**DEPARTMENT OF HEALTH AND HUMAN SERVICES**
FOOD AND DRUG ADMINISTRATION

| DISTRICT ADDRESS AND PHONE NUMBER | DATE(S) OF INSPECTION |
|---|---|
| 12420 Parklawn Drive, Room 2032<br>Rockville, MD 20857<br>ORAPHARMInternational483responses@fda.hhs.gov | 11/12/2024-11/19/2024<br>FEI NUMBER<br>3007058211 |

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED

Mr. Eric Putiti, General Manager

| FIRM NAME | STREET ADDRESS |
|---|---|
| Excelvision | 27 Rue de La Lombardiere |
| CITY, STATE, ZIP CODE, COUNTRY | TYPE ESTABLISHMENT INSPECTED |
| Annonay, Ardeche, 07100 France | 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**

**Written records of investigations into unexplained discrepancies do not always include the conclusions and follow-up. Specifically,**

From 01/2023 to date, about 120 complaints from the U.S. market were received regarding mold, black specks, and discoloration being observed on the (b) (4) caps, and inside of the (b) (4) drug products manufactured in Building (b) (4) fill lines (b) (4) The mold complaints impact (b) (4) U.S. products (b) (4) and involved (b) (4) different batches. Your firm's complaint investigations are inadequate to assure product quality and patient safety. Specifically,

**A.** We reviewed about 40 investigations, all concluded that the mold is probably due to improper use and/or storage of the product bottle by the patients. No non-conformity could be identified within Excelvision. However, you do not have documented evidence to support that improper handling by the end-users being the root cause or probable root cause. No patients or end-users were contacted or interviewed indicating improper use of the products.

**B.** Investigations do not always include microbiological testing of the returned samples to confirm the identity of the black specks, mold, or discoloration. The following are examples of U.S.

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complaint samples returned to the firm. No microbiological tests (i.e., sterility test) were performed, these samples were later discarded.

| Complaint # & Date | Product Name | Batch Information | Complaint Description | Returned Sample |
|---|---|---|---|---|
| B11131<br>08/06/2024 | (b) (4) | | Black spots on (b) (4) and inside cap. 6th for this type complaint for this batch | Not tested |
| B11132<br>08/07/2024 | | | Emitting an ugly black material. | Not tested |
| B11183<br>09/10/2024 | | | Black particles inside the cap. 2nd for this type complaint for this batch | Not tested |
| B11248<br>10/07/2024 | | | Black foreign substance came out along with the gel. | Not tested |

C. Retention samples from the complaint batches are examined by quality assurance (QA) technicians. However, the QA technicians are not trained and qualified in visual inspection for the presence of microbial growth including mold species in (b) (4) products.

**OBSERVATION 2**

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

Smoke Studies:

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**A.** Air flow visualization studies (smoke studies) do not provide assurance that unidirectional air flow (first air) is maintained. We reviewed smoke studies conducted on 06/2024 for the [(b) (4)] fill line [(b) (4)] located in Building [(b) (4)] The [(b) (4)] line is being used to aseptically fill [(b) (4)] products for the U.S. market and for [(b) (4)] Deficiencies observed including but were not limited to the following:

a) Aseptic operators did not observe slow and deliberate movement while working in the classified Grade A and Grade B cleanrooms. They performed aseptic activities using quick and abrupt motions that disrupted the HEPA laminar airflow.

b) Operator's body was observed leaning into the Grade A area while performing interventions.

c) During [(b) (4)] interventions, smoke was observed blown horizontally toward the operator and out to the grade B areas, leaving the Grade A critical zones without any unidirectional and downward HEPA coverage.

d) Swirl and stagnate airflow was observed in the [(b) (4)] set up (Zone [(b) (4)] near the Grade A Air Supply area.

e) During [(b) (4)] interventions, the Grade A side of the [(b) (4)] became exposed to the Grade B environment. However, it was not sanitized prior to [(b) (4)] the [(b) (4)] after each intervention.

f) Operators sanitized their hands but not their wrist and forearm areas with [(b) (4)] before reaching into the Grade A fill line. Additionally, they did not wait for the [(b) (4)] to dry before conducting interventions.

g) Operators' were observed spraying [(b) (4)] near open primary components (bottles and [(b) (4)] or open [(b) (4)] plate inside the Grade A fill line.

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| | Eileen A. Liu<br>AMH | Eileen A. Liu, Investigator (Lead)<br>Angelica M. Hernandez, Investigator | 11/19/2024 |

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Media Fills (MFs):

**B.** We watched videos of aseptic process simulation (APS) or media fills (MFs) studies for batch [(b) (4)] conducted in [(b) (4)] fill line on 10/23/2024. The [(b) (4)] line is being used to aseptically fill [(b) (4)] products for the U.S. market and for [(b) (4)] The following deficiency was noted:

We watched the video footage of [(b) (4)] aseptic operators each moved a bag of sterile bottles from the Grade B storage area to the bottle loading Zone [(b) (4)] to dispense the bottles into the Grade A [(b) (4)] [(b) (4)] We observed one of the operators sanitized only one side of the bag containing sterile bottles. We saw [(b) (4)] operators transported the bags inside the Grade A [(b) (4)] and dispensed the bottles in a quick motion. Material surfaces should be adequately sanitized before moving them into the Grade A fill line area. Bottles, [(b) (4)] or capsules should be dispensed in a slow and deliberate motion to avoid disrupting the laminar HEPA airflow.

**C.** Interventions performed during commercial filling operations are not tracked and trended based on intervention type, frequency, and duration to determine the worst-case conditions during MFs. There is a lack of sterility assurance for aseptic filling performed and for sterile [(b) (4)] products already in the market if MF simulations are not appropriately conducted. The following was noted:

a) Interventions identified as worst case are required to be simulated only [(b) (4)] during a MF study.

b) Commercial filling interventions are not always included in a MF. For example, during the filling of [(b) (4)] Batch [(b) (4)] in the [(b) (4)] line on 09/07/2024, interventions performed including but not limited to:

- Intervention 110 [(b) (4)] was performed 2 times
- Intervention 117 (overload of [(b) (4)] was performed 5 times

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- The filling line was stopped/paused for 2 hours and 45 minutes waiting for a maintenance personnel to perform machine adjustment.

However, the above intervention types and durations were not simulated during the MF Batch (b) (4) dated 10/23/2024.

**OBSERVATION 3**

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

**A.** (b) (4) and (b) (4) are being used to clean the (b) (4) Grade A filling machine surfaces. However, you do not have a validation study to show that the (b) (4) is effective against mold species.

**B.** Work instruction (WI) (b) (4) does not contain sufficient details on how to clean the (b) (4) filling machine surfaces. For example, the bottle bowl comes into contact with sterile bottles used to fill the sterile (b) (4) drug products. However, the only instruction written in the above WI is to "Clean the inside of the bottle bowl". (b) (4) does not have adequate cleaning details to prevent microbial contamination of drug products purporting to be sterile.

**OBSERVATION 4**

**Aseptic processing areas are deficient regarding systems for maintaining any equipment used to control the aseptic conditions. Specifically,**

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Your firm's aseptic fill line does not always contain smooth and easy to clean surfaces to prevent microbial contamination. On 11/18/2024, I (AMH) conducted a walkthrough inspection of the (b) (4) fill line (b) (4) located in Room (b) (4) of Building (b) (4) The (b) (4) fill line is being used to manufacture (b) (4) products for the U.S. market. I observed what appeared to be deep cracks and heavy scratch marks on the outside of the Grade A fill line (b) (4) in Zone (b) (4) bottle loading and conveying) and Zone (b) (4) bottle conveying). As per the Contamination Strategy Report (CCS100), the classified cleanroom surfaces should be smooth and easy to clean.

**OBSERVATION 5**

**Laboratory records do not include the initials or signature of a second person showing that the original records have been reviewed for accuracy, completeness, compliance with established standards. Specifically,**

On 11/13/2024, I (EL) reviewed the (b) (4) fill lines Grade D (gowning room) viable (b) (4) air and surface monitoring records. (b) (4) out of the total (b) (4) plates reviewed showed inaccurate colony enumerations. The discrepancy was confirmed by the QC Microbiology supervisor. Your environmental monitoring data is not subject to second-person review to make certain that all test results and associated information are appropriately reported.

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