DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
12420 Parklawn Drive, Room 2032 Rockville, MD 20857	06/03/2024-06/14/2024
	FEI NUMBER 3001623073

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
Mr. Jerad Holcomb, Vice President of Quality

FIRM NAME	STREET ADDRESS
Jubilant HollisterStier General Partnership	16751 Rte Transcanadienne
CITY, STATE, ZIP CODE, COUNTRY	TYPE ESTABLISHMENT INSPECTED
Kirkland, H9H 4J4	Sterile Products 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:

OBSERVATION 1

The statistical quality control criteria fail to include appropriate acceptance levels and rejection levels.

A. Your firm failed to perform an adequate evaluation for (b) (4) Ointment (b) (4) g/(b) (4) kg, lot (b) (4) Expiration Date July 2025, and partially released the batch without justification.

For example:

1. You filled (b) (4) lot (b) (4) from (b) (4) and at the time of set-up on (b) (4), non-viable particle (NVP) alert and action limit alarms were detected through your Particle Measurement System (PAS) for particles ≥(b) (4) µm. Your firm reviewed the alarms as part of your routine procedure and during batch review for release you reviewed the PMS data report, which not only showed alert and action limit excursions for particles ≥(b) (4) µm but also showed alert and action limits were exceeded for particles ≥ (b) (4) µm. However, you failed to identify these alarms during review of your PMS data reports. Your PMS sampling reports were reviewed by production and approved on February 20, 2024, by your Quality Unit.

2. On March 05, 2024, during a batch retrospective review, you found (b) (4) lot (b) (4) had NVP alarms exceeding both alert and action level limits for particles ≥(b) (4) µm, which were not initially recognized at the time of filling. Investigation PR 230970 was opened to evaluate the alarms and as part of your investigation you identified two (2) events where particles exceeded action limits for ≥(b) (4) µm. However, your review was inadequate because your PMS NVP data report showed there were approximately 85 alert excursions and approximately 36 action level excursions during the filling of lot (b) (4) at (b) (4), which were not defined in your investigation. Furthermore, your corrective action (CAPA) was to reject (b) (4) baskets of product (i.e., baskets (b) (4)) for this lot. However, your investigation lacks supporting justification

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		Jose E Melendez, DDC Investigator Crystal Monroy, Investigator Philip F. Istafanos, Microbiologist	June 14, 2024

for the rejection of selected baskets and your CAPA is inadequate as your procedures do not define allowing a partial release of a batch as a corrective action following an investigation.

3. On March 11, 2024, you opened Investigation PR 231442 for (b) (4) lot (b) (4) due to 100% visual inspection showing a result of (b) (4)% ((b) (4) units out of (b) (4) inspected units) for critical defects. In your investigation you state there was a compromised seal integrity with your primary packaging and the root cause was due to an equipment malfunctioning issue. Nonetheless, in your impact assessment you state there is no impact to (b) (4) lot (b) (4) because 100% visual inspection was carried out and because your AQL was conforming. However, your investigation states there are no established reject limits for your product, including reject limits for critical defects. Furthermore, during review of the batch record it was determined your firm had completed over (b) (4) units of product leaving approximately leaving (b) (4) units unaccounted for 100% visual inspection.

Repeat Observation

(B) Your visual inspection program is deficient in that you have failed to establish limits for you for destructive testing in your (b) (4) sterile products (i.e., topical solutions and ointment) and in your 100% visual inspection of your (b) (4) sterile ointment products. Although your firm has initiated supplemental destructive testing in your sterile (b) (4) products and begun 100% visual inspection for your (b) (4) ointments, your tests are currently for informational purposes. You stated that to establish your limits, you need (b) (4) batches for each product; however, according to your Quality Director, it may take approximately (b) (4) year to complete your destructive testing assessment for topical solutions and up to (b) (4) years to complete your destructive testing and 100% visual inspection assessment for your topical ointments.

Repeat Observation

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OBSERVATION 2

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

Specifically,

A. Your Quality Control Unit (QCU) did not conduct a thorough evaluation and implement appropriate and effective corrective actions in a timely manner for alarms observed in your Nonviable Particle Measuring System located in your aseptic fill areas. From November 14, 2023, to March 1, 2024, particle counter alarms were inaccurately assessed in at least (b) (4) batches due to incorrect limits set up in the particle counter. Of the (b) (4) batches 13 had critical alarms exceeding alert and action limits that were not identified for particles ≥ (b) (4) µm.

Your firm investigated as part of PR 230695 and attributed this discrepancy as a validation error due to incorrect limits being placed in your Particle Measuring System (PMS). However, your firm failed to carry out a comprehensive assessment of your alarm review process to establish actions for preventing reoccurrence within production and quality oversight.

1. You do not evaluate the complete nonviable particulate data reports for all the batches you manufacture in your aseptic processing rooms. Your firm reviews summary reports of alarms for (b) (4) batch prior to release; however, you only review the complete nonviable particulate data reports if the summaries show alert and action limits are exceeded during batch production.

2. Your firm does not perform a verification check to ensure the limits for the particle counter system are accurate prior to production in your aseptic processing rooms.

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B. Environmental Monitoring investigations for action limits excursions in Grade A area were found to be deficient.

1. Investigation PR 234186 was opened on April 05, 2024, for an action-level result of 1 CFU for a surface sample taken on a (b) (4) in the (b) (4) zone in the Grade A air supply area of the (b) (4) room (b) (4) The following deficiencies were noted in your investigation:

a. Your investigation does not define the actions take to address the excursion within the Grade A area such as cleaning. There is no documentation as part of your investigation to verify cleaning was performed for the room following this excursion.

b. Your firm does not document the locations where (b) (4) are sampled within the (b) (4) area. According to Working Instructions JHSM-SOP-2003INS13, Revision 23, Effective Date Apr 30, 2024, Sampling Plan in (b) (4) Filling, Manufacturing and (b) (4) Room (b) (4), the sampling of (b) (4) in the (b) (4) zone is to be at a random location. You do not document the (b) (4) or location on the (b) (4) and there is no way to know if your resample was taken on at the same location as your initial sample that resulted in the action limit excursion.

2. Investigation PR 223437 was opened on December 21, 2023, for an action-level result of (b) CFU personnel monitoring (finger-dabs) for an environmental monitoring quality inspector during the filling setup of (b) (4) (b) (4) (b) nL, lot (b) (4) As part of the investigation, you performed a risk assessment and determined the organism identified, Pseudombrophila sp. (Heydenia sp.), was a high-risk organism and you rejected this batch. Your investigation is deficient in that, although your firm rejected the batch, you failed to establish the overall impact this excursion had to your Grade A area. You did not define the actions taken or provide evidence showing you address the excursion within the Grade A area to ensure a high-risk organism does not affect your aseptic processing core.

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OBSERVATION 3

Separate or defined areas to prevent contamination or mix-ups are deficient regarding operations related to aseptic processing of drug products.

A. There is no assurance that the current flow of personnel through the different rooms in the aseptic area is designed to prevent microbial contamination in the aseptic core. Your current procedures require personnel to leave the aseptic processing room and its critical areas and travel through the shared corridors to perform activities during manufacturing operation.

For example:

1. JHSM-SOP-2003INS17, Revision 15, Effective date Dec 18, 2023, procedure for "Sampling Plan- Gown and Gloves Monitoring", requires (b) (4) [redacted] (room [redacted] for (b) (4) [redacted] Your aseptic area is not designed with methods to prevent operators from (b) (4) [redacted] the aseptic processing rooms. In addition, operators can remain in the corridors (b) (4) [redacted] the aseptic processing rooms.

2. JHSM-SOP-1072, Revision 20, effective date Nov 15, 2023, procedure for "Good Manufacturing Practices and Gowning Procedure for the Aseptic Zones" requires personnel to "(b) (4) [redacted]" located at the (b) (4) [redacted] aseptic area in room (b) (4) [redacted] To change (b) (4) [redacted] personnel must leave the aseptic processing room and the critical areas and enter the shared corridors to the (b) (4) [redacted]. The corridors are uncontrolled areas and personnel working in different rooms cross paths in the corridors. Moreover, your firm does not record the number of times operators leave the aseptic processing rooms to change their damaged (b) (4) [redacted]

3. JHSM-SOP-1072, Revision 20, effective date Nov 15, 2023, procedure for "Good Manufacturing Practices and Gowning Procedure for the Aseptic Zones" requires (b) (4) [redacted]

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(b) (4) Although entry and exit to the aseptic area is documented, you do not document the reasons for exit including if your operators left the aseptic area due to (b) (4) issues.

The distance between the fill rooms to the (b) (4) room (b) (4) and (b) (4) room (b) (4) is below:

Aseptic Processing Room Room # (b) (4) b) (4) (b) (4) b) (4) (b) (4)

B. Differential pressure is not being monitored in the Grade A area of the (b) (4) filling line, Room (b) (4). Your firm only monitors the Grade B room differential pressure and the adjacent (b) (4) Room (b) (4), and you monitor differential pressure for your (b) (4) which is in the Grade C area. However, you have not established a system to continuously monitor differential pressure within the aseptic core to ensure a positive differential pressure is continuously maintained during (b) (4) filling operation.

C. The design of your (b) (4) line located in Filling Room (b) (4) and the flow of your manufacturing operators throughout the Grade A/B areas do not provide adequate protection, separation, and controls to prevent the risk of contamination of your aseptically filled sterile drug products.

For example,

(b) (4) Human-Machine Interface (HMIs) panels are located (b) (4) (b) (4) line (Grade A area) in Room (b) (4) where sterile drugs are filled. These HMI panels act as the interface between your manufacturing operators and the (b) (4) filling line zones (i.e., filling, (b) (4) and (b) (4), which operate within the aseptic core. Operators were observed in direct contact with the interface located in the filling zone (Grade A area) at least three (3) times in a period of (b) (4) during filling of the (b) (4) (b) (4) mg/(b) (4) ml vial; lot (b) (4)

The distance of the HMIs and the conveyor in the different aseptic processing zones are:
(b) (4)

The current design of the (b) (4) line does not prevent potential contamination originating from the HMI panels themselves, since any particles emitted by the panels could compromise the cleanliness of the aseptic core. Each time a process parameter is monitored or adjusted; the manufacturing operator regularly enters the aseptic core of the (b) (4) line.

OBSERVATION 4

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

A. The aseptic process simulations (media fills) performed in (b) (4) filling line does not simulate the actual commercial aseptic filling process.

Specifically,

1. Operators do not record or document in your commercial batch records routine corrective interventions if such interventions have a duration of (b) (4). Similarly, your operators do not record filling line stops. Additionally, none of the microbiological interventions performed during EM monitoring of the commercial filling are documented in the commercial batch records. Therefore, there is no assurance that the frequency at which such interventions are simulated during aseptic process simulation is a true representation of your commercial filling.

2. The manufacturing operator can perform (N) times the same routine corrective intervention and it will not be documented if it is carried out within (b) (4). Frequency of the interventions is currently based

on the number of manufacturing operators needing qualification. Each operator performs a media fill intervention (b) (4) time during the media fill to be qualified.

3. There are instances in which multiple interventions are carried out within the aseptic core and not documented. For example, on June 3, 2024, we observed the commercial filling process of the (b) (4) (b) (4) (b) (4) mg/(b) (4) ml vial; lot (b) (4) on (b) (4) filling line. That day an operator was observed removing an empty vial from the conveyor just before the filling area. Then, the same operator went to the stoppering station and performed the "stopper sensor adjustment" intervention.

4. PR 220186 was initiated on November 22, 2023, due to a finger dab sample showed an action-level result of (b) (4) CFU of Micrococcus luteus during the filling activities of (b) (4) ; lot (b) (4) . According to PR 220186, the sample was taken after an intervention in the Grade A area (b) (4) in the topical filling room (b) (4) However, this intervention is not documented in the batch records of (b) (4) mL (b) (4) L; lot (b) (4) .

Repeat Observation

B. All integral filled units are not incubated during the process simulation study. For example, Media Fill Batch Records (MFBR) (b) (4) mL; lot (b) (4) reports that (b) (4) vials were manually removed during the filling portion of the media fill run. However, MFBR lot (b) (4) does not document the specific cause that compromised the integrity of the vials that were manually rejected during the aseptic process simulation.

C. The air flow pattern study [a.k.a. smoke studies] conducted in accordance with Report: (b) (4) (b) (4) (b) (4) , titled "Operational Performance Qualification Report For HVAC System 52 Over The Filling and Loading/Unloading Area (In Operation, With Interventions)", approved on July 19, 2021, is inadequate.

Specifically,

- Sufficient smoke is not generated to allow demonstrate flow laminarity during filling.

- There are interventions where the smoke source is not positioned to allow sufficient smoke to enter the airflow over the operator/tools (e.g., forceps) during the intervention to visualize the impact of this activity on the airflow.

- There are interventions in which the video camera is placed behind the operator and the impact of the intervention on the airflow cannot be visualized.

- There are interventions in which the video camera is too close to the operator's hands and the impact of the intervention on the airflow cannot be visualized.

- There is no assurance that in critical areas of the (b) (4) line unidirectional airflow is delivered to the point of use. The distance between the HEPA filters and floor is about (b) (4) and the distance between the HEPA filters and the (b) (4) filling line (b) (4) is approximately (b) (4) During the airflow evaluation for dynamic conditions, the smoke source was positioned at the (b) (4) or at the (b) (4) The study does not include an evaluation of the airflow patterns from the HEPA filters to critical areas, including areas (b) (4) to demonstrate a unidirectional airflow pattern and (b) (4) under dynamic conditions. Additionally, there is no documented evidence of air velocity at the critical (b) (4) and at HEPA filters when evaluating (b) (4) line airflow pattern under dynamic conditions.

Repeat Observation

D. Inadequate aseptic behavior pattern during commercial filling of the (b) (4) (b) (4) mg (b) (4) ml vial; lot (b) (4) on the (b) (4) filling line.

Specifically,

- We observed two (2) manufacturing operators and one (1) microbiologist within the aseptic core (Grade A area) during the filling process of lot (b) (4) The two manufacturing operators were observed in the (b) (4) zone while the microbiologist was observed in the filling zone of the (b) (4) line, respectively.

- We observed that two (2) operators at different times performed the (b) (4) intervention in the (b) (4) zone. This intervention was performed approximately (b) (4) using the (b) (4) for the intervention. The equipment was never wiped after the intervention.
- (b) (4) line (b) (4) repeatedly overlapped when operators exited the aseptic core. We observed one (1) manufacturing operator touching the (b) (4) with his elbows several times trying to adjust them

OBSERVATION 5

Each batch of product required to be free of objectionable microorganisms is not tested through appropriate laboratory testing.

Your QC laboratory does not follow the United States Pharmacopeia (USP) compendium for finished drug product sterility testing in that the product that cause turbidity of the media are not further tested after the original 14 days incubation as per the USP. According to the USP chapter <71> Sterility Test, "*If the material being tested renders the medium turbid so that the presence or absence of microbial growth cannot be readily determined by visual examination, 14 days after the beginning of incubation transfer portions (each not less than 1 mL) of the medium to fresh vessels of the same medium, and then incubate the original and transfer vessels for not less than 4 days*".

For example:

A. (b) (4) (b) (4) Ointment (b) (4) % (b) (4) g lot (b) (4) tested for sterility on (b) (4), and (b) (4) read on However, there is no assurance that product will show result as expected (i.e., no growth) after subculture. Your QC laboratory completed the sterility test without any further testing. The reading of the test was observed on (b) (4)

B. (b) (4) Ointment (b) (4) g, lot (b) (4) manufactured on (b) (4) and shipped to the USA was tested for sterility and released after the 14 days of incubation.

OBSERVATION 6

Laboratory controls do not include the establishment of scientifically sound and appropriate test procedures design to assure that in process materials conform to appropriate standards of quality and purity.

A. Control procedures SOP # JHSM-MOA-000199, "Bacterial Endotoxin Test-LAL Gel-Clot Method" Rev. 16, effective 31 May 2023, SOP # JHSM-MOA-000194, "Bacterial Endotoxin Test Using the LAL Kinetic Turbidimetric System" Rev. 10, effective 09Mar 2023 and SOP # JHSM-MOA-000198, "Bacterial Endotoxin Test Using the LAL Kinetic Chromogenic System" Rev. 12, effective 09Mar 2023 do not state any instructions of how to mix the samples to be tested for endotoxin before they are tested for endotoxin.

For example:

1. During the observation of the endotoxin testing of (b) (4) samples of (b) (4) from a cleaning validation of (b) (4) lot number (b) (4) by Kinetic method on 06/05/2024, the analyst did not (b) (4) before a portion of (b) (4) sample was taken for the analysis.

2. During the observation of the endotoxin testing of (b) (4) samples, by Gel Clot method on 6/11/2024, a different analyst did not (b) (4) before a portion of (b) (4) sample taken for the analysis.

3. During the observation of the endotoxin testing of (b) (4) injection (b) mg/vial by gel clot method, on 06/12/2024, the analyst did not (b) (4) (b) (4) The product was transferred to a tube for testing immediately after (b) (4)

B. Your QC laboratory uses (b) (4) in the (b) (4) process of the (b) (4) utensils used in the endotoxin test of products, (b) (4) and cleaning validation samples. The (b) (4) is set at (b) (4) °C. The (b) (4) runs for (b) (4) as per the Qualification Study # (b) (4) B-206 SAP-QS-

B206-EU-PRPQ-4206 performed in April 2022. Your QC laboratory does not verify the (b) (4) the (b) (4) during the (b) (4). There is no way to measure/monitor the (b) (4) during the (b) (4) (b) (4). In addition, there is no control procedure for the use of this equipment.

OBSERVATION 7

Each batch of drug product required to be free of objectionable microorganisms is not tested through appropriate laboratory testing.

Your QC laboratory uses unvalidated method to disinfect product containers by (b) (4) (b) (4) Standard Operating procedures (SOP) number JHSM-MOA-000205, Method No. 999997. "Procedure for Sterility Testing" Rev.41, effective 29Nov.2023, states that (b) (4) (b) (4)

Your latest logbook for disinfection (b) (4) started on April 22, 2023, indicated the (b) (4) product to be tested. In addition, the logbook does not indicate how long each product was (b) (4). The following are examples of products disinfected using this (b) (4) disinfection method:

(b) (4)

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OBSERVATION 8

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

A. Your Environmental Monitoring program is inadequate to assess the conditions of your aseptic processing environment and the ancillary clean areas.

For example:

1. Your environmental monitoring program does not cover all critical surfaces of the aseptic core, including the floors, walls, and all (b) (4) of your Grade A and Grade B areas.

2. Your firm does not investigate Environmental Monitoring alert and action level excursions that occurred in areas outside of your aseptic processing zones. You perform environmental monitoring in Grade B and Grade C areas per JHSM-SOP-2003, Revision 21, effective date Apr 05, 2024, for Environmental Monitoring-Sampling Plans and Conditions; however, when alert and action limits occur your Work Instruction, JHSM-SOP1396INS02, Revision 19, effective Apr 02, 2024, for Viable Monitoring Requirements and Steps to Follow, states that you do not investigate an alert or action level excursion unless it occurred within an aseptic processing room. Furthermore, excursions where objectionable microorganisms are identified in Grade B and C areas are not investigated unless they occur in the aseptic processing rooms.

3. Your firms environmental monitoring alert and action levels are based on recommended guidance data and not based on your facilities historical environmental monitoring and trends data. For example, your action limit for active air sampling in Grade C area is > (b) (4) cfu/m3 and alert limit is > (b) (4) cfu/m3. However, in the past 2 years, you have exceeded your alert level limits approximately 87 times, but your active air excursion levels have remained below (b) (4) cfu /m3 in the Grade C area.

B. Your procedures for personnel sampling and monitoring are deficient in that you do not monitor all areas of personnel gowning that interact with the aseptic core areas. JHSM-SOP-1072, Revision 20, effective date Nov 15, 2023, procedure for "Good manufacturing practices and gowning procedure for aseptic zones" states that personnel use elbow or forearms to move the curtains to access the Grade A areas. However, your sampling plan

for Gown and Gloves Monitoring, JHSM-SOP-2003INS17, Revision 15, Effective date Dec 18, 2023, does not require elbows to be monitored for personnel gowning. On June 03, 2024, during aseptic filling of (b) (4) (b) (4) (b) (4) mg/(b) (4) ml vial; lot (b) (4) operators were observed to be using their elbows to enter and exit the Grade A area and use their elbows in consecutive motion to adjust the (b) (4) separating the Grade A and B areas of the (b) (4) filling line.

C. Sampling plan- Glove and Gowns monitoring, JHSM-SOP-2003INS17, Revision 15, Effective date Dec 18, 2023, is inadequate in that it does not define the types of interventions that would require glove sampling. Diagrams (b) (4) of Appendix (b) in your SOP list the "major interventions" for each filling line that would require glove monitoring; however, the lists do not describe these interventions. For example, Diagram (b) (4) for the (b) (4) Line (Room (b) (4) states major interventions during filling (b) (4) as (b) (4) (b) (4) These descriptions do not provide adequate information to establish the types of interventions require glove monitoring.

D. Your report for Environmental Monitoring locations assessment for Aseptic Grade A classification, Document # S-VARIOUS-EU-ST400, approved March 22, 2019, used to re-assess the current environmental sampling locations for classified Grade A environments, including the location of your (b) (4) within the (b) (4) filling line Room (b) (4) Grade A areas was found to be inadequate.

1. In your assessment, you defined (b) (4) critical points for filling and (b) (4) critical points for caping in your (b) (4) filling line. Your assessment is deficient in that there is no documented evidence in the report defining the critical operations, such as operator interventions, within each critical point and how these operators were are evaluated to consider the current locations of the (b) (4) . Furthermore, your assessment is based on the review of movement of personnel in dynamic smoke studies, however, your smoke studies were found to be inadequate (See Observation 4).

2. Your firm established a minimum of (b) (4) sampling locations in your (b) (4) line Grade A located in the following areas: (b) (4) (b) (4) . However, your assessment does not capture the overall impact of the distance between each (b) (4) locations from the critical

operations to ensure accurate monitoring of NVP during the routine filling commercial process in the (b) (4) line. The distance between each (b) (4) is as follows:

(b) (4)

OBSERVATION 9

Written procedures describing the handling of complaints do not include provisions for review by the quality control unit of any complaint involving the possible failure of a drug product to meet any of its specifications and a determination as to the need for an investigation of any unexplained discrepancy.

Your Quality Unit did not conduct a thorough evaluation or establish corrective and preventive actions (CAPAs) in a timely manner to address the complaints received for (b) (4) Injection (b) (4) mg/vial (b) (4) mg drug product.

For example, from the period from June 16, 2022, to April 29, 2024, your firm received multiple consumer complaints related to the presence of (b) (4) particles in vials from (b) (4) lots (i.e., (b) (4) (b) (4) of (b) (4) Injection (b) (4) mg/vial (b) (4) mg drug product.

For all the cases, your Quality Unit concluded that the (b) (4) piece was most likely a fragment of the (b) (4) stopper of the (b) (4) vial, which would have been improperly (b) (4) with the (b) (4) during product (b) (4) causing a coring defect. Therefore, no CAPA was implemented. However, as part of the complaint investigations, control samples were never (b) (4) to confirm whether the identified defect was caused during product (b) (4) or is associated with the quality attributes of the (b) (4) stopper. Only a visual examination of the control samples has been carried out. Your Quality Unit states that incoming testing carried out on the (b) (4) stopper yielded the expected results. However, these testing focus on the physical attributes (e.g., size, dimensions) of the stoppers and not their functionality. You only perform functionality testing to the (b) (4) stopper during the qualification of your supplier.

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12420 Parklawn Drive, Room 2032 Rockville, MD 20857	06/03/2024-06/14/2024
	FEI NUMBER 3001623073

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
Mr. Jerad Holcomb, Vice President of Quality

FIRM NAME	STREET ADDRESS
Jubilant HollisterStier General Partnership	16751 Rte Transcanadienne
CITY, STATE, ZIP CODE, COUNTRY Kirkland, H9H 4J4	TYPE ESTABLISHMENT INSPECTED Sterile Products Manufacturer

OBSERVATION 10

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

Your firm performs aseptic filling on (b) (4) filling. The aseptic core of this filling line is protected by (b) (4) (b) (4) To carry out the aseptic process interventions, the manufacturing operators must enter inside the aseptic core (Grade A) through the (b) (4) The classification of the filling Room (b) (4) is Grade B.

On 03 June 2024, we observed the commercial filling process of (b) (4) (b) (4) mg (b) (4) mL vial; lot (b) (4) Numerous operator interventions were observed in production, which were not documented in the manufacturing batch records. The following operator activities/interventions were observed within a period of (b) (4) (b) (4).

For example,

- We observe three (3) manufacturing operators within the aseptic core simultaneously. There is no maximum number of operators that can enter the Grade A area at the same time.
- There is no documentation in the batch records about the microbiological interventions performed during EM monitoring of the commercial filling.
- An operator was observed removing an empty vial from the conveyor just before the filling area. Then, the same operator went to the stoppering station and performed the (b) (4) intervention.
- The filling line was stopped, and an operator was observed wiping the (b) (4) with a wipe sprayed with (b) (4).
- The filling line was stopped, and an operator was observed wiping the (b) (4) (b) (4) with a wipe sprayed with (b) (4).

- An operator was observed removing an empty vial from the conveyor just before the filling area (2 times).
- An operator was observed removing an empty vial from the (b) (4) (3 times).
- Operators were observed performing the intervention identified as (b) (4) in the stoppering area approximately (8 times). During this intervention, the operator must (b) (4)

Additionally, your current practice is to not document routine corrective operator interventions that show a duration of less than (b) (4) in commercial batch records. The same approach applies to filling line stops.

OBSERVATION 11

Written procedures for cleaning and maintenance fail to include parameter relevant to the operation Specifically,

Your firm does not use sterile disinfectants to clean the aseptic processing and filling areas. As per your SOP # JHSM-SOP-1131, Preparation of Cleaning Solution and Disinfectant, Revision 10, effective, 14 June 2023, (b) (4) (b) (4) (b) (4)

For example:

A. (b) (4) lot (b) (4) (b) (4) prepared on June 02, 2024. This solution was used to disinfect Room (b) (4) filling area.

B. (b) (4) lot (b) (4) (b) (4) prepared on June 06, 2024, and used to disinfect Room # (b) (4) filling room for (b) (4) sterile products.

C. (b) (4) lot (b) (4) (b) (4) prepared on June 16, 2024, to disinfect Room (b) (4) (b) (4) filling area.

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OBSERVATION 12

Aseptic processing areas are deficient regarding the system for cleaning and disinfecting the equipment to produce aseptic conditions.

On June 10, 2024, we observed (b) (4) line cleaning activities in Room (b) (4) This line is used for aseptically filled (b) (4) products and sterile liquids for the US market. As part of the cleaning activities, the manufacturing operator was cleaning the capping area of the line. The operator was observed cleaning the conveyor in the capping area with a (b) (4) wipe containing a cleaning solution. Once the operator finished cleaning the conveyor, the cloth was observed with (b) (4) stains.

According to Production Manager, the (b) (4) spots are apparently "*accumulated residues*" in sections of the conveyor that manufacturing operators do not have access to during manual cleaning. Specifically, it was explained that during cleaning the (b) (4) cleaning solution is used, and this solution causes "accumulated residue" to come out of the conveyor during cleaning.

OBSERVATION 13

Each lot of a component that is liable to microbiological contamination that is objectionable in view of its intended use is not subjected to microbiological tests before use.

Your firm failed to test the purchased sterile components used to produce the sterile (b) (4) and sterile (b) (4) ointment, for sterility before use. Your firm only relies on the Certificate Of Analysis (COA) received from the vendor.

For example,

A. The (b) (4) sterile (b) (4) ml bottles, (b) (4) sterile (b) (4) and (b) (4) sterile cap-(b) (4) ml used to produce (b) (4) USP.
B. The (b) (4) sterilized (b) (4) g sterile tubes used to produce (b) (4) ointment.
C. The (b) (4) sterilized bottles, (b) (4) and caps used to produce (b) (4) solution.

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE *(Print or Type)*	DATE ISSUED
		Jose E Melendez, DDC Investigator Crystal Monroy, Investigator Philip F. Istafanos, Microbiologist	June 14, 2024

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OBSERVATION 14

Procedures describing the calibration of instruments, apparatus, gauges and recording devices are not written.

Your QC laboratory uses Previ-Color Gram, a gram staining automated machine from BioMerieux, Equipment #JH-U577 to perform gram stain test. Your QC laboratory failed to qualify this equipment before use, there was no Installation Qualification (IQ), Operational Qualification (OQ) or Performance Qualification (PQ) performed.

This automated gram stain machine is in your identification laboratory and is used routinely in the identification process of all organisms detected across your facility. There are 1,796 organisms identified in 2022, 1,474 organisms identified in 2023 and 569 organisms identified in 2024 until now.

OBSERVATION 15

Reserve samples from representative sample lots or batches of drug products selected by acceptable statistical procedures are not examined visually at least once a year for evidence of deterioration.

Your procedures for Annual Inspection of Reserve Samples, JHSM-SOP-1502INS03, Revision 07, effective date June 08 2022, are inadequate in that you do not perform a review at least once a year for all your products on reserve during their shelf life.

For example, on June 13, 2024, during a walkthrough of your retains warehouse, it was determined that (b) (4) (b) mg/ml, lot (b) (4) expiration date (b) (4) was not reviewed by your Quality Unit as part of your annual inspection. The lot was manufactured on (b) (4) and (b) (4) units were placed on reserve on (b) (4) The shelf life of this product is (b) (4).

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