DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
555 Winderly Place, Suite 200 Maitland, FL 32751 (407)475-4700 Fax:(407)475-4768	2/8/2016-2/25/2016* FEI NUMBER 1000113778

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
Ivan (nmi) Cartagena , Executive Director of Plant Operations

FIRM NAME	STREET ADDRESS
Bausch & Lomb, Inc.	8500 Hidden River Pkwy
CITY, STATE, ZIP CODE, COUNTRY	TYPE ESTABLISHMENT INSPECTED
Tampa, FL 33637-1014	Sterile Drug 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 of investigations into unexplained discrepancies do not include the conclusions and follow-up.

The following investigations pertain to non-viable particles exceeding action limits in Class A (ISO 5) locations on Aseptic Filling Lines (b) (4) during a (b) (4) period from (b) (4) (b) (4) (the start of this inspection). These lines are used in the manufacturing of approved and marketed sterile drug products manufactured at your facility such as Latantoprost Ophthalmic Solution (0.005%), Opcon-A, Ketotifen Fumarate Ophthalmic Solution (0.025%), and Tobramycin Ophthalmic Solution, USP (0.3%). Additionally, Aseptic Filling Lines (b) (4) and (b) (4) are proposed for the filling of (b) (4) (b) (4) (b) (4) that is subject of this (b) (4) inspection.

A. Specifically, 20 out of 20 Nonconformance Reports (NCRs) reviewed as well as their associated Root Cause/CAPA Investigation Reports were inadequate based on the following:

1. Investigations are not complete and potential root causes are not always identified. For example, NCRs #474179, 473135 & 473465 initiated for action level excursions for non-viable particle counts were attributed to the bottle (b) (4) and a bottle component without scientific justification. Review of the associated documentation for these NCRs revealed that as part of the investigation a sample (b) (4) . Review of the laboratory report revealed that metal particles were observed in the sample

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however there was no mention of the metal particles included in the investigation reports nor was a root cause analysis conducted to determine the source of the metal particles, product impact and a corrective action.

2. There was no scientific justification for the root cause assigned to action level excursion investigations for non-viable particle testing for aseptic filling lines. Specifically, sampling method/technique and/or the (b) (4) equipment was assigned as the root cause; however there was no scientific justification or documentation provided to verify that the sampling techniques or equipment that was used caused the elevated non-viable particle reading.

   For example, NCR #524351 states that curtain movement during the time of sampling caused the out of specification non-viable particle count, thus the NCR was classified as sampling error. However, no scientific rationale could be provided for why this was a sampling error; since during this inspection we observed on Aseptic Fill Line (b) (4) continuous curtain movement (b) (4) during the production of aseptic drug products.

B. The investigation report submitted with (b) (4) (b) (4) dated (b) (4) on Aseptic Filling line (b) (4) is not complete and does not identify the root cause or offer effective corrective action.
Two submission stability batches (Lot #'s (b) (4) and (b) (4) for (b) (4) ((b) (4) fill), failed particulate matter testing during routine stability testing (b) (4) and accelerated stability testing ((b) (4)), respectively. The investigation filed with (b) (4) states that the (b) (4) manufactured under (b) (4) did not demonstrate that the following corrective actions that were implemented (e.g., new filler change parts, bottle (b) (4) maintenance, and the preventative maintenance performed to the core rod used

during bottle molding at the bottle manufacturer) were sufficient to manufacture product in compliance with (b) (4) The investigation concludes that "additional studies are required to further evaluate potential root cause factors on the particulate levels found with the (b) (4) (b) (4) (b) (4) (b) (4) and determine corrective actions to minimize their impact." At the time of the inspection, there was an additional investigation underway to identify potential root causes; however it was in draft form.

The RC/CAPA #408329 (opened on March 3, 2014) that is associated with these submission stability failures for (b) (4) (b) (4) (b) (4) (b) (4), Lot #'s (b) (4) and (b) (4) is still open after almost 2 years and an effective CAPA has not been implemented to mitigate the risk of particulate contamination on Aseptic Filling Lines (b) (4) and (b) (4)

According to RC/CAPA #408329, the particulates identified in Lot # (b) (4) were amorphous flakes of (b) (4) and the particulates identified in Lot # (b) (4) were (b) (4), cellulose based polymer, and amorphous particulates of both (b) (4) and skin flakes. The bottle and tip for both the (b) (4) bottle and (b) (4) bottle are made of (b) (4) and the cap for both the (b) (4) bottle and (b) (4) ml bottle is made of (b) (4). The firm has (b) (4) the (b) (4) bottle ((b) (4) ml fill) from (b) (4) The (b) (4) bottle ((b) (4) fill) and the (b) (4) bottle ((b) (4) fill) are manufactured by the same process, on the same filling lines and under the same quality system. The only difference is the (b) (4) used to make the bottle and tip. There is no assurance that the (b) (4) (b) (4) (b) (4) (b) (4) bottle ((b) (4) fill) product will not also be impacted by potential particulate contamination that caused the stability failures of Lot #'s (b) (4) and (b) (4)

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C. There was no investigation conducted into the failure of the particle count test (by (b) (4) microscopic particle count method) for the post (b) (4) (b) (4) simulated use test for (b) (4) Submission stability batch (Lot # (b) (4) of (b) (4) (b) (4) (b) (4) (b) (4) (b) (4) ml bottle (b) (4) fill) failed particulate matter testing with the following results:

- 54 particles/ml ≥10µm (b) (4)
- 9 particles/ml ≥25µm (b) (4)
- 3 particles/ml ≥50µm (b) (4)

There was no investigation conducted into the failure to determine the root cause or to offer a corrective action.

D. The Nonconformance Investigation Report (NCR) # 540800 into several HEPA filters that were found leaking during the October 2015 shutdown (10/10-15/2015) and were replaced or repaired is inadequate. Specifically for Aseptic Fill Line (b) (4) the investigation states "the only area that was identified with a potential impact was (b) (4) L (b) (4) (filling line (b) (4) A NCR investigation was issued for each of the (non-viable particulate) action level results obtained on AFL (b) (4) (relevant to the leaking filters). No further actions are required at this time."

The review of the non-viable particle testing for Aseptic Fill Line (b) (4) (room (b) (4) found that there were five action level excursions between the spring and fall shutdowns of 2015, at the following locations that correspond to the locations under HEPA filters #'s (b) (4) and (b) (4) respectively that failed leak testing:

- (b) (4) – hopper bowl (dated 8/26/2015 and 9/23/2015)
- – bottle (b) (4) (dated 5/3/15, 10/2/15 and 10/4/15).

After the leak was detected, filter # (b) (4) was replaced and filter # (b) (4) was repaired. Both HEPA filters were located in areas above the (b) (4) areas with filter # (b) (4) above the (b) (4) and filter # (b) (4) above the bottle (b) (4) and conveyor area. The five action level excursions were attributed to sampling equipment or sampling error without justification

and the HEPA filters were not leak tested at the time of the excursions. As a result, it is unclear when the filters began to fail and when product may have been impacted by potential particulate contamination. Significantly, the non-viable particle testing action level excursions for Aseptic Fill Line (b)(4) were not discussed in the HEPA filter failure investigation to provide important input into the assessment of process control as it relates to non-viable particulate contamination and to the preventative maintenance program of the HEPA filters.

FACILITIES AND EQUIPMENT SYSTEM

OBSERVATION 2

Procedures designed to prevent microbiological contamination of drug products purporting to be sterile are not established , written and followed.

A. Environmental sampling is not conducted during dynamic conditions as required by SOP 72-001, section 6.5.2 that states (b)(4) Specifically, for 3 out of the 4 Environmental Monitoring samples I observed equipment was not operational while all non-viable particle samples were collected:

- On 2/10/16, Aseptic Fill Line (b)(4) filling Lot # (b)(4) (Neomycin, Polymyxin B Sulfates and Dexamethasone Ophthalmic Suspension, USP) and 5 out of the 5 Class A (ISO 100) non-viable particle air sampling locations were collected while no equipment was in operation.
- On 2/10/16, Aseptic Fill Line (b)(4) was filling Lot # (b)(4) (Neomycin, Polymyxin B Sulfates and Dexamethasone Ophthalmic Suspension, USP) and 2 out of the 5 Class A (ISO 100) non-viable particle air sampling locations were collected while no equipment was in operation.

- On 2/12/16, Aseptic Fill Line (b)(4) was filling Lot # (b)(4) (Opcon-A) and 5 out of the 5 Class A (ISO 100) non-viable particle air sampling locations were collected while no equipment was in operation.

B. The written environmental sampling program is inadequate in that there is a lack of scientific justification for sampling locations. No documentation could be provided to verify that the locations of the new (b)(4) probe bracket holders installed on your Aseptic Fill Lines (e.g., (b)(4) & (b)(4) were selected as representative locations to monitor environmental conditions (e.g., non-viable particles). In addition the use of these holders is not mentioned in your current SOP-72-001, rev 65, which dictates your environmental sampling procedure.

For example, the location of Aseptic Fill Line (b)(4)'s non-viable sampling point (b)(4) the filler (b)(4)) does not match the sampling point that was documented in your firm's Performance Qualification of the Aseptic Fill Line (b)(4) (Doc. # 009A-D-12 & Doc. #009A-12A). No documentation or scientific rationale was provided for why this sampling point was changed from its original location.

C. Smoke studies were inadequate to demonstrate unidirectional airflow and sweeping action over and away from the critical processing areas under dynamic conditions in classified areas of the ophthalmic filling area. For example, smoke studies for Aseptic Fill Line (b)(4) has not been conducted after room and equipment changes have occurred to show that changes have not adversely affected the room's unidirectional air flow during manufacturing operations (e.g., Class A curtain layout changes performed in (b)(4)).

D. There is no assurance that your firm's current method used to monitor non-viable particulates during aseptic filling is reliable. For routine manufacturing for the U.S. market and proposed for manufacturing of (b)(4) (b)(4) , the firm currently uses the (b)(4) samplers (b)(4) shift and takes a (b)(4) sample at each sampling location. Aseptic Fill Lines (b)(4) and (b)(4) both have the

capability for continuous monitoring of non-viable particles via Continuous Particle Monitoring system (b) (4) during filling.

Currently, your firm only uses the continuous particle monitoring system for routine manufacturing for products manufactured for (b) (4) markets. The firm has no justification or data to support that the (b) (4) samplers and the sample frequency is superior to continuous non-viable particulate monitoring to detect and record changes that might compromise the facility's environment and to alert personnel of such changes.

OBSERVATION 3

Equipment and utensils are not maintained at appropriate intervals to prevent contamination that would alter the safety, identity, strength, quality or purity of the drug product.

Specifically, your firm has not validated appropriate hold times that ensure equipment components and utensils that are used in aseptic fill lines are free of microbiological contamination. This includes (b) (4) (b) (4) and valves that come in direct product contact during the manufacturing of sterile drug products on aseptic filling lines at your facility.

PRODUCTION SYSTEM

OBSERVATION 4

Control procedures are not established which monitor the output of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product.

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Specifically, there is no assurance that the in-process controls established after the compounding of (b) (4) is adequate to monitor, address variability and to assure that during routine production the process remains in a state of control. The firm proposes bulk in-process tests for (b) (4); however during development, the process parameter risk assessment identified, in part, (b) (4) preparation manufacturing steps, while (b) (4) were classified as low risk. The current in-process controls do not adequately monitor the output of the manufacturing process and address potential variability.

***DATES OF INSPECTION**

2/08/2016(Mon),2/09/2016(Tue),2/10/2016(Wed),2/11/2016(Thu),2/12/2016(Fri),2/16/2016(Tue),2/18/2016(Thu),2/25/2016(Thu)

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