DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
10903 New Hampshire Ave,Bldg 51,Rm 4225 Silver Springs, MD 20993 (301) 796-3334 Fax:(301) 847-8738 Industry Information: www.fda.gov/oc/industry	10/05/2015 - 10/13/2015
	FEI NUMBER 3003369660

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED

TO: Mr. Sirjiwan Singh, Managing Director

FIRM NAME	STREET ADDRESS
CP Pharmaceuticals	Ash Road North Wrexham Industrial Estate
CITY, STATE, ZIP CODE, COUNTRY	TYPE ESTABLISHMENT INSPECTED
Wrexham LL13 9UF, United Kingdom	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 I OBSERVED:

OBSERVATION 1

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

Specifically, your firm has not established and followed all necessary procedures to prevent contamination of aseptically filled sterile drug products. Aseptic filling occurs in EU Grade A (b) (4) RABS systems that reside in a EU Grade B background. Control of aseptic interventions are described in SOP #SPOP-075-09-1643, ver 7, and personnel behavior in ISO Class 100 is described SOP #SPOP-121-06-1526, ver 5.

A) My review of procedures noted that disinfection of RABS (b) (4) opened during set-up operations is required to be performed at the (b) (4) of the set-up operation at not after each opening.

B) On 10/5/15, I observed the set-up of (b) (4) Line # (b) (4) for the aseptic filling of (b) (4) (b) (4) mg/ml in a (b) (4) ml (b) (4) lot # (b) (4). I noted the following:

- During the Engineering Set-up, the RABS (b) (4) remained opened to Grade B for -(b) (4) without being closed.
- The (b) (4) for (b) (4) remained opened until the (b) (4) were installed near the (b) (4) of the Engineering Set-up. The (b) (4) are reportedly removed during cleaning after the (b) (4) (b) (4) and the (b) (4) remain open until the next time the line is set up.
- (b) (4) parts for the aseptic filler, which are (b) (4) in a (b) (4) (b) (4) and (b) (4) sterilized, are exposed to Grade B and entered into the Grade A RABS without any disinfection. I observed multiple packages enter the RABS and come into contact with internal equipment surfaces. I also observed multiple packages come into contact with the (b) (4) in the Grade B as they were entered into the RABS.
- The product tubing connected to the (b) (4) -sterilized bulk product tank was entered into the RABS without disinfecting.
- The internal surfaces of the RABS (b) (4) were not disinfected prior to closing on multiple occasions, by

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multiple employees. The wiping of the internal (b) (4) surface was observed to not always be executed in a (b) (4) (b) (4) approach and the area near the bottom of the (b) (4) was not wiped in entirety.

- Movement of employees within the Grade A RABS and in the Grade B area (with the RABS (b) (4) open and closed) appeared brisk, abrupt and rapid. I also noted that each time the (b) (4) were pushed aside and allowed to (b) (4), they potential created air turbulence in the room.

- I observed multiple personnel, on multiple occasions, touch surfaces and items in the Grade B area and then enter the Grade A RABS and touch sterile surfaces without disinfecting gloved hands, including:

  1) a cart with supplies,

  2) (b) (4) surrounding the RABS,

  3) filling equipment controls attached to the (b) (4) and

  4) the (b) (4) on the RABS

  This included the engineer opening the RABS (b) (4) on (b) (4) successive occasions during set-up to adjust the filling (b) (4) with a tool ((b) (4)) without disinfecting gloved hands.

C) On 10/7/15, I reviewed recorded CCTV footage of Ampule Line # (b) (4) set-up, dated 9/9/15, and interventions into the same Grade A RABS, during filling of (b) (4) (b) (4) ampules, lot # (b) (4), dated 9/29/15. I observed multiple employees display the same behaviors as described above on a repeated basis.

D) The protective covering, post-sterilization handling, and introduction into Grade A areas for (b) (4) /SOP equipment, components and container closures (stoppers and (b) (4), are not designed to prevent contamination of sterile drug products. For example,

- Protective covering includes wrapping equipment/components in a (b) (4) provided by (b) (4) bagging material, as described in SOP #SPOP-051-10-1351, ver 10. There is no (b) (4) to be (b) (4) in Grade B areas prior to entering the Grade A RABS.

- Receipt and storage of sterilized equipment/components/closures into the Class 100 area is described in SOP #SPTM-021-09-1611, ver 5. The procedure includes passing exposed items (in (b) (4) bags) through Grade B for storage in Grade A without any (b) (4) barrier.

- There is no requirement to disinfect hands prior to selecting (b) (4) items for the Grade A filling lines.

- (b) (4) items (wrapped in (b) (4) bags) are openly transported and held on a cart in Grade B area while being used to set up filling equipment.

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OBSERVATION 2

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

Specifically, your firm has not established a suitable system to monitor for viable and non-viable particulates for sterile drug products as follows:

A) On 10/6/15, I observed fully incubated plates for monitoring of employee gloves (finger dabs) in the microbiology lab that did not bear any indication that fingers had been in contact with the media. The only evidence the plates had been contacted during sampling was where the thumb had left an imprint. A review of SOP #GTM-108-18-1131, ver 9, for monitoring techniques describes gently pressing digits onto the surface of the (b) (4) and taking care not to damage the (b) (4) The collection does not include any information related to the contact time required. Further, your firm has not conducted any studies to demonstrate the capability and reliability for your method of collection.

B) Monitoring of personnel gowning for the Class 100 area is according to SOP #QCOPMB-004-22-1260, ver 15. This procedure describes that monitoring only occurs at the (b) (4) Personnel present and participating during set-up, filling, cleaning or any other activity in Class 100 are not monitored unless they participate in batch filling that (b) (4) or they are part of a routine audit.

C) The study protocol (TECHHP-509-0-1673) approved by the QCU to support the monitoring location of non-viable particulates in the Grade B background where aseptic filling occurs did not include the location of sample points. The production department executed the study and independently determined the sample locations.

D) Monitoring locations for viable microorganisms for (b) (4) Line # (b) in the Grade A RABS and Grade B background are justified in risk assessment document #RAS-026-2518, ver 2. A review of this document found the following areas were excluded from the assessment:

- A (b) (4) where IPC tests are performed
- The portable cart used to hold sterile parts/equipment which are assembled inside the RABS for filling

These locations have not been assessed for the need to monitor for viable microorganisms.

OBSERVATION 3

Procedures describing the handling of all written and oral complaints regarding a drug product are not followed.

Specifically, complaint investigations according to SOP #QAP-005-17-1147, ver 8, do not ensure a root cause determination is made, when possible. Section 6 of the procedure includes a brief note on complaint samples; however, the procedure and

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form for documenting complaint investigations is not specific on the process of obtaining a complaint sample nor provides a suitable system of documenting what actions have been executed in order to obtain a complaint sample, including when complaint samples are not available. I reviewed complaint #C15A03 and #C15A05 for reported foreign matter described as "floaters" in two batches of (b) (4) (b) (4) nl (b) (4) injection and complaint #C14K04 for (b) (4) particles in the same product. There is no documentation of any attempt to recover complaint samples for evaluation. Both investigations determined the event was an isolated incidence and no root cause was identified. These three complaints were reported as Field Alerts by the applicant holder.

This is a repeat observation.

OBSERVATION 4

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

Specifically,

A) Your firm did not execute a change control as described in SOP #GOP-744-5-1742, ver 5. For example,

1) The root cause of deviation #6274 determined a seized filling piston on Ampule Line # (b) resulted in metal particulates in filled product. The CAPA included an update to line clearance procedures and sub-batching. This was communicated to employees via Training Note #753; however, no change control was opened to update any impacted procedures and records.

2) A new (b) (4) system was installed to be the (b) (4) (b) (4) for the (b) (4) and (b) (4) systems. The system qualification included (b) (4) sampling for (b) (4) (sample all (b) (4) (b) (4) followed by (b) (4) (b) (4) sampling for (b) (4) (b) (4) sampling for (b) (4)). A review of change control #387 revealed that the qualification approach was based solely upon the requirements of Validation Master Plan for Sterile Products (VMP-219-0-13515), which is not scientifically based and is not supported by any risk assessment.

In addition, the QCU approves the plan for implementing changes, but does not review executed changes to ensure changes are implemented as approved.

B) Your firm has not implemented the controls to ensure all data used to make quality based decisions is maintained. I reviewed deviation investigation #6374 for an action level excursion for an environmental isolate recovered from a settling plate in a Grade A filling area. The investigation included the review of recorded CCTV video footage for the filling operation to asses if proper aseptic technique and employee behavior was followed. The incident occurred October 13, 2014 and your firm reported this data is only maintained until the data is over-written with new data due to storage space limitations. The estimated time for CCTV data maintenance is ~ (b) (4) I also observed deviation #6679 included a review of CCTV footage and this data was not maintained as well. In addition, it was also reported that this data system has not been validated.

C) Your records for the QCU's observation of activities in the Class 100 areas (Grade A and B) do not accurately reflect the actual operations as they occurred. SOP #QAP-199-0-1704, ver 7, describes the activities to perform with the stated objective of providing "assurance and confidence that applied process are in control and that they are completed satisfactorily". The activities include observing employee behavior and aseptic technique, as described in SOP #SPOP-121-06-1526, ver 5, via viewing windows or CCTV footage. I reviewed the record for the QCU's observation of Class 100 activities for the month of September 2015 and compared the recorded comments against the recorded CCTV footage for 1) engineer and operator set-up of Ampule Line # (b) on 9/9/15, and Grade A intervention on the same line dated 9/29/15. The record notes that proper technique and behavior was observed in all cases; however, my review of the recorded CCTV footage on 10/7/15 of the same footage reportedly reviewed by the QCU noted the following:

- Rapid employee movements and causing excessive movements of the (b) (4) surrounding the Grade A RABS with the RABS (b) (4) open and closed.
- Failure to disinfect hands prior to making a Grade A intervention after touching non-sterile surfaces and entering the Grade A RABS during set-up on repeated instances.
- Failure to wipe the interior surface of the RABS (b) (4) prior to closing (b) (4) time.
- Failure to spray both hands when disinfecting.
- Entering the body from approximately the (b) (4) up into the Grade A RABS during set-up.

OBSERVATION 5

Employees engaged in the processing of a drug product lack the training required to perform their assigned functions.

Specifically,

A) Your firm's training program for the manual visual inspection of filled drug products does not ensure that employees engaged in the process can accurately detect defective units on a routine basis. The training program is described in SOP #SPTM-081-1367, ver 3, and is accomplished in (b) (4) The (b) (4) (b) (4) . I compared the defect categories described in SOP #SPOP-204-2-1196, ver 14, and the defect library that is part of the above procedure found that not all known defects are present. I compared the critical defects known against the challenge library and found that only 8 of 18 critical defects for solutions were included. Further, there is no photograph library of the known defects.

B) Your firm training for employees engaged in the manufacture of sterile drug products and QCU employees

responsible for the observation of the same employees does not ensure suitable employee practices are followed in the set-up and filling of sterile-filled drug products.

1. Expected behavior for employees in the Class 100 area is described in SOP #SPOP-121-06-1526, ver 5, and training for the area is described in SOP #223-02-1691, ver 1. As evidenced by the observations of poor practices during the inspection, the observed employees training is not suitable ensure proper aseptic technique and employee behavior in the Class 100.

2. The QCU's oversight of operators working in the Class 100 area is described in SOP #QAP-199-0-1704, ver 7, and training of the QCU personnel engaged in the oversight is described in the same. This training is evaluated with a written knowledge assessment. As evidenced by the September 2015 record of the QCU's observation of acceptable employee practices in the Class 100 areas and my observation of poor employee practices during the review of the recorded CCTV footage of the same operations, the training is not suitable to ensure suitable practices in Class 100 areas.

OBSERVATION 6

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

Specifically,

A) Your firm's cleaning of the Class 100 area does not include all surfaces necessary for the decontamination of the Grade A RABS. For example, the (b) (4) ((b) (4) forming the RABS (b) (4) and (b) (4)) is not cleaned (b) (4) the level of the (b) (4) which extends to the (b) (4) where the HEPA filters are located. This area is inside the Grade A RABS and (b) (4) where products are aseptically filled.

B) There is no data to support the clean status hold time for the Grade A RABS and included parts which are (b) (4) via hand disinfection (wiping). This equipment is reportedly cleaned (b) (4) and is not re-cleaned (b) (4) regardless of the time elapsed.

C) Your firm has not established the efficacy of disinfectants used to clean the surfaces of the Grade A RABS, including parts which are (b) (4) via hand disinfection. Your firm (b) (4) (b) (4) disinfectants, (b) (4), and has stipulated a (b) (4) contact time. You have no data to support this contact time, have no data to demonstrate the effectiveness on any surface present, and have no data to demonstrate the lethality for isolates recovered during environmental monitoring.

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OBSERVATION 7

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

Specifically, your firm has not performed any studies to ensure the set-up of filling equipment in Grade A RABS for aseptic filling does not result in contamination of the area. Your firm has performed smoke studies during static and dynamic conditions during filling operations; however, your firm has no data support the Grade A conditions inside the RABS is not comprised during the set-up of the filling equipment.

OBSERVATION 8

Laboratory controls do not include the establishment of scientifically sound and appropriate specifications designed to assure that components, drug product containers, and closures conform to appropriate standards of identity, strength, quality and purity.

Specifically, your firm has not established appropriate specifications for components, containers, closures used in the manufacture of sterile drug products. For example, I reviewed the specification for (b) (4) API, (b) (4) (container) and (b) (4) (closure), and observed that no material specification include the attribute of bioburden or endotoxins. These materials are used in the aseptic filling of (b) (4) (b) (4) injection.

OBSERVATION 9

Representative samples are not taken of each shipment of each lot of components, drug product containers, and closures for testing or examination.

Specifically, your firm does not collect a representative sample for all containers, closures and components used in the manufacture of sterile drug products; instead relying on companion samples collected and supplied by the manufacturer, which you have not verified. My review of records for the receipt of (b) (4) API, (b) (4) (container) and (b) (4) (closure) found that in each case the supplier provided a companion sample. You have not verified that these samples are representative of the lot used for manufacturing and have no scientific justification for not collecting the samples in-house upon receipt.

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OBSERVATION 10

There are no written procedures for production and process controls designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess.

Specifically,

A) Your firm has not validated all manufacturing processes for [redacted] mg/ml [redacted] injection, a [redacted] sterilized product filled into ampules. Your process validation report, doc #VAL/R/3746/01, dated 12/5/03, does not include subjecting a batch to a [redacted] sterilization cycle. My review of records found on two occasions that your firm had subjected batches to a [redacted] sterilization cycle due to deviations during the [redacted] sterilization. Your firm has not fully evaluated the impact of the [redacted] sterilization cycle on the product.

B) The established reject action level for the manual visual inspection process of filled drug products is not scientifically based. The reject action level for defects are described in SOP #SPOP-2-1196, ver 14. A review of document #TECHR-531-0-1733, ver 2, found that the statistical limit for rejects was adjusted to a higher limit for most categories and the justification includes, in part, for "practical expediency".

OBSERVATION 11

There is no written testing program designed to assess the stability characteristics of drug products.

Specifically, your firm has not implemented a program to assess the stability characteristics for [redacted] mg/ml [redacted] injection, which has been subjected to [redacted] sterilization cycle. During my review of records for investigations (deviation #7031 and #7058), I encountered two lots that were subjected to a [redacted] sterilization cycle and there exists no data to ensure the quality characteristics of the product for the labeled shelf-life. Your current study protocol, document #VALP-8469-013726, to support the [redacted] expiry, is silent to any requirement to place any lot on stability subjected to [redacted] sterilization cycle. No past or current lot on study was reported to have been subjected to [redacted] sterilization cycle.

OBSERVATION 12

Written procedures are not established for evaluations conducted at least annually to review records associated with a representative number of batches, whether approved or rejected.

Specifically,

A) Your firm has not implemented a system to evaluate data from relevant process trends and quality of incoming

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materials or components, in-process material, and finished products, in order to detect unplanned departures from the process. This is necessary to allow detection of undesired process variability and to verify that the quality attributes are being appropriately controlled throughout the process.

B) The September 2014 to September 2015 APQR for (b) (4) mg/ml (b) (4) injection failed to identify and explain two batches that required a (b) (4) sterilization cycle due to deviations. The record only mentions that three minor deviations occurred, but there is no reference to the products required a (b) (4) cycle.

OBSERVATION 13

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.

Specifically, your firm does not perform an annual visual assessment of retain samples in order to detect deterioration. SOP #QAP-124-5-1012, ver 8, states that an assessment will only be completed if described in a technical agreement with the application holder.