DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
19701 Fairchild Irvine, CA 92612 (949) 608-2900 Fax: (949) 608-4417 Industry Information: www.fda.gov/oc/industry	01/05/2015 - 01/15/2015* FEI NUMBER 1000160734

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED

TO: Medhat S. Gorgy, President & CEO

FIRM NAME	STREET ADDRESS
Pyramid Laboratories, Inc.	3598 Cadillac Ave
CITY, STATE, ZIP CODE, COUNTRY	TYPE ESTABLISHMENT INSPECTED
Costa Mesa, CA 92626-1416	Sterile drug and biologic manufacturer

This document lists observations made by the FDA representative(s) during the inspection of your facility. They are inspectional observations, and do not represent a final Agency determination regarding your compliance. If you have an objection regarding an observation, or have implemented, or plan to implement, corrective action in response to an observation, you may discuss the objection or action with the FDA representative(s) during the inspection or submit this information to FDA at the address above. If you have any questions, please contact FDA at the phone number and address above.

DURING AN INSPECTION OF YOUR FIRM WE OBSERVED:

QUALITY SYSTEM

OBSERVATION 1

Written records are not always made of investigations into unexplained discrepancies.

Specifically,

a. The firm did not investigate approximately (b) (4) of the action level environmental excursions which occurred in 2014. Six action level excursions out of a total of nineteen excursions were not investigated.

b. The firm did not investigate a non-viable particle excursion which occurred on 11/14/2014 in the Class 10,000 component preparation room.

OBSERVATION 2

The quality control unit lacks responsibility to approve and reject all procedures or specifications impacting on the identity, strength, quality, and purity of drug products.

Specifically, the December 2014 shut down for maintenance and repairs was not performed under formal change control procedures. The firm performed numerous activities including (b) (4) . There is no QA assessment of the activities to be performed to determine if they impact validated systems. Furthermore, there is no formal release of the facility back into production by QA based on review of required cleaning, environmental monitoring, and media fills.

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	DATE ISSUED
	Caryn M. Mcnab, Investigator Jennifer M. Gogley, Microbiologist	01/15/2015

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OBSERVATION 3

Reports of analysis from component suppliers are accepted in lieu of testing each component for conformity with all appropriate written specifications, without establishing the reliability of the supplier's analyses through appropriate validation of the supplier's test results at appropriate intervals.

Specifically, qualification of the supplier of Sodium Acetate Trihydrate Crystals, USP, used to make the (b) (4) buffer for rhPDGF-BB drug substance is inadequate:

a. Prior to August 8, 2014, Sodium Acetate Trihydrate Crystals, USP was routinely only tested for identity without establishing the reliability of the supplier's C of A. The firm's SOP W023 "Procedure for Sampling, Testing, Releasing or Rejecting of Chemical Ingredients" requires that (b) (4) [redacted].

b. Starting in August 2014, the firm began performing (b) (4) testing on (b) (4) lots of Sodium Acetate Trihydrate Crystals, USP from (b) (4) [redacted] This testing did not include verification of the supplier's test results for endotoxin.

c. The firm has not set an internal specification for endotoxin and there is no written requirement for the distrubutor to provide material from a supplier that provides endotoxin results on the C of A.

OBSERVATION 4

The quality control unit lacks authority to fully investigate errors that have occurred.

Specifically, the quality control unit does not investigate and evaluate the failure of filling operators to perform specified interventions during aseptic media fills. For example:

a. For Media Fill Lot Number PLI001-14, project number (b) (4) filled on 1/8/2014 the required interventions: (b) (4) [redacted] were not performed.

b. For Media Fill PLI Lot Number PLI042-12, project number (b) (4) filled on 6/25/2014 and 6/26/2014 the required interventions: "Jammed vials on filling line, remove", the second required "Mask change during fill, record" and the second required "Spill on filling line, stop and clean" were not performed.

c. For Media Fill Lot Number PLI055-14, project number (b) (4) filled on 9/23/2014 the required intervention: (b) (4) [redacted]" was not performed.

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OBSERVATION 5

Employees are not given training in the particular operations they perform as part of their function.

Specifically, the process to qualify employees to perform 100% visual inspection of injectable drug and/or biologic products is inadequate, in that:

a. There are no criteria for establishing and maintaining the vial inspection qualification library such as the number and type of defects required. The test library includes only (b) (4) of which are rejects.

b. Operator '(b) (4), (b) (6) was not qualified for visual inspection at the time of inspecting lots of rhPDGF-BB (a sterile biologic product) such as (b) (4) on 8/27/14 and lot (b) (4) on 9/10/14. (b) (4), (b) (6) was later qualified on 12/30/14.

c. SOP QS088 "Qualification of Visual Inspectors" holds new inspectors to a lower standard than experienced inspectors (b) (4).

d. Operator '(b) (4), (b) received a score of (b) (4) on his 4/18/13 qualification test. Although this was not his first time being qualified he was held to the standard of a new inspector (b) (4) but he would have failed if he were held to the standard of an experienced inspector (b) (4) The same operator received a score of (b) (4) on his 12/30/14 qualification, but no conclusion of pass or fail was recorded by QA.

PRODUCTION SYSTEM

OBSERVATION 6

Time limits are not established when appropriate for the completion of each production phase to assure the quality of the drug product.

Specifically, batch records for rhPGDF-BB do not specify the allowable maximum hold time and temperature conditions for storage of the prepared Sodium Acetate buffer which is used to (b) (4) the rh-PDGF-BB bulk drug substance during the (b) (4). The buffer is typically (b) (4). In addition, limits for bioburden and endotoxin have not been established and there is no in-process bioburden and endotoxin testing performed on the Sodium Acetate buffer after holding and prior to use.

OBSERVATION 7

Aseptic processing areas are deficient regarding the system for monitoring environmental conditions.

Specifically,

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a. Non-viable particulate and active viable particulate monitoring is not conducted during the shift nor during the day of filling operations in the following classified rooms: Room (b)(4) which surrounds the Class 100 filling area, the aseptic corridor, the aseptic gown room and the classified component storage room. During filling operations aseptically gowned filling operators move throughout these rooms.

b. The air volume sampled for routine non-viable particulate monitoring in the formulation and component preparation areas is insufficient to determine if the air quality meets current standards.

c. The firm's current environmental monitoring limit specifications are not based on historical data obtained from their facility and are not consistent within the classified areas. For example:

   i. The action limit specification for active viable air monitoring for the Class 10,000 aseptic gown room is (b)(4) CFU/m^3.
   ii. The action limit specification for settling plates in the Class 10,000 aseptic gown room is (b)(4) CFU/plate.
   iii. The Class 10,000 aseptic gown room used for final gowning to enter the filling operations area has an action limit of (b)(4) CFU/plate for settling plates and (b)(4) CFU/plate for surface samples compared to the Class 10,000 support rooms such as the formulation room which have action levels of (b) CFU/plate for settling plate samples and surface samples.

OBSERVATION 8

Aseptic processing areas are deficient regarding systems for maintaining any equipment used to control the aseptic conditions.

Specifically, the firm allows maintenance to (b) (4) The study entitled "Building(b) (4) (b) (4) Study" which was intended to verify that this process did not adversely impact the clean rooms did not include an assessment of particulate levels in the air following (b) (4) of the air handlers. The study does not determine the time required for the air handlers to (b) (4) the classifed rooms to a controlled state.

OBSERVATION 9

Procedures designed to prevent microbiological contamination of drug products purporting to be sterile do not include adequate validation of the sterilization process.

Specifically, the firm's (b) (4) qualifications executed in 2011 (Document #M-11-004) and 2013 (Document #M-13-001) do not include the (b) (4) of the stoppers with (b) (4); instead the firm uses (b) (4) (b) (4). The use of a(b) (4) does not challenge the ability of the (b) (4) to

adequately sterilize the surface of the rubber stoppers.

LABORATORY CONTROL SYSTEM

OBSERVATION 10

The accuracy, sensitivity, and specificity of test methods have not been established.

Specifically, the firm does not have a suitability test to support the current sterility test method used to perform release testing for rhPDGF-BB 0.3mg/ml, a sterile biologic product.

OBSERVATION 11

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.

Specifically, the firm's growth promotion testing conducted on purchased media is inadequate in that:

a. (b) (4) are the only microorganisms included in the growth promotion testing to release (b) (4) plates used for surface sampling, settling plates and active air sampling for environmental monitoring. The testing does not include a Gram negative microorganism or a yeast microorganism.

b. (b) (4) is the only microorganism included in the growth promotion testing to release (b) (4) plates used for active air monitoring. The testing does not include a yeast microorganism.

c. The media used to perform (b) (4) testing of (b) (4) samples, (b) (4), does not undergo any growth promotion testing prior to its use in the test.

EQUIPMENT AND FACILITY SYSTEM

OBSERVATION 12

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

Specifically, the firm has not performed a qualification study demonstrating that the (b) (4)

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adequately (b) (4) 3mL serum vials used for rhPDGF-BB, a sterile biologic product.

OBSERVATION 13

Written records of major equipment use are not included in individual equipment logs.

Specifically, the firm does not have individual equipment logs for the (b) (4) in building (b) (4) and the (b) (4) in building (b) (4) showing the date, time, product, and lot number of each batch processed. These pieces of equipment are used in the manufacture of rhPDGF-BB, a sterile biologic product.

*** DATES OF INSPECTION:**
01/05/2015(Mon), 01/06/2015(Tue), 01/07/2015(Wed), 01/08/2015(Thu), 01/09/2015(Fri), 01/12/2015(Mon), 01/13/2015(Tue), 01/15/2015(Thu)