DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
60 Eighth Street NE Atlanta, GA 30309 (404)253-1161 Fax:(404)253-1202	6/10/2019-7/18/2019* FEI NUMBER 3008563008

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
Gary J. Brennan, Vice President of Quality

FIRM NAME	STREET ADDRESS
Exela Pharma Sciences LLC	1245 Blowing Rock Blvd
CITY, STATE, ZIP CODE, COUNTRY	TYPE ESTABLISHMENT INSPECTED
Lenoir, NC 28645-3618	Outsourcing Facility

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 I OBSERVED:

OBSERVATION 1

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

Specifically, on 6/13/2019, during the "Compounding" and "Filling" of Norepinephrine Bitartrate Injection, USP, Lot Number PROT-000656, I observed poor aseptic technique. For example,

a) During "Compounding" operations in Room 138 (Class 100,000):
   i. Operators frequently placed themselves over the open product. They reached directly across the product to reach equipment on the wall and I observed an operator's hair, covered with a hair-net, directly above the open product while she adjusted the mixing bag.
   ii. The equipment used to monitor (b) (4) was not disinfected before or in-between measurements, which required the (b) (4) be submerged in the compounded product and the (b) (4) to rest on the interior surface of the (b) (4) used for additions.

b) During "Filling" operations in Room 139 (Class 10,000) and Fill Line (b) (4) Class 100):
   i. During needle installation, I noted the operator responsible for passing the needles to the other operator had his head slightly inside the Class 100 RABS (restricted access barrier system).
   ii. The operator responsible for transferring the (b) (4) trays into the Class 100 (b) (4) was observed to open the (b) (4) bags, expose the trays in the Class 10,000 environment, and then use the exposed trays to physically part the (b) (4) surrounding the

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Class 100 (b) (4) before being taken by the operator within the Class 100 (b) (4) and placed in the Class 100 transfer cart.

iii. The operator responsible for moving filled, (b) (4) vials into the transfer trays was observed to rest her wrists on the trays and use her hand to hold the tray at the Class 100/Class 10,000 interface during operations.

iv. The operator within the Class 100 (b) (4) was not observed to sanitize her hands frequently, including after handling trays which were outside of the Class 100 conditions. During the entire filling process, I observed her sanitize her hands twice towards the end of operations and she appeared to use a minimal amount of sterile (b) (4)

OBSERVATION 2

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

Specifically,

a) EM excursions are often not associated with potentially impacted products and lot numbers. Corrective actions do not include cleaning or verification of cleaning, which is of particular concern when an investigation identifies a spore-forming organism.

b) The environmental data being captured by (b) (4)) is not routinely reviewed, tracked, or trended. (b) (4) is used to monitor temperature, relative humidity, differential pressure, and total particles. The system is only reviewed when alarms trigger due to an excursion event for differential pressure, temperature, and relative humidity.

i. Per SOP-OP-000021, Monitoring of Differential Pressures for Cleanroom Areas, a (b) (4) report will be printed and attached to each batch record for filling activities. This is not

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being performed. No similar procedures exist which require temperature and relative humidity to be printed, reviewed, and attached to applicable batch records.

c) Personnel do not always use best practices during finger-plating. On 6/13/2019, I observed numerous operators using quick, light touches on the media.

d) Gowning rooms are only being monitored for production activities if they are nearest the fill room in use (either Room 139 or Room 161). No practice or procedure is in place to preclude personnel from using either gowning room for entry to either fill room. Additionally, some products use rooms which are supported by both gowning rooms, such as Erythromycin Lactobionate, which is aseptically filled in Room 139 and (b) (4) in (b) (4) (Room 165).

e) EM sampling locations are not always representative of the air to which the vials and product are exposed. On 6/13/2019, I observed the settling plate within Fill Line (b) (4) positioned underneath the vial (b) (4)

f) Unique sampling locations have not been established for the (b) (4) Class 100 transfer carts used for aseptically transporting (b) (4) vials in the Michelle facility. (b) (4) new carts started being used on 3/1/2019. The same sample ID used for the original cart is being used for all carts and the unique cart asset number is input into the notes within the system. Individual cart results cannot be tracked and trended by the system without unique sample IDs.

OBSERVATION 3

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

Specifically,

a) During a media fill for Protocol 2018-PQ-053, an incubated vial exhibited growth and was inappropriately reclassified as non-integral, invalidating the positive result. The vial was part of

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Lot XMHA1806 and had been segregated as an integral reject prior to incubation due to it missing an over-seal but having a fully-seated stopper. The investigation found no obvious breach in the vial integrity yet concludes the vial should not have been included as an integral reject because it was missing its over-seal. The growth was not identified due to its reclassification. The investigation lacks scientific justification to invalidate the growth observed during the media fill.

b) Static and dynamic smoke studies have not been performed in Class 100 Rooms 165 and 139L showing air movement during (b) (4) loading activities.

OBSERVATION 4

Drug product containers and closures were not sterilized and processed to remove pyrogenic properties to assure that they are suitable for their intended use.

Specifically, the IV bags used for Sodium Chloride 0.9% injection, a (b) (4) product, are not purchased or rendered sterile, pyrogen-free, or particle-free.

OBSERVATION 5

There is a failure to thoroughly review any unexplained discrepancy whether or not the batch has been already distributed.

Specifically, during review of quality investigations, numerous concerns were observed. For example, regarding Sodium Bicarbonate (84 mg/mL), Lot BMHG1802, a 503B product which was "Compounded" on 7/31/2018:

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a) DEV-00238 was initiated on 7/31/2018 due to 4 alert and action level alarms for (b) (4) µm particulates during the first (b) (4) of filling, though the (b) (4) records indicate the alarms were triggered for both (b) (4) µm and (b) (4) µm sized particles. Batch documentation indicates there were numerous alarms but does not provide the approximate time every alarm sounded nor the activity which was being performed, if any, at the time of each alarm. Additionally, operators noticed a drip from (b) (4) needles, specifically, needle (b) (4) when the filler was stopped. It states there was no drip during production. There is no indication the issue was resolved and the aerosolization of dried product due to the fill-needles dripping was not considered as part of the investigation.

b) DEV-00564 was initiated on 1/2/2019 due to active and inactive ingredient data missing from the carton labeling. The investigation does not identify how much product was distributed, if any, whether the missing information was only on the carton or also on the vial label, and whether the batch was reworked.

c) DEV-00808 was initiated on 3/26/2019 for OOT particulate test results during stability testing. The OOT findings were confirmed and the shelf life was shortened from 24 months to 18 months. There is no indication that the particulates were the result of a compound coming out of solution. The investigation does not include an assessment of DEV-00238, which was initiated for high particulates during filling. Additionally, during OOT investigative testing, an OOS particulate level was identified for (b) (4) µ counts for Sodium Bicarbonate, Lot BMHG1802. No actions were taken in response to this OOS finding.

OBSERVATION 6

Batch production and control records do not include complete information relating to the production and control of each batch.

Specifically,

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a) During review of the batch documentation for Erythromycin Lactobionate (500 mg/vial), 20 mL vial, (b) (4) batch, Lot CMHG1822, "Compounded" on 7/19/2018, which has not been released, I noted the following:

i. During "Compounding" Step (b) (4) the operators did not follow the recommended instructions for the addition of the erythromycin base, an API, by adding it in (b) (4) divisions with a (b) (4) stir time for each division. The recommended method for API addition would result in a minimum of (b) (4) and this batch had the erythromycin added over (b) (4) Additionally, later in this step, the mix start- and end-time are recorded, but there is no verification the mix time does not exceed the (b) (4) maximum mixing time specified in bold within the instructions.

ii. There is no verification the unfiltered, bulk solution was maintained at less than (b) (4) prior to being (b) (4) into the holding bag/vessel. Per the manufacturing specification, this is a temperature sensitive product and it can be held up to (b) (4) hours prior to transfer provided it is (b) (4) , held under (b) (4), and under (b) (4) . There is no data for bulk product temperature after its Q.S. to final weight at approximately (b) (4) on 7/25/18. (b) (4) began at (b) (4) on 7/25/18.

iii. During a routine vial fill-weight check, a vial was taken from Tray 6 and was found to have a weight of 8.57 g. The reject limit for low fill-weight is (b) (4) g. No actions were taken in response to this result. The previous fill-weights were taken from Tray 3 and the subsequent fill-weights were taken from Tray 9. Each tray holds somewhere between (b) (4) and (b) (4) vials, meaning potentially hundreds of vials had unidentified low fill-weights. This is a (b) (4) product making identification of impacted vials only possible for gross under- or over-fills during visual inspection.

iv. The interventions record for this batch indicates there were fallen vials with product in them during the filling of vials loaded in Tray 8 and Tray 20. There is no documentation indicating cleaning occurred, how long the Class 100 RABS was open during cleaning, or that vials were cleared from the line in response to a cleaning intervention.

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b) On 6/13/2019, during the filling of Norepinephrine Bitartrate Injection, USP, Lot Number PROT-000656, I observed numerous interventions into the Class 100 RABS and noted there was no documentation of the interventions made in the record. Toward the end of the batch, I noted a total of 2 entries into the RABS had been documented. I had seen at least 10 different entries for stopper loading, stopper jam clearing, and vial jam clearing.

OBSERVATION 7

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

Specifically, the Class 100 (b) (4) Exela Asset OP4015.018, used to provide ISO 5 grade air during (b) (4) vial transfer, has not been fully certified. The (b) (4) also referred to as the (b) (4) or the Portable Class 5 Enclosure, has failed for (b) (4) testing during the previous two certifications, performed in August 2018 and February 2019. The certification report indicates the acceptance criteria is NLT (b) (4) air changes per hour. The results were 172 air changes per hour and 223 air changes per hour, respectively.

Additionally, SOP-VA-000002, Certification of HEPA Filters, indicates the (b) (4) should be tested per the (b) (4) test with an acceptance criterium of (b) (4) per minute at (b) (4) from the filter face. The previous two certifications were performed for air changes per hour.

The test failures and use of the incorrect test criteria were not identified. Both certification reports were reviewed and signed by Exela personnel.

***DATES OF INSPECTION**

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6/10/2019(Mon), 6/11/2019(Tue), 6/12/2019(Wed), 6/13/2019(Thu), 6/18/2019(Tue), 6/19/2019(Wed), 6/20/2019(Thu), 6/21/2019(Fri), 7/08/2019(Mon), 7/09/2019(Tue), 7/10/2019(Wed), 7/11/2019(Thu), 7/15/2019(Mon), 7/18/2019(Thu)

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