US in January 2008.

In addition to not complying with 21 CFR 200.50, as set forth below, the 1% (b)(4) product is labeled in a manner that suggests that the (b)(4) properties (b)(4) may have this effect directly on the (b)(4) of the person using the (b)(4). This raises "new drug" issues that would require the product to be approved in a new drug application (NDA) to be legally marketed in the United States. Therefore, if these are not the intended uses, the product should be labeled to clearly indicate that the (b)(4) properties only relate to the (b)(4) effect on the (b)(4) itself and does not have this effect on the (b)(4).

In addition, the product does not contain the required labeling information in a drug facts panel in accordance with 21 CFR 201.66. Therefore, this product is misbranded under section 502(c) of the FD&C Act because the information that is required to appear on the labeling is not prominently placed thereon with such conspicuousness and in such terms as to render it likely to be read and understood by the ordinary individual under customary conditions of purchase and use.

Please provide in your written response the appropriate and immediate corrective actions taken to address this issue.

Current Good Manufacturing Practice

1. Your firm has not established appropriate written procedures designed to prevent microbiological contamination of drug products purporting to be sterile, including procedures for validation of any sterilization process. [21 CFR 211.113(b)]

The (b)(4) product is an (b)(4) that must be sterile in accordance with 21 CFR 200.50. However, the review disclosed that the product is not subjected to a validated sterilization process; in fact, our investigators observed that

your firm manufactures only non-sterile products.

It also appears from the labeling that the sterility test described in the United States Pharmacopeia (USP) 30 <(b)(4)> is not performed for this product; the product is only labeled as complying with the USP 30 <(b)(4)> (b)(4) effectiveness test. The failure to perform sterility testing for an (b)(4) product purporting to be sterile (see 21 CFR 200.50) is a violation of21 CFR 211.67(a).

This is of significance since the unsterilized product may pose a potential risk of contamination to the public. Please provide in your written response the appropriate and immediate corrective actions taken to address this issue, including the specific type of sterilization process that will be used for this product. Please also note that, in accordance with 21 CFR 310.502, if the product is sterilized by irradiation it requires NDA approval.

According to your manufacturing coding system for finished product lot, lot# (b)(4) represents the (b)(4) batch manufactured in November 2008. Our review found that this same lot of (b)(4) was shipped on December 17, 2007, one year earlier from being produced, and received by your US consignee on January 11, 2008. Please provide clarification regarding this discrepancy, along with the supportive
documentation.

2. Unexplained discrepancies and failure of a batch or any of its components to meet specifications are not adequately investigated by the quality control unit. [21 CFR 211.192]

a. Your firm failed to identify microbial contaminates isolated from the (b)(4) system, failed to investigate the source and cause of microbial contamination and failed to take appropriate corrective and preventive actions. The (b)(4) is used to manufacture the (b)(4) and for cleaning of manufacturing equipment.

The inspection revealed that between August 2007 and 2008, (b)(4) samples of USP (b)(4), tested by the contract laboratory, were outside the limits for total aerobic microbial counts of (b)(4). These (b)(4) samples of USP (b)(4) were obtained from distribution line (b)(4) used for the final rinse of all manufacturing equipment, including (b)(4) tanks and (b)(4) hoses used for the production of (b)(4)

The inspection also found that seven (7) additional samples of USP (b)(4) collected between February 2008 and August 2008, from distribution lines (b)(4) were above the alert limit of (b)(4), as reported by your contract laboratory. Although results above your alert limits may be an indication of an ongoing uncorrected problem, no investigation was conducted to identify a potential root cause of the problem. Additionally, three (3) out of these seven (7) USP (b)(4) samples were used as a pharmaceutical component for production batches. The microbial count results for these three (b)(4) samples (b)(4) were (b)(4) (tested on 06/26/2008), (b)(4) (tested on 02/21/2008), and (b)(4) (tested on 03/06/2009), respectively.

According to your limits for (b)(4) issued on May 01, 2008, in cases where microbial test results are above the alert or action limits, "You must notify the Director of Quality Control (QC) to take corrective action to restore the situation". The SOP also states, "You must also register the warning on the form LAB-2056 and need to monitor the situation by comparing the results." Please provide documentation showing what corrective actions were taken by your Firm to address the exceeded alert or action limits and to ensure that the pharmaceutical products made using (b)(4) were not impacted.

In your written response to the FDA-483, you submitted a copy of a retrospective investigation No. DL-08-07 conducted after the conclusion of the recent inspection. This investigation failed to address an evaluation of the distribution line involved in the contamination of all five (5) microbial test failures. Please explain your assessment of all the sampling points and production lines, along with information regarding any requalification of your water system. You should include supportive documentation.

b. Your firm invalidated failing microbial test results of (b)(4) obtained from your contract testing laboratory and retested four of the five samples without conducting an investigation or providing scientific justification.

The following five (5) out-of-limit (OOL) microbial test results ((b)(4)) of USP (b)(4) reported by your contract laboratory were discarded without conducting any investigation or justification. Specifically, (1) sample (b)(4), tested on 08/23/2007 obtained (b)(4) (2) sample (b)(4), tested on 01/17/2008 obtained (b)(4), while a retest of 01/21/2008 obtained (b)(4); (3) sample# (b)(4) tested on 01/31/2008 obtained (b)(4); (4) sample # (b)(4), tested on 05/22/2008 obtained (b)(4); and (5) sample # (b)(4), tested on 07/24/2008 obtained (b)(4).

Your firm's retests were used to inappropriately replace four of five failing

samples with the following results: (b)(4). Further, no investigation was conducted for the last (b)(4) sample, (b)(4), when the retest reached the alert limit. Your Firm accepted the passing results obtained by your firm's laboratory without conducting any investigation or providing any scientific justification for invalidating the initial failing results.

Please include in your written response to this letter your sampling and retest SOP for (b)(4) tested for microbial counts, along with your scientific rational to identify (b)(4) results tested by different laboratories as retest samples.

c. In your response you indicated that after the FDA inspection your firm tested twenty three (23) retain samples of (b)(4) finished products manufactured during the same dates in which the OOL test results in (b)(4) were obtained. These samples were found within limits for total microbial counts. Based on your results your firm concluded that the five OOL results obtained in your (b)(4) had no impact on the microbial quality of the finished product.

Your response fails to demonstrate that the batches of finished products tested are representative of all the products manufactured during the date and time of the OOL occurrences. In addition, relying on finished product test results to conclude that the product is free of microbial contamination without conducting a thorough investigation to identify the root cause(s) of the problem and implement corrective and preventive actions is unacceptable.

Your firm also lacked a trend analysis of your (b)(4) sample results and failed to monitor the (b)(4) level prior to or after the (b)(4). These issues were discussed during the inspection but not addressed in your response to the 483 observation.

Please include in your response to this letter the corrective actions implemented to address these deficiencies and provide a copy of your standard operation procedure (SOP) for cleaning, sanitizing and monitoring of your (b)(4) system. The corrective actions should include your (b)(4) sampling methods, frequency and sites of sampling, the frequency and methods of sanitization, your program for monitoring the chemical and microbial quality of the (b)(4), trending analysis of your (b)(4) samples, and periodic review of the (b)(4) system's performance and requalification.

The (b)(4) produced by your firm must comply with the USP standards and related regulatory requirements whether the (b)(4) is used as a raw material during the manufacturing of your pharmaceutical products or to rinse the equipment, or both. Furthermore, all OOL results obtained from the in house

laboratory or a contract laboratory must be fully investigated and documented, and appropriate corrective and preventive action should be taken to maintain adequate control of the system.

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

There is no procedure that delineates the timeliness of microbial enumeration testing of (b)(4) samples after collection. (b)(4) sample # (b)(4) was tested on 01/17/2008 by the contract laboratory with an initial microbial OOL result of (b)(4) This same sample was retested by the same contract laboratory on 01/21/2008 with a result of (b)(4). No investigation was conducted either by your firm or the contract laboratory to determine why the microbial test results were significantly different. Additionally, there is no data available to assure that the recovered microbial levels obtained after the delayed retesting would have been the same had the testing been performed shortly after sample collection. The number of recoverable bacteria in the sample can decrease or increase over time after sample collection due to various factors (i.e., either poor nutrient for certain microorganism to grow or unclean sample container). It is generally appropriate for microbial testing of (b)(4) samples by contract laboratories to be completed within 48 hours after sample collection, provided the samples are held at (b)(4).

Please clarify this issue in your response to this Warning Letter. Provide a copy of your current (b)(4) sampling procedure with further details on how (b)(4) samples are collected, conditions of sample transport and storage, and the time interval between sampling and testing.

In addition, according to your manufacturing coding system for raw materials and bulks, the above (b)(4) sample (b)(4) appears to have been collected in November 2007. Our review found that this same (b)(4) sample was tested on 01/17/2008, two months after sample collection. The similar discrepancy was also found in the (b)(4) samples (b)(4) (collected in Nov 2007 and microbial test results dated 01/31/2008) and (b)(4) (collected in Feb 2008 and microbial test results date 05/22/2008).

Please clarify these discrepancies and provide supportive documentation.

4. Equipment used in the manufacture, processing, packing or holding of drug products is not of appropriate design to facilitate operations for its intended use. [21 CFR 211.63]

In July 2007 your firm upgraded your (b)(4) system by installing a new (b)(4) system (b)(4) to increase its total output capacity from (b)(4) to (b)(4) However, the (b)(4) system has not been adequately qualified to ensure that it is capable of producing USP (b)(4) since increasing the capacity of the system.

In your response to the FDA 483 you indicated that the Installation Qualification and Operation Qualification have been completed and that the Performance Qualification of your (b)(4) system is expected to be completed by the end of 2009. You stated that a preliminary study and periodic monitoring of the system has to be done. However, no details of protocol, short term or long term action plan with supportive documentation were included in your response. Most of your products are anti-infective, oral and topical products where is used in large quantities either as a component or for rinsing equipment. Please provide documentation that demonstrates that your (b)(4) system is operating and maintained under controlled conditions and capable of producing USP (b)(4) when operated over extended time periods.

In addition, there is no assurance that the (b)(4) used in the preparation of your (b)(4) (for (b)(4)) meets the USP requirements for (b)(4) because your facility has not completed the requalification of the (b)(4) system.

5. The responsibilities and procedures applicable to the quality control unit are not fully followed. [21CFR 211.22(d)]

During upgrading your (b)(4) system in July 2007, your distribution loop and (b)(4) pump were accordingly modified for purportedly eliminating dead legs and allowing continuous recirculation for both distribution line (b)(4) and (b)(4). However, your Quality Control Unit failed to follow your change control procedure (SOP-3141, dated on December 15, 1998) to document and also assess the impact of these changes on the new (b)(4) system prior to commissioning of this new equipment.

Your firm's response indicated that your firm modified the distribution loop after updating the system in July 2007 and again after inspection. Please provide details, including a scientific rationale, of the two modifications implemented, especially for the post-inspection modifications.

Meanwhile, your response provided only one training record to showing that one person from the production department has received training. Your response did not demonstrate that other people who have been involved with

the change control procedure have been trained, as well. Please clarify and provide any supportive documentation if applicable.

6. Adequate written procedures for the storage of drug products under appropriate conditions of temperature, humidity, and light so that the identity, strength, quality, and purity of the drug products are not affected have not been established and followed. [21 CFR 211.142(b)]

Your firm's warehouse used for the storage of raw materials and finished products is not controlled and adequately monitored. SOP #3229 requires the warehouse to be monitored for temperature and humidity, on a bi-monthly basis, in six different locations. Our inspection disclosed that only 16 log recordings were made between January, 2006 and July, 2008. Thirteen out of sixteen readings were taken prior to noon and no readings were taken after 4:00pm.

We acknowledge your revision of the SOP and your commitment to improve your temperature monitoring system by conducting temperature mapping studies and installing appropriate recorders (data loggers). However, your response does not provide information on the corrective and preventive actions taken to ensure that the warehouse temperature can be maintained and controlled within the acceptable USP storage requirement for (b)(4), (e.g., preserved in tight containers, protected from light, at controlled room temperature). Please revise your SOP and address this issue with supportive documents.

7. Adequate laboratory facilities for testing and approval or rejection of components are not available to the quality control unit. [21 CFR 211.22(b)]

Your firm did not qualify the contract laboratories used for the testing of (b)(4).

We acknowledge your commitment included in the October 2008 response to create an SOP related to the audit of contract-testing laboratories by the end of February 2009 for the (b)(4). Please include in your response to this letter a copy of the revised or new SOP implemented, along with the related training records.

Meanwhile, it is FDA's expectation that your firm have a quality agreement with the contract laboratories in place. We recommend that this agreement be signed by all parties involved and that it include, as a minimum, specific details delineating the roles and responsibilities of each party. A description

of the materials, services, communication, and all testing expected to be performed by each party should also be included. Your firm should ensure that the contract laboratory facility is compelled to produce accurate analytical results for the tested material, conduct adequate laboratory investigations of out-of-specification results, and report to the client such investigations or any changes.

8. Written procedures are not established for evaluating, at least annually, the quality standards of each drug product to determine the need for changes in drug product specifications or manufacturing or control procedures. [21 CFR 211.180(e)(2)]

Your firm lacks established written procedures for the review of drug products on an annual basis, to include provisions of reviewing complaints, recalls, returned or salvaged drug products. We acknowledge that your firm and the applicant will be jointly responsible for the annual report and planned to issue an SOP related to all aspects of annual product review by the end of February 2009. Please provide a copy of that SOP and of your 2008 annual product review quality standard evaluation for each current pharmaceutical product marketed in US.

9. Individuals responsible for supervising the manufacture, processing, packing, holding of a drug product lack the education, training, experience to perform their assigned functions in such a manner as to assure the drug product has the safety, identity, strength, quality and purity that it purports or is represented to possess. [21 CFR 211.25(b)]

During the inspection, your Director of Quality Control, acknowledged not being familiar with the US CGMP regulations. Our review of your firm's training program disclosed that there was no requirement for on-going CGMP training of employees. The firm only had an initial CGMP training and did not provide regular CGMP training to all employees involved in the manufacture of drug products. There is no reference to CGMP training of supervisors or directors.

Please provide in your written response the appropriate and immediate corrective actions taken to address this issue.

The CGMP deviations identified above or on the FDA 483 issued to your firm are not an all-inclusive list of the deficiencies at your facility. FDA inspections are audits, which are not intended to address all deviations from CGMP and all violations that may exist at a firm. If you wish to continue to ship drug products to the United States, it is the responsibility of your firm to ensure compliance with U.S. standards for CGMP and all applicable laws and regulations.

Until FDA has confirmed correction of the deficiencies and compliance with CGMP, this office may recommend withholding approval of any new applications or supplements listing your Ville d'Anjou facility as a manufacturer of finished drug products. In addition, shipments of articles manufactured by your firm are 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)].

Additionally, your firm is neither registered nor has it listed with FDA every product in the commercial distribution in US, as required by 21 CFR 207.40. The FDA investigators had discussed this issue with you during the inspection. Your response did not address this issue. Information on how to register is available on-line at the following internet website: http://www.fda.gov/cder/drls/registrationlisting.htm.This should be completed and evidence of its completion included with your response to this letter.

Please respond to this letter within thirty days of receipt and identify your response with FEI #3007083710. We also recommend that you contact Giuseppe Randazzo at Giuseppe.Randazzo@fda.hhs.gov or at (301) 796-3277 within five days of receipt of this letter to schedule a meeting. For any questions or concerns regarding this letter, contact Yanyan (Jenny) Qin, Compliance Officer, at the address and telephone number shown below.

U.S. Food & Drug Administration
Center for Drug Evaluation and Research
Division of Manufacturing and Product Quality
International Compliance Team
White Oak Building 51
10903 New Hampshire Avenue
Silver Spring, Maryland 20993
Tel: (301) 796-3207
Fax: (301) 847-8742

Sincerely,

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