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	10/28/2021-11/10/2021*
	FEI NUMBER 3015685305

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
Mr. Srinivas Avirneni, Head Site Operations

FIRM NAME	STREET ADDRESS
Alembic Pharmaceuticals Limited	Formulation Division Iii, Plot No. 779p/790p, Village - Karakhadi, Taluka - Padra
CITY, STATE, ZIP CODE, COUNTRY Vadodara, Gujarat, 391450 India	TYPE ESTABLISHMENT INSPECTED 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:

OBSERVATION 1

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

Specifically, your firm failed to fully qualify and validate critical process equipment and processes used in the manufacture of sterile products which may cause variability in the characteristics of the in-process material and sterile drug product. Your firm failed to provide assurance through empirical scientific data and qualification and validation of critical equipment and processes that your processes have the ability to product sterile products that are safe for their intended use. For example, but not limited to the following:

A. Your firm failed to conduct cleaning validation for non-dedicated Line (b) (4) (b) (4) filling and (b) (4) where the following application products are manufactured:

(b) (4)

And submitted pending application:

(b) (4)

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B. Further, cleaning validation procedure, "F3/QA/SOP/0056, Cleaning Validation, Version 1.0, Effective Date: 13 Sept 2021", establishes in section 4.4.2, "Cleaning validation shall be performed on (b) (4) batches of each product. The acceptance limits generated through cleaning validation (software) CLEEN for each product shall be followed to check reproducibility of results." Your firm has manufactured (b) (4) commercial batches of (b) (4) Injection, (b) (4) mg/vial (b) (4) n July 2021 on manufacturing Line (b) (4) and have not performed cleaning validation to show cleaning of the worst-case product, which was identified as application product (b) (4) Injection (b) (4) mg/mL for Line (b) (4) Additionally, cleaning and dirty hold times have not been validated in a cleaning validation; however, you have established a (b) (4) clean hold time for product contact surface equipment.

Subpoints B-E of this observation impact the following application products:
(b) (4)

C. Your firm failed to fully qualify (b) (4) Line (b) (4)). Per Performance Qualification, SD/PD/PQ-031-00, Performance Qualification Protocol for (b) (4) (b) (4) Effective Date 26 Apr 2019", your firm failed to conduct filter integrity testing for the (b) (4) (Line (b) (4) , nor was it performed at the time the (b) (4) (b) (4) exhibit batches (b) (4) (b) (4) for (b) (4) (b) (4) manufactured. Filter integrity testing has not been performed to date. Additionally, there is no empirical data/ risk assessment which confirms the (b) (4) does not contribute to contamination of the (b) (4) products (b) (4) Your Head-Technical Operations reported, "The (b) (4) integrity test was not performed in the qualification of the (b) (4)

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D. Your firm failed to establish critical process parameters (upper and lower limits), including, but not limited to, (b) (4) Your Head-Site Operation (b) (4) reported, "We have recorded the times, so there is a minimum and maximum time, but have not specified upper and lower limits."

E. During the manufacture of the (b) (4) exhibit batches (b) (4) of (b) (4) calibrate (b) (4) Your firm only calibrated the (b) (4) exhibit batches were manufactured, and on a (b) (4) chedule, which does not provide assurance that the data derived from the (b) (4) was both reliable and accurate at the time of use in manufacturing the exhibit batches. Your firm relies on the (b) (4) value to determine (b) (4) which is determined using the (b) (4) Your Head-Site Operation (b) (4) reported, "We only checked the (b) (4) the study.

Additionally, your firm does not use biological indicators (BIs) per (b) (4) to assure (b) (4) has been reached. Your Head-Site Operation (b) (4) reported, "We only ing qualification of the equipment and annually. We only use (b) (4) (b) (4)

F. Your firm failed to monitor the (b) (4) in the (b) (4) (Line (b) (4) . The (b) (4) of the (b) (4) noted (b) (4) identified as (b) (4) but are no ng the (b) (4) process. The Head-Site Validation (b) (4) reported, "The (b) (4) during routine manufacturing." Further, your firm reported 2 of the (b) (4) were being monitored;

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however, there is no empirical data/ risk assessment which provides a scientific rationale or justification for the selected locations chosen for monitoring and why the other (b) (4) identified are not monitored.

G. Your firm failed to (b) (4) (Line (b) (4)) to prevent (b) (4) during the (b) (4) as (b) (4) is a source of contamination, and to reduce the (b) (4). Further, your firm failed to perform tests to ensure that the (b) (4) along with the assembly is integral and the results can be correlated to the bacterial retention capability of the (b) (4) and the (b) (4) assembly. (b) (4) are used and are tested mo (b) (4) for the (b) (4) (b) (4) Further, there is no empirical date/risk assessment performed to scientifically justify the action not being completed.

OBSERVATION 2

Procedures designed to prevent microbiological contamination of drug products purporting to be (b) (4) did not include adequate validation of the (b) (4) process.

Specifically, your media fill studies are inadequate for sterile manufacturing Line (b) (4) and Line (b) (4) and are not representative of the actual manufacturing process. For example, but not limite o:

(b) (4)

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A. Interventions simulated in media fills for manufacturing Lines (b) (4) is not representative of the (b) (4) manufacturing process. Interventions in the following batch records are performed more times than what was simulated in the media fill. For example, but not limited to:

(b) (4)

- The minimum number of times of interventions to be stimulated is not always provided, for example, (b) (4) (b) (4) The value is provided as "as per batch size is given; however, a specifications have not been established for these interventions, which were reported to have been simulated (b) (4) times, though the batch records for (b) (4) Injection USP, (b) (4) (b) (4) show the interventio an the number of times simulated in the media fill. No justification was provided, as your firm failed to initiate an investigation to determine the impact of the additional interventions on the product from what was validated in the media fill for all batches in (b) (4) Injection USP, (b) (4)

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(b) (4) Line (b) (4)) and (b) (4) (b) (4) (Line (b) (4).

B. Intervention records are inconsistently reviewed and approved by Quality Assurance in the batch record to determine compliance with all established, approved and written procedures before the batch is approved for release. For example, but not limited to, for (b) (4) Injection USP, (b) (4) mg-ml -Batch (b) (4) "Quality Assurance did not sign the document as "Reviewed by QA" on Page 2 of 2 of I n Record. This exhibit batch was approved by QA.

C. Intervention records for (b) (4) Injection USP, (b) (4) (Line (b) (4) and (b) (4) (Line (b) (4) batch records are not attributable to the batch or product in the manufacturing batch record. For example, each intervention record fails to list the name and strength of the product and the batch number.

D. Your (b) (4) physical verification is required as required per Step (b) (4) and subparts and (b) (4) Integrity Testing and Step (b) (4) of SOP #F3\PR\SOP\0041 Rev. 1.0 (*Handling of* (b) (4) (b) (4) *RABS*), September 01, 2021 effective date) is inadequate. Your most recent (b) (4) integrity test conducted on 21 Oct 2021 passed. However, on 28 Oct 2021 during the walkthrough of Line (b) (4) we observed a (b) (4) in (b) (4) between the (b) (4) located on the (b) (4) RAB (Grade A); however, the barrie (b) (4) barrier i unable to be determined at which point the (b) (4) happened, a was not captured in routine (b) (4) integrity test. There was no investigation initiated to determine the impact of the (b) (4) r on the line or the products produced on it. The following exhibit batches of (b) (4) injection (b) (4) mcg/ mL were manufactured on this line between dates of the passed (b) (4) est and the observation of the (b) (4) in (b) (4) (b) (4) These exhibit batches are planned to be submitted to the agency in an (b) (4)

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REPEAT OBSERVATION.

You processed change control CCF #PC-PD-21-0021 where the operators are to visually check the (b) (4) for defects (b) (4) after (b) (4) . er, you did not implement similar practices for the (b) (4) RAB (b) (4) afte d from manufacturing for cleaning out place. The (b) (4) RAB is classified as Grade (b) (4) and it is utilized for the filling and capping operations of (b) (4) Injection USP, (b) (4) (b) (4) and (b) (4) Injection USP, (b) (4) mg/via

OBSERVATION 3

There is a failure to thoroughly review any unexplained discrepancy and 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,

The investigations for three out-of-specifications failures between April 2020 and February 2011 were not adequate.

A. Your firm invalidated an OOS test result in error. During the testing of (b) (4) (b) (4) Injection USP (b) (4) mg/vial finished product, submission Batch (b) (4) for elemental impurities, you obtai an OOS for (b) (4)

Test Parameters and Results	Specifications
(b) (4) (b) (4) µg/g	Spec.: (b) (4) µg/g

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You attributed the root cause to "contamination of (b) (4) used for sample collection and transfer". Your Senior Manager QC (ID # (b) (6) state (b) (4) stored next to Balance (ID #QC-157) was contaminated with (b) (4) during the last weighing on the balance on 21 Apr 20, 23 Apr 20, 25 Apr 20, and 27 Apr 20. You simulated a hypothesis study where you intentionally contaminated the (b) (4) with (b) (4) which yielded another OOS.

Test Parameters and Results	Specifications
(b) (4) (b) (4) µg/g	Spec.: (b) (4) µg/g

You then used a (b) (4) and (b) (4) scoop for weighing a new sample of (b) (4) SP (b) (4) mg/vial (b) (4) Batch (b) (4) which were not used during the initial sample testing of the material which yielded the OOS and not described in STP #SD/STP/FP028 Rev. 02. You obtained a passing result and invalidated the initial result.

Test Parameters and Results	Specifications
(b) (4) : (b) (4) µg/g	Spec.: (b) (4) µg/g

However, you failed to utilize one of the (b) (4) which is already cut and stored next to the balance for testing which you claimed e of contamination. You utilized a (b) (4) (b) (4) and (b) (4) scoop for weighing a new sample of (b) (4) Injection USP (b) (4) mg/vial (b) (4) Batch (b) (4) which was not utilize as part of STP #SD/STP/FP028 Rev. 02 as affirmed by your Senior Manager QC (ID # (b) (6) and your Senior Executive, QC (ID # (b) (6) . You then proposed to revise STP #SD/STP/FP028 Rev. 02 (b) (4) Injection USP (b) (4) mg/vial) to incorporate the use of (b) (4) (b) (4) (b) (4) er CAPA/SD/20/092.

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B. Your firm failed to validate the test method post corrective and preventive action (CAPA). During the effectiveness check of CAPA-SD-20-092 where you revised STP #SD/STP/FP028 Rev. 02 (b) (4) *Injection USP* (b) (4) *mg/vial, May 06, 2020 effective date*) without performing a method validation. you obtained OOS-SD-ST-20-015) (b) (4) Injection USP (b) (4) mg/vial (3-month stability 25C/60RH, submission Batch (b) (4) during the elemental impurities test for (b) (4) and the CAPA effectiveness failed.

Test Parameters and Results	Specifications
(b) (4) (b) (4) µg/g	Spec.: (b) (4) µg/g
(b) (4) (b) (4) µg/g	Spec.: µg/g

You added the following in the STP after an OOS was recorded for application product (b) (4) Injection USP (b) (4) mg/vial, which stated the following in the investigation:

- Use the (b) (4) for weighing sample,
- Use the (b) (4) scoop while transferring of sample.

You reported in the investigation the plastic used for sample preparation (i.e. (b) (4) ml volumetric flask) is dedicated for ICPM analysis (Request Test Methods). However, usage of contaminated (b) (4) (b) (4) could not be ignored.

You then attributed the root cause after conducting your hypothesis analysis to the contamination of the (b) (4) used for sample (b) (4) and reported the exact source of contamination of (b) (4) was not identified n proposed to increase the sample weight from (b) (4) gm to (b) (4) gm and to utilize the balance available in the isolated environment (ICP-MS preparation area) by keeping the (b) (4) oncentration same as per STP without any scientific rationale

and revalidation of the test method. Additionally, you failed to consider in your root cause analysis, the sample was tested for these parameters (b) (4) after being pulled from the stability chamber which is contrary to Step # (b) (4) of SOP #QA-SOP-0067 Rev. 2 (*Stability Management*). Per Step # (b) (4) testing with sample review shall be completed within (b) (4) after pull samples for Long term, Intermediate condition and accelerated condition. The sample was pulled from stability chamber #QAE-002 (Stability Condition: 25C/60%RH) on 23 Jul 20, stored at sample storage room #QCR-12 under 20°-25°C, and tested on 15 Sept 20. In addition, you failed to initiate a deviation for exceeding the (b) (4) for testing.

You invalidated the initial results after yielded a passing result during the replacement of analysis and initiated CAPA-SD-20-092 to revise STP #SD/STP/FP028 which failed the CAPA effectiveness check. You also added the (b) (4) in the test method and you did not perform a method validation and/or verification after adding that component as part of your test method.

Test Parameters and Results	Specifications
(b) (4) (b) (4) µg/g	Spec.: (b) (4) µg/g
(b) (4) (b) (4) µg/g	Spec.: µg/g

C. Your OOS investigation for #OOS/SD/ST/21/009 (b) (4) (b) (4) Solution (b) (4) % / (b) (4) % (b) (4) ml) (Submission batch), 6-Month intermediate (b) (4) Stability study, Batch (b) (4) was adequate. You obtained an OOS value of (b) (4) % (Spec. NLT (b) (4) %) during the analysis of "Quantitative Color Test" using Ultrascan Spectrophotometer (Hunter Lab Pro, ID #QCE-222) and concluded the probable root cause was lamp module misfiring and failure to sufficiently illuminate the sample which was confirmed by your service engineer during the visit. You performed a partial calibration of the equipment which is not described in SOP #SD/QC/IOCP080-03 (*Operation and Calibration Procedure for Ultrascan Spectrophotometer (Make Hunter Lab), 06/03/2020 effective date*). The Sample was pulled from stability chamber on (b) (4)

Dec 20 and tested on 24 Feb 21, which is more than (b) (4) as required per your #QA-SOP-0067 Rev. 2 (*Stability Management*).

Test Parameters and Results	Specifications
(b) (4) %	Spec.: NLT (b) (4) %

Your preliminary investigation was performed by employee (ID # (b) (6) who is no longer with your firm. His training records revealed he failed to successfully complete the investigation awareness training three (3) times and never obtained a passing score afterwards but continued to perform QC investigations. In addition, SOP #SD/QC/IOCP080-03 (*Operation and Calibration Procedure for Ultrascan Spectrophotometer (Make Hunter Lab)*, 03 Jun 2020 effective date) does not include a suitability check prior to using the equipment. You invalidated the initial result after obtaining a passing result on 09 Mar 2021.

Test Parameters and Results	Specifications
(b) (4) %	Spec.: NLT (b) (4) %

D. You recorded a total of eight (8) out-of-calibration (OOC) results on eight different occasions during the calibration of the (b) (4) nstrument ID #QCE-056, which is used to perform (b) (4) esting for (b) (4) listed in the table below. You attributed five (5) of the 8 out-of-calibration investigations to human error/document error/other by the same analyst and two of the remaining 8 OOC investigations by another analyst. You failed to implement an effective corrective and preventive actions to prevent reoccurrence and to establish reliable results for product release testing. In addition, you failed to perform an impact assessment for all the samples that ran on the instrument and for each occasion recorded as required per (b) (4) and

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(b) (4) of SOP # F3\QC\SOP\0038 Rev. 1.0 (*Handling of Out of Calibration*). Yet, your Quality Control Unit approved all the out-of-calibration investigations and have not performed trending and Evaluation of out of calibration as required per SOP # F3\QC\SOP\0038 Rev. 1.0 (*Handling of Out of Calibration*). Lastly, the investigations failed to state whether or not the equipment was placed out of use and when the (b) (4) was contacted by your firm for services.

(b) (4)

(b) (4)

(b) (4)

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For example, you tested (b) (4) Injection USP (b) (4) mg/vial) and several pending applications (i.e. (b) (4) USP, (b) (4) Injection USP, (b) (4) Injection, etc.) batches on the equipment. which is not all-inclusive

(b) (4)	Testing Date
	04/29/2020
	04/29/2020
	06/26/2020
	07/10/2020
	08/19/2020
	08/19/2020

*day format mm/dd/yyyy

E. Your firm has a minimum of 700 non- conformance investigation reports and failed to establish a written procedure for initiating performing, monitoring and trending non-conformance investigations. You initiated Non-Conformance Report (NCR) for Document #SD/PDPQ-021-00/AD-14/001 during the performance qualification for (b) (4) ID #PDAE-001 (b) (4) (b) (4) where you observed growth in the biological indicator (b) (4) tube on 13 July 2021 after incubation which was exposed in dispensing (b) (4) minimum (b) (4) Run (b) (4) You classified the non-conformance as a Type (b) (4) (Major). Your microbiology department performed an investigation to determine the growth and speciation of the organism. Based on the speciation performed by your contracted laboratory, the specie was identified as "Geobacillus Stearothermophillus". In addition, you failed to perform the following:

- Operator Training documentation- whether the operator was trained on the protocol and if it is the first incident ever recorded for the equipment and/or operator.
- Assigning an investigation number to the NCR investigation including the investigation performed by the microbiology department.
- Recording and reporting the NCR under microbiology investigation log.
- Maintaining a log for all NCRs recorded at the site.
- Recording the operator's name who was operating the (b) (4)

Your attributed the root cause to (b) (4) BI of Run (b) (4) with the (b) (4) BI of Run (b) (4) during handling and (b) (4) BI sent to the Microbiology for incubation and classified it as "Human Error". However, you failed to report whether the operator was trained on the protocol, and if it is the first incident ever recorded for the equipment and/or operator. The (b) (4) is utilized on Line (b) (4) for the manufacturing of (b) (4) Injection USP, (b) (4) mg/vial (b) (4) and (b) (4) Injection USP (b) (4)

You Head-Sterile Operations reported, "We are making a log now, it is incomplete, but we have currently 800 NCRs." Again, these NCR investigations were conducted without an established procedure, and appropriate tracking and trending for ensuring adequate corrective and preventive actions to prevent the reoccurrence of events and ensure integrity in the manufacturing process and operations on-site.

OBSERVATION 4

Written records are not always made of investigations into unexplained discrepancies and the failure of a batch or any of its components to meet specifications.

Specifically, you failed to initiate a new investigation following the failure of CAPA effectiveness for CAPA/SD/20/092 as required per Step (b) (4) and (b) (4) of SOP #SD/QA/SOP020 Rev. 02 (*Handling of Corrective Action and Preventive Action*, 20 Oct 2018 effective date). Step (b) (4) tates " where it states "If CAPA is found not effective during any stage of effectiveness verification, QA personal shall inform to respective department Head/ Designee whose team is responsible for implementation of CAPA." Step (b) (4) states "A new investigation shall be initiated as per investigation procedure with reference to the original CAPA effectiveness verification, by initiator of CAPA. Based on the investigation if any CAPA's are identified they shall follow the same handling process as described in this procedure and effectiveness verification is mandatory for these CAPA's."

OBSERVATION 5

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

Specifically, you failed to provide scientific justification demonstrating that samples collected for environmental monitoring represent the greatest risk of product contamination. Line (b) (4) s utilized for the manufacturing of (b) (4) Injection USP, (b) (4) and (b) (4) njection USP, (b) (4) mg/vial. For Example;

A. You failed to provide a scientific justification why surface sampling is not conducted for your telephone and computer system (keyboard, monitor, and computer tower) located in Grade (b) (4) ((b) (4) (b) (4) Cleaning Room). Currently, you perform settle plate and air sampling monitoring in Grade (b) (4) ((b) (4) Cleaning Room). In addition, the computer keyboard is not covered with a cover preventing buildup between the keys. These items are utilized by the operators located in the room during operations including the manufacturing of (b) (4) Injection USP, (b) (4) (b) (4) (b) (4) Injection USP, (b) (4) mg/vial, and (b) (4) Injection (b) (4) mg/mL.

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12420 Parklawn Drive, Room 2032 Rockville, MD 20857	10/28/2021-11/10/2021*
	FEI NUMBER 3015685305

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED

Mr. Srinivas Avirneni, Head Site Operations

FIRM NAME	STREET ADDRESS
Alembic Pharmaceuticals Limited	Formulation Division Iii, Plot No. 779p/790p, Village - Karakhadi, Taluka - Padra
CITY, STATE, ZIP CODE, COUNTRY Vadodara, Gujarat, 391450 India	TYPE ESTABLISHMENT INSPECTED Sterile Drug Manufacturer

B. You failed to provide a scientific justification why surface sampling is not conducted for the (b) (4) in Grade (b) (4) for Line (b) (4). No assessment was performed by your firm providing do not ha e to perform environmental monitoring (EM) for the (b) (4) and it is not currently being monitored. Your QA Manager/Microbiologist who performs EM activities on site affirmed the firm did not include the (b) (4) in the EM program and in the schematic for the room (Grade (b) (4). Line (b) (4) is utilized for the manufacturing of (b) (4) Injection USP, (b) (4) (b) (4) Injection USP, (b) (4) mg/vial, and (b) (4) Injection (b) (4) mg/mL.

OBSERVATION 6

(b) (4) processing areas are deficient regarding the system for cleaning and disinfecting the room and ent to produce (b) (4) conditions.

Specifically,

According to SOP #F3\PR\SOP\0037 Rev. 1.0 *(Operation and Cleaning of* (b) (4) *(Make: MRC)*, 09/30/2021 effective date), (b) (4) (Make: MRC) located in Line (b) (4) (ID #PDAE-037, PDAE-038), Line (b) (4) ID #PDBE-024), and Line (b) (4) ID #PDCE-034) (b) (4) (b) (4) or whenever required regardless how many items are (b) (4) (b) (4) during batching operations in a (b) (4). This practice was affirmed by your (b) (4) production. Line (b) (4) s utilized for the manufacturing of (b) (4) Injection USP, (b) (4) (b) (4) and (b) (4) USP, (b) (4) mg/vial).

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Line (b) (4) is utilized for the manufacturing (b) (4) Solution (b) (4)

OBSERVATION 7

(b) (4) processing areas are deficient regarding systems for maintaining any equipment used to control the (b) (4) conditions.

Specifically,

On 10/28/2021 during the walkthrough of Line (b) (4) we observed several equipment utilized in the manufacturing of (b) (4) Injection USP, (b) (4) (b) (4) was (b) (4) (i.e. (b) (4) Vessel #PDAE-007, Mettler Toledo Balances #PDAE-002, PDAE-004 and PDAE-049, (b) (4) . Line (b) (4) is utilized for the manufacturing of (b) (4) Injection USP, (b) (4) and (b) (4) (b) (4) Injection USP, (b) (4) mg/vial.

OBSERVATION 8

The responsibilities and procedures applicable to the quality control unit are not in writing and fully followed.

Specifically,

Your firm failed to adequately monitor quality metrics for the continuous control and optimization of manufacturing processes including but not limited to the following (b) (4) Injection USP, (b) (4) and (b) (4) Injection USP, (b) (4)

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mg/vial. For example but not limited to, change controls are not adequately reviewed and assessed by the Quality Unit and the respective departments which can affect the equipment and the process at the firm.

A. You initiated change control #PC\PD\21\0079 on 17 May 2021 where you proposed to qualify a new (b) (4) as (b) (4) in Line (b) (4) (b) (4) (PDAE-001). Your justification stated the equipment (b) (4) (WHE-106) is procured and qualification is under progress per CCF #PC/SD/19/0377. (b) (4) (WHE-106) is intended for (b) (4) Hence, it is recommended to (b) (4) all the items which are used for (b) (4) The new (b) (4) shall be used in routine operation only after su ualification

However, you failed to state in the change control documents and associated records what are the existing approved (b) (4) Instead you stated "Proposed (b) (4) is not part of existing qualified (b) (4) n line (b) (4) (PDAE-001). Yet, your Quality Assurance, Regulatory Affairs, and Validation Departments assessed and approved the change control. This equipment is used for the manufacturing of for (b) (4) Injection USP, (b) (4) (b) (4) and (b) (4) Injection USP, (b) (4) mg/vial.

In addition, we observed two change controls (listed below) that were not adequately assessed and classified by your Quality Control Unit which were approved.

Change Control #	Descriptions	Classification
PC\PD\21\0079	(b) (4) in Line (b) (4) PDAE-001). Your justification stated the equipment (b) (4) (b) (4) WHE-106) is procured and qualification is under	Major

	progress per CCF #PC/SD/19/0377.	
PC/PD/21/0025	Performing trending of (b) (4) integrity test results, adding pre-verification checkpoints, and implementing a pre-verification checklist for (b) (4) integrity test **(not all-inclusive)**	Minor
PC/QM/21/0011	Implement "immediate actions" to be taken for environmental monitoring, incorporating a table on actions to be taken during excursions, identifying of source for additional monitoring, and actions to be taken for (b) (4) monitoring excursions **(not all-inclusive).**	Minor

B. You do not process change controls where required. For example, you (b) (4) (b) (4) stand into Line (b) (4) Grade B as part of your remedial action to the last U.S. FDA inspection and you did not process a change control but a work order (#WRF\PDA\21-019). Line (b) (4) is utilized for the manufacturing of (b) (4) Injection USP, (b) (4) mg/vial and (b) (4) (b) (4) Injection USP, (b) (4)

C. Your quality control unit failed to effectively assess CAPA implementation and methodology/recommendation for CAPA effectiveness verification. For example, you recommend as part of your methodology to perform CAPA effectiveness for #CAPA/SD/20-141 during 9 month and 12 month stability analysis. However, you failed to perform the effectiveness check for the CAPA when you identified that that elemental impurity is not part of next stages of stability study where it is only performed during 3-month stability study. As a result, you extended the CAPA effectiveness to be checked during new batches of (b) (4) njection USP (b) (4) mg/vial.

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D. SOP #F3\QA\SOP\0005 Rev. 2.0 (*Vendor qualification of raw materials and packaging materials*, 09/16/2021 effective date) is deficient. Non-sterile excipient/medium risk excipients vendors are qualified only through an audit questionnaire and no audit frequency is established for routinely monitoring these excipients vendors. However, sterile excipients are audited on-site and an audit frequency is established. These non-sterile excipient/medium risk excipients vendors listed in the table below are utilized in the compounding operations along with the (b) (4) excipients for (b) (4) (b) (4) (b) (4) (b) (4) Injection USP, (b) (4) (b) (4) Injection USP, (b) (4) mg/vial), and (b) (4) (b) (4)

Further review of these paper audits (b) (4) revealed these self-assessment were reviewed and approved by your firm 2 years later after receiving them.

Material/Service	Current Approval Status	Process Stage Where Used & RM #	Last Audit Date	Approval Date	Audit Frequency	Next Audit Date
(b) (4)	Approved	(b) (4)	03/08/2015 07/28/2015	12/11/2017	N/A	N/A
	Approved		03/08/2015 11/19/2015	12/11/2017	N/A	N/A
	Approved		03/06/2015 07/28/2015	12/11/2017	N/A	N/A
	Approved		12/14/2017	12/19/17	N/A	N/A

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(b) (4)	Approved	(b) (4)	03/07/2016	12/11/2017	N/A	N/A
	Approved		03/08/2015	12/11/2017	N/A	N/A
	Approved		04/24/2015	12/11/2017	N/A	N/A
	Approved		10/25/2018	10/25/2018	N/A	N/A

E. You have not established a Quality Agreement with the supplier/vendor of (b) (4) (API) which is utilized for the manufacturing of (b) (4) (b) (4)

F. You have not established a procedure for addressing non-conforming report (NCR). In addition, you do not maintain a log for nonconformances (NCRs), you do not track and trend all non-conformance reports/investigations raised or encountered during equipment qualifications. The NCRs affect equipment and/or process for (b) (4) (b) (4) (b) (4)

G. You do not provide training for all implemented standard test procedures (STPs) in the QC laboratories as affirmed by your QC Deputy Manager (ID #20356). In addition, you failed to adequately monitor your training program through Quality Metrics. For example, we observed your

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(b) (6) ID (b) (6) failed training for #SD/PD/SOP028 Rev. 06 (*Cleaning and Disinfection of Floor Drain,* 04/26/2021 effective date) which was never repeated. However, he continues to perform cleaning of the production areas including Grade C.

OBSERVATION 9

Verification of the suitability of the testing methods is deficient in that they are not performed under actual conditions of use.

Specifically,

On 03 Nov 2021, we observed the (b) (4) equipment (ID #QCE-121) located next to HPLC ID #QCE-106 in Room unplugged. Per your QC Head, the equipment is utilized on HPLCs to maintain the (b) (4) for specific tests. In addition, it was qualified as a stationary equipment for the HPLC used during the equipment qualification and test methods verification/validation. Further investigation revealed that the equipment is normally unplugged and utilized as a mobile equipment for other HPLCs use in the QC laboratory. In addition, this practice is not described in SOP # F3\QC\IOCP\0044 Rev. 1.0 (*Operation and Calibration procedure for* (b) (4) (b) (4) *(Make: Waters)*, 5 Oct 2021 effective date).

You performed Method Verification Report #MVR/Ex/19/007 Ver. 00 (*Analytical Method Verification Study Report for the Determination of Assay* (b) (4) *and Related Substances of* (b) (4) *USP by HPLC*) which was made effective on July 12, 2019 using HPLC (QCE-020) and (b) (4) (b) (4) (ID #QCE-121). However, you failed to provide a scientific justification to demonstrate there is no impact on the validated test methods and the equipment qualification when unplugged and utilized (b) (4) ID #QCE-121) as a mobile equipment.

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For example, this equipment is being used for performing release testing for the following submitted (b) (4)

Product Name	Test	Purpose of use
(b) (4)		

OBSERVATION 10

Appropriate controls are not exercised over computers or related systems to assure that changes in master production and control records or other records are instituted only by authorized personnel.

Specifically,

Appropriate controls are not exercised over computers or related systems to assure that changes in master production and control records or other records are instituted only by authorized personnel. Specifically, you assigned "Reviewer (b) (6)" roles and privileges to QC, QA, and Administrator in the data acquisition software (Pyris) for Perkin Elmer DSC 8000 (ID #QCE-136). However, you have not justified the reason for assigning "Reviewer (b) (6) roles and privileges to QA and Administrator. There are eight (8) user groups in the software (i.e. Analyst, Pyris Administrator, Pyris Developers, Pyris Technicians, Pyris Users, Reviewer (b) (6) Reviewer (b) (6) and Service Engineers) including Administrator. However, you have not defined the roles and privileges of each group in SOP #F3\QC\IOCP\0053 Rev.

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2.0 (*Operation and Calibration of Differential Scanning Calorimeter (Model DSC 8000, Make Perkin Elmer*), October 8, 2021 effective date). The equipment is utilized to test packaging components for (i.e. bottles) for (b) (4) [redacted]

***DATES OF INSPECTION**

10/28/2021(Thu), 10/29/2021(Fri), 11/01/2021(Mon), 11/02/2021(Tue), 11/03/2021(Wed), 11/08/2021(Mon), 11/09/2021(Tue), 11/10/2021(Wed)

X Kellia N Hicks
Office of Global Policy and Strategy Employee
Signed By: Kellia N. Hicks -S-
Date Signed: 11-10-2021 03:29:23

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