Inspections, Compliance, Enforcement, and Criminal Investigations

Instituto Bioclon, S.A. de C.V. 4/16/14

Department of Health and Human Services

Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and
Research
1401 Rockville Pike
Rockville, MD 20852-1448

WARNING LETTER

April 16, 2014

CBER-14-01

UPS EXPRESS MAIL

Antonio Lopez de Silanes Perez
President and Chairman of the Board
Instituto Bioclon S.A. de C.V
Miguel Laurent No. 427
03100, Mexico City, Mexico

Dear Mr. Lopez de Silanes Perez:

The Food and Drug Administration (FDA) conducted an inspection of Instituto Bioclon S.A. de C.V., located at Calzada de Tlalpan No. 4687, Mexico City, Distrito Federal 14050, Mexico, from January 14 – 23, 2014. During the inspection, FDA investigators documented deviations from current good manufacturing practice (CGMP) requirements in the manufacture of your licensed biological drug product Anascorp® and its intermediates. Deviations from CGMP include non-compliance with 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 (BLA) approved under Section 351(a) of the Public Health Service Act (PHS Act), and Title 21, Code of Federal Regulations (21 CFR) Parts 210 and 211. 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 facility's compliance with CGMP. Significant deviations observed during the inspections include, but were not limited to, the following:

1) You failed to assure that appropriate written procedures designed to prevent microbiological contamination of drug products purporting to be sterile, are established and followed. Such procedures include validation of all aseptic and sterilization processes [21 CFR 211.113(b)]. For example:

a. Your environmental monitoring program is deficient as follows:

i. Standard Operating Procedure (SOP) P-MB-038, "Standard Operational Procedure for the Static Monitoring of the **(b)(4)** Manufacturing Area Surfaces,"

requires that surface monitoring in Aseptic Area **(b)(4)** take place only after cleaning and before starting production, **(b)(4)**, and not on a per batch basis.

ii. You do not conduct surface sampling of the table in the ISO **(b)(4)** area of Aseptic Area **(b)(4)** where manual filling of Anascorp® is performed.

iii. You do not conduct surface sampling of the trays that contain depyrogenated vials used in the production of Anascorp®. The trays containing the depyrogenated vials are manually unloaded in the ISO **(b)(4)** area of Aseptic Area **(b)(4)** prior to placing them into the ISO **(b)(4)** area.

iv. You do not perform surface sampling of the lyophilizer used in the production of Anascorp®. The interior of this lyophilizer is sanitized but not sterilized prior to use.

v. You only perform environmental monitoring of surfaces immediately after cleaning, not before.

vi. You never identify any organisms found during environmental monitoring.

b. You require media fill vials to be incubated at **(b)(4)**. However, there is no temperature control in the room where the vials are incubated.

c. Growth promotion testing of media is inadequate. Specifically, vials from media fill runs are required to be incubated at **(b)(4)**. However, growth promotion testing of the media for bacterial growth is performed at **(b)(4)**. There is no assurance that the media will support microbial growth at the media fill incubation temperature.

2) You failed to investigate the failure of a batch or any of its components to meet any of its specifications, whether or not the batch has already been distributed [21 CFR 211.192]. For example:

a. You do not document all invalidated test results, test results that fail to meet licensed product specifications (OOS), and laboratory investigations of initial and retest OOS test results.

b. You did not open a deviation or investigate rejected Anascorp® Lot **(b)(4)**.

c. No investigations are performed for Anascorp® lots that are rejected for exceeding the visual inspection reject rate.

3) You failed to assure drug products failing to meet established standards or specifications and any other relevant quality control criteria are rejected [21 CFR 211.165(f)]. Specifically, Anascorp® finished product lot **(b)(4)** was on a list of rejected lots provided during the inspection, however, it was in the computer system **(b)(4)** as an active lot being stored in the Warehouse of Retention Samples with no manufacturing status tag.

4) You failed to establish laboratory controls that include the establishment of scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that components, drug product containers, closures, in-process materials, labeling, and drug products conform to appropriate standards of identity, strength, quality, and purity [21 CFR 211.160(b)]. Specifically, you do not have SOPs that provide adequate instructions for situations that are encountered during routine HPLC setup, calibration, and use.

5) You failed to assure that each person engaged in the manufacture, processing, packing, or holding of a drug product has the education, training or experience, or any combination thereof, to enable that person to perform the assigned functions [21 CFR 211.25(a)]. For example:

a. Our investigators discovered a water bottle under one of the labeling tables in the product labeling room. As per SOP #P-PB-052, "It is prohibited to eat, drink and smoke in

the plant, only drinking is allowed outside the manufacturing areas (corridors)."

b. Your investigation confirmed that an analyst assigned to run the **(b)(4)** active air sampler did not set up and run the air sampler correctly, but labeled and incubated the plates anyway. Visual inspection of the incubated plates on January 16, 2014, did not show evidence of exposure in the **(b)(4)** active viable air sampler.

6) You failed to assure each person responsible for supervising the manufacture, processing, packing, or holding of a drug product has the education, training or experience, or any combination thereof, to perform assigned functions in such a manner as to provide assurance that the drug product has the safety, identity, strength, quality, and purity that it purports or is represented to possess [21 CFR 211.25(b)]. For example:

a. During a review of retention samples for Complaint #QC-13-002 regarding missing lot numbers and expiration dates on two product packages of Anascorp® lot **(b)(4)**, the analyst, at the direction of the supervisor, documented that "no missing batch #'s or expiration dates have been located within these samples." However, your investigation confirmed that there are no retention samples for this lot at your firm.

b. Sterility testing records for Anascorp® Bulk lots **(b)(4)** and Anascorp® Final Filled lots **(b)(4)** all show negative results for each day of the **(b)(4)** day incubation period. However, no analysts work on weekends and plates are only read Monday – Friday. An investigation revealed that microbiology personnel are instructed to record Saturday and Sunday results as negative if Monday's results are negative as well.

c. Four different company personnel performed a secondary signoff on environmental monitoring records that had no documented results.

7) You failed to assure that there are an adequate number of qualified personnel to perform and supervise the manufacture, processing, packing, or holding of each drug product [21 CFR 211.25(c)]. Specifically, during an interview, the Quality manager stated that investigations are often not conducted due to a lack of personnel.

8) You failed to perform operations within specifically defined areas of adequate size with separate control systems as are necessary to prevent contamination or mix-ups [21 CFR 42(c)]. Specifically, the room designated as "Almacén De Muestras De Retención" (Warehouse of Retention Samples) contained the following:

a. Lot **(b)(4)** of Anascorp® finished product. Additionally the product had no manufacturing status tag.

b. A partially opened box containing 800 unlabeled lyophilized vials of Anascorp® lot **(b)(4)**, documented as released in **(b)(4)**, was found stored with Anascorp® retention samples and Research and Development lots, as well as labeled and unlabeled boxes of approved, rejected, in process, and quarantined material.

9) You failed to establish time limits for the completion of each phase of production to assure the quality of the drug product [21 CFR 211.111]. Specifically, you have not established time limits for Anascorp® sterile filtration and aseptic filling.

10) You failed to retain an appropriately identified reserve sample that is representative of each lot or batch of drug product stored under conditions consistent with product labeling, selected by acceptable statistical procedures, and examined visually at least **(b)(4)** for evidence of deterioration [21 CFR 211.170(b)]. Specifically, there were no retention samples available for four of the five released lots examined during the inspection. Additionally, there are no procedures to regularly inspect retention samples at your facility.

11) You failed to assure strict control is exercised over labeling issued for use in drug product labeling operations [21 CFR 211.125(a)]. Specifically, during the inspection the packaging components warehouse door was unlocked and therefore access to the room was not limited to

authorized personnel.

Additionally, significant deviations in the manufacture of your intermediates were observed during the inspection. These deviations violate Section 501(a)(2)(B) of the FD&C Act and the requirements of your BLA approved under Section 351(a) of the PHS Act. Specific areas of concern include, but are not limited to:

ORGANIZATION AND PERSONNEL

12) Employees are not adequately trained. For example:

a. An employee dressed in an animal control uniform walked through the production gowning area without stopping to gown, and sidestepped three "antibacterial adhesive rugs" as he walked through the gowning area. He failed to follow SOP #P-PB-052, Plant Access Control, section D4.

b. An operator working in the fractionation Area had his facemask pulled down while having a conversation with another operator in the area. All employees must wear masks while working in the fractionation area as required by SOP P-PB-052.

PRODUCTION AND PROCESS CONTROL

13) You did not perform hold time studies for **(b)(4)** containers used in the manufacturing process of Anascorp®.

14) Your procedures for controlling inventory of process intermediates are inadequate. Specifically, **(b)(4)** tracks in-process intermediates as the number of potential doses **(b)(4)** x volume). However, the system does not show the actual volume, the number of containers in inventory, or **(b)(4)**, so volume cannot be back calculated.

BUILDINGS AND FACILITIES

15) The gowning area for production is also used by animal care personnel as an entrance to the animal facility. There are no procedures in place to prevent cross contamination from each facility, and the only entrance and exit to the animal facility is through production.

The deficiencies described in the Form FDA 483 issued at the close of the inspection referenced above and this letter are an indication of your quality control unit not fulfilling its responsibility to assure the identity, strength, quality, and purity of your licensed biological drug product and intermediates. FDA expects Bioclon and Rare Disease Therapeutics (RDT) to undertake a comprehensive and global assessment of all of its manufacturing operations to ensure that all products conform to FDA requirements. Please describe in detail how Bioclon and RDT will attain CGMP compliance with regard to the above observations

REVIEW OF YOUR INSPECTIONAL RESPONSES

We acknowledge receipt of your written response dated February 12, 2014, which addresses the inspectional observations on the Form FDA 483 issued at the close of the inspection of Instituto Bioclon S.A. de C.V., Mexico. Additionally, we acknowledge your commitments of corrective and preventive actions you have planned to address the above deficiencies. However, you have provided insufficient detail in your response. Further information and discussion with Bioclon and RDT will be necessary to adequately review and assess your planned actions.

To facilitate your remediation efforts, we request a meeting with you and other senior management at Bioclon and RDT to further discuss the issues cited in this letter and your proposed responses to address them.

Given the potential contributions of Anascorp® to the public health, we encourage frequent interaction between your management and technical staff with FDA to help Bioclon and RDT move forward with corrective actions as rapidly as possible.

Neither this letter, nor the observations listed on the Form FDA 483 presented at the conclusion of the inspection, is intended to be an all-inclusive list of deviations that may exist at your facilities. We remind you that it is the responsibility of Bioclon and RDT to ensure that your establishment is in compliance 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 products so that they may take this information into account when considering the award of contracts.

You should take prompt action to correct these deviations. Failure to promptly correct these deviations may result in regulatory action without further notice. Such actions may include license suspension and/or revocation.

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.

Your reply should be sent to me at the following address: U.S. Food and Drug Administration, Center for Biologics Evaluation and Research, HFM-600, 1401 Rockville Pike, Suite 200N, Rockville, Maryland 20852-1448. To schedule a meeting at your earliest convenience, please contact Robert McElwain, Consumer Safety Officer, in the Division of Case Management at (301) 827-6201.

Sincerely,
/S/
Mary A. Malarkey
Director
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research

cc:
Milton Ellis
President
Rare Disease Therapeutics, Inc.
1101 Kermit Drive, Ste 608
Nashville, TN 37217

Jennifer Spinella
VP of Regulatory Affairs and QA
Rare Disease Therapeutics, Inc.
9550 Cuyamaca Street, Suite 203
Santee, CA 92071

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