WARNING LETTER

Excelvision Fareva

MARCS-CMS 703245 — MAY 07, 2025

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Delivery Method:

VIA EMAIL WITH READ RECEIPT

Reference #:

320-25-70

Product:

Drugs

Recipient:

Mr. Bernard Fraisse
President & CEO
Excelvision Fareva
32 Pl. de la Gare, 1616
Gare Luxembourg
France

Issuing Office:

Center for Drug Evaluation and Research (CDER)
United States

Warning Letter 320-25-70

May 7, 2025

Dear Mr. Fraisse:

The United States Food and Drug Administration (FDA) inspected your drug manufacturing facility, Excelvision, FEI 3007058211, at 27 Rue de la Lombardiere, Annonay, Ardeche, France, from November 12 to 19, 2024.

This warning letter summarizes significant violations of Current Good Manufacturing Practice (CGMP) regulations for finished pharmaceuticals. See Title 21 Code of Federal Regulations (CFR), parts 210 and 211 (21 CFR parts 210 and 211).

Because your methods, facilities, or controls for manufacturing, processing, packing, or holding do not conform to CGMP, your drug products are adulterated within the meaning of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 351(a)(2)(B).

We reviewed your December 10, 2024 response to our Form FDA 483 in detail and acknowledge receipt of your subsequent correspondence.

During our inspection, our investigators observed specific violations including, but not limited to, the following.

1. Your firm failed to thoroughly investigate any unexplained discrepancy or failure of a batch or any of its components to meet any of its specifications, whether or not the batch has already been distributed (21 CFR 211.192).

You failed to adequately investigate customer complaints for the various sterile **(b)(4)** drug products (prescription and over-the-counter) you manufacture. Your investigations were not thorough, did not appropriately expand in scope, and lacked a scientifically supported determination of root cause(s). Additionally, they failed to include an evaluation of customer complaint samples from the affected batches. You did not identify or implement adequate corrective actions and preventive actions (CAPAs).

Specifically, between January 2023 and November 2024, you received multiple complaints related to the presence of mold, black specks, and discoloration on the **(b)(4)**, and inside the product container of your **(b)(4)** drug products. Without supporting evidence, you attributed the root causes to the inadequate handling by customers who used your products (i.e., complainant leaving product residues in the container closure system) and determined that no further action was necessary.

In August 2024, environmental sampling of Room **(b)(4)**, corridor **(b)(4)**, and **(b)(4)** revealed the presence of *Penicillium citrinum, Fusarium oxysporum*, and *Aspergillus* mold species, respectively. On September 25, 2024, during environmental monitoring, an operator involved in the installation of the **(b)(4)** inside the ISO 5 (Grade A) of the additional **(b)(4)** filling line tested positive for *Penicillium citrinum* mold species on their right glove. Your investigation documented that water was found underneath the **(b)(4)** floor in the compounding tank in room **(b)(4)**, which is used to manufacture sterile **(b)(4)** drug. You attributed the root cause of the mold excursions in the building **(b)(4)** to the water leaks discovered. On November 8, 2024, and as a corrective action to mold detection, the floors were replaced with a new **(b)(4)**.

Notably, you had recovered mold species such as *Aspergillus* (July 13, 2022, filling room **(b)(4)**), *Zygomycete* (March 9, 2022, filling room **(b)(4)**), and *Penicillin* (November 2, 2022, filling room **(b)(4)**) in the building **(b)(4)**. However, as part of the investigations, you failed to consider the presence of mold in the ISO7 (Grade B) manufacturing areas over a 3-year period.

The presence of mold, black specks, and discoloration in **(b)(4)** drug products presents serious risks to consumers, especially since these are sterile products intended for **(b)(4)** application. Furthermore, the documented history of mold recovery in the aseptic filling lines and water leaks in the compounding room suggests a persistent environmental control issue that, if left unaddressed, compromises the sterility and safety of your drug products. It also indicates that your CAPAs have been ineffective to eliminate the present of mold in your manufacturing areas.

In your response, you state that the standard operating procedure has been revised to include a “questionnaire” for customers related to microbial contamination, as well as a new indicator to require microbial determination and sterility test for all returned samples. Additionally, you indicate that you will update your procedure for all returned and retained

samples related to potential microbial contamination that will be sent to the microbiology laboratory for further examination. Also, the procedure will include genetic identification (i.e., genus and species) of molds to be performed on return samples and compare with mold identified in filling areas.

Your response is inadequate. It fails to provide a comprehensive investigation into the customer complaints related to mold and black speck samples deviations. Additionally, you did not extend your investigations to other batches to determine the full scope and impact of the deviations on the product. In addition, you have not implemented an effective CAPA plan for the complaint investigations to prevent reoccurrence. You have not indicated whether the mold excursions in the aseptic filling lines have been corrected.

In response to this letter, provide the following:

- A comprehensive, independent assessment of your overall system for investigating deviations, discrepancies, complaints, OOS results, and failures. Provide a detailed action plan to remediate this system. Your action plan should include, but not be limited to, significant improvements in investigation competencies, scope determination, root cause evaluation, CAPA effectiveness, quality assurance unit oversight, and written procedures. Address how your firm will ensure all phases of investigations are appropriately conducted.
- An independent assessment and remediation plan for your CAPA program. Provide a report that evaluates if staff with proper investigation competencies effectively conducts root cause analysis, assures CAPA effectiveness, regularly reviews investigations trends, implements improvements to the CAPA program when needed, ensures appropriate quality assurance unit decision rights, and is fully supported by executive management.
- A management strategy including the interim measures describing the actions you have taken to ensure the safety and quality of your drugs currently in the market, such as notifying customers, recalling potentially affected drug products, conducting additional testing, adding batches to your stability program, and enhancements to your complaint system.
- For your **(b)(4)** container closure system **(b)(4)** drug products, provide your risk assessment for the current container closure system (i.e., **(b)(4)**) that describes the effectiveness of the **(b)(4)** mechanism. Also, we recommend that you conduct your own testing to determine the effectiveness of your CCS in preserving the sterility of drugs in products.

2. Your firm failed to establish and follow appropriate written procedures that are designed to prevent microbiological contamination of drug products purporting to be sterile, and that include validation of all aseptic and sterilization processes (21 CFR 211.113(b)).

Your air flow visualization studies (i.e., smoke studies) performed for your ISO 5 (Grade A) **(b)(4)** traditional aseptic filling line, used to fill **(b)(4)** drug products for the U.S. market, did not demonstrate unidirectional airflow. For example, airflow was observed to swirl, stagnate, and move sideways and upward toward the air return vent in the ceiling of the room when the **(b)(4)** of the **(b)(4)** filling line was **(b)(4)** to Room **(b)(4)** to introduce materials.

Additionally, our investigators observed various instances of poor aseptic techniques during a manual intervention, specifically when connecting the **(b)(4)** in the ISO 5 (Grade A) filling line. Also, operators leaned against or blocked the first air inside the line and extended their non-sanitized forearms near the **(b)(4)**, where the product bottles are open.

The ISO 5 (Grade A) area is critical because sterile products are exposed and therefore vulnerable to contamination. Your aseptic manufacturing process should be designed, and operations executed, to prevent contamination hazards to your sterile product. Flaws in the design of cleanrooms and aseptic processing lines, or improper execution of aseptic operations, can promote influx of contamination into the critical processing area.

In your response, you acknowledge the deficiencies on the air flow visualization and concur with the risk associated to drugs with the manual aseptic practices and thus will implement training and update procedures. You commit to perform new air flow visualizations in the filling lines. Also, to implement the use of long gloves (able to sanitize wrists and forearms) before ISO 5 (Grade A) interventions and **(b)(4)** operator to support interventions.

Your response is inadequate. You do not clearly specify how you will improve your air flow visualization, interventions in your ISO5 area, and how you intend to address potential deficiencies. Without adequate smoke studies, you cannot substantively assess whether your unidirectional airflow in the ISO 5 (Grade A) area protects the sterile drug products. Your response does not sufficiently address the lack of oversight of aseptic behavior of operators. Further, you do not adequately investigate poor aseptic practices to determine the impact on sterile drug products manufactured and aseptic processing areas.

In response to this letter, provide the following:

- Smoke studies under dynamic conditions, with thorough and complete evaluations of aseptic interventions and operator positioning within the critical filling areas. After you remediate your aseptic operation, provide smoke studies that visualize airflow and critically evaluate unidirectional airflow. Include a video of your dynamic smoke studies.
- A comprehensive risk assessment of all contamination hazards with respect to your aseptic processes, equipment, and facilities, including an independent assessment that includes, but is not limited to:
  o All human interactions within the ISO 5 area
  o Equipment placement and ergonomics
  o Air quality in the ISO 5 area and surrounding room
  o Facility layout
  o Personnel flows and material flows throughout all rooms used to conduct and support sterile operations.
  o Building management systems (e.g., address insufficiencies in differential pressure recording frequency)
- A detailed remediation plan based on review and recommendations by a qualified third party with specific expertise in aseptic processes, with timelines, to address the findings of the contamination hazards risk assessment. Describe how you will significantly improve aseptic processing operation design and control. Include comprehensive improvements in the design of both your aseptic processing lines and cleanrooms. Also describe your plans for qualification and validation of your extensively remediated operations.

3. Your firm failed to establish an adequate system for cleaning and disinfecting the room and equipment to produce aseptic conditions and an adequate system for maintaining equipment used to control the aseptic conditions (21 CFR 211.42(c)(10)(v) and 211.42(c)(10)(vi)).

Your aseptic processing operation is inadequately designed to prevent contamination of your sterile **(b)(4)** drug products. For example, the **(b)(4)** product ISO 5 (Grade A) filling line **(b)(4)**, is cleaned and sanitized using **(b)(4)**. However, critical equipment components, such as bowls and **(b)(4)** are not sterilized prior to installation and setup of the filling line. You rely on swab samples taken from equipment surfaces to determine whether the filling line has been properly cleaned and sanitized.

Additionally, during the current inspection, scratch marks were observed on the **(b)(4)** of the **(b)(4)** aseptic filling line. On April 8, 2024, and September 16, 2024, the preventive maintenance (PM) program documented the presence of scratches and cracks on the **(b)(4)** cover and **(b)(4)** in the equipment checklist. These issues were also observed during the July 2023 inspection. However, CAPAs were not implemented until after the current inspection, when the deficiency was again noted.

Aseptic processes should be designed to minimize exposure of sterile articles to potential contamination hazards, including, but not limited to, an adequate cleaning, disinfection, and sterilization process of movable parts. A suitable facility monitoring system is critical to maintain appropriate environmental conditions throughout all your cleanrooms. All deviations from established limits should be appropriately investigated to rapidly detect atypical changes that can compromise the facility's environment. Prompt detection of an emerging problem is essential to preventing contamination of your aseptic production operations. Additionally, your clean rooms should be designed as a functional unit and for a specific purpose. For example, an adequate design includes seamless and rounded floor-to-wall junctions, as well as readily accessible corners that are easy to clean.

In your response, you state **(b)(4)** are used to clean and disinfect the filling line surfaces **(b)(4)**, and that sporicidal decontamination using **(b)(4)** solution is performed **(b)(4)**. You also indicated that you would conduct a study to evaluate the efficacy of **(b)(4)** against mold species. Additionally, you state that a bio-decontamination process of filling machine surfaces ISO 5 (Grade A) will be implemented using a sporicidal product within defined frequency. You also indicate that the **(b)(4)** aseptic filling **(b)(4)** doors were changed.

Your response is inadequate. You did not provide a risk assessment to determine if the drug products manufactured by your facility for the U.S. market are not compromised for sterility. Additionally, we are concerned that your preventive maintenance program did not correct the improper equipment conditions (i.e., scratches and cracks on the **(b)(4)**) which were documented but not repaired.

In response to this letter, provide the following:

- A CAPA plan, based on the retrospective assessment of your cleaning and disinfection program, that includes appropriate remediations to your cleaning and disinfection processes and practices, and timelines for completion. Provide a detailed summary of vulnerabilities in your process for lifecycle management of equipment cleaning and disinfection. Describe improvements to your cleaning and disinfection program, including enhancements to cleaning effectiveness; improved ongoing verification of proper cleaning and disinfection execution for all products and equipment; and all other needed remediations.
- Your CAPA plan to implement routine, vigilant operations management oversight of facilities and equipment. This plan should ensure, among other things, prompt detection of equipment/facilities performance issues, effective execution of repairs, adherence to appropriate preventive maintenance schedules, timely technological upgrades to the equipment/facility infrastructure, and improved systems for ongoing management review.
- A comprehensive assessment of your facility, especially of those areas and rooms where mold species have been identified. This assessment should include a detailed remediation plan describing root causes for the presence of the mold species found and how you intend to reduce or eliminate potential sources to prevent recurrence.

Drug Production Ceased

We acknowledge your commitment to cease production of the traditional **(b)(4)** fill lines **(b)(4)** at this facility. In response to this letter, clarify whether you intend to resume manufacturing drugs for the U.S. market at this facility in the future.

If you plan to resume any manufacturing operations regulated under the FD&C Act, notify this office before resuming your drug manufacturing operations. You are responsible for resolving all deficiencies and systemic flaws to ensure your firm is capable of ongoing CGMP compliance. In your notification to the Agency, provide a summary of your remediations to demonstrate that you have appropriately completed all CAPAs.

Conclusion

The violations cited in this letter are not intended to be an all-inclusive list of violations that exist at your facility. You are responsible for investigating and determining the causes of any violations and for preventing their recurrence or the occurrence of other violations.

If you are considering an action that is likely to lead to a disruption in the supply of drugs produced at your facility, FDA requests that you contact CDER's Drug Shortages Staff immediately, at drugshortages@fda.hhs.gov, so that FDA can work with you on the most effective way to bring your operations into compliance with the law. Contacting the Drug Shortages Staff also allows you to meet any obligations you may have to report discontinuances or interruptions in your drug manufacture under 21 U.S.C. 356C(b). This also allows FDA to consider, as soon as possible, what actions, if any, may be needed to avoid shortages and protect the health of patients who depend on your products.

Correct any violations promptly. FDA may withhold approval of new applications or supplements listing your firm as a drug manufacturer until any violations are completely addressed and we confirm your compliance with CGMP. We may re-inspect to verify that you have completed corrective actions to any violations.

Failure to address any violations may also result in the FDA refusing admission of articles manufactured at Excelvision, located at Rue de la Lombardiere, Annonay, Ardeche, France, into the United States under section 801(a)(3) of the FD&C Act, 21 U.S.C. 381(a)(3). Articles under this authority that appear to be adulterated may be detained or refused admission, in that the methods and controls used in their manufacture do not appear to conform to CGMP within the meaning of section 501(a)(2)(B) of the FD&C Act, 21 U.S.C. 351(a)(2)(B).

This letter notifies you of our findings and provides you an opportunity to address the above deficiencies. After you receive this letter, respond to this office in writing within 15 working days[1]. Specify what you have done to address any violations and to prevent their recurrence. In response to this letter, you may provide additional information for our consideration as we continue to assess your activities and practices. If you cannot complete corrective actions within 15 working days, state your reasons for delay and your schedule for completion.

Send your electronic reply to CDER-OC-OMQ-Communications@fda.hhs.gov. Identify your response with FEI 3007058211and ATTN: Rafael E. Arroyo.

Sincerely,
/S/

Francis Godwin
Director
Office of Manufacturing Quality
Office of Compliance
Center for Drug Evaluation and Research

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1 Under program enhancements for the Generic Drug User Fee Amendments (GDUFA) reauthorization for fiscal years (FYs) 2023-2027, also known as the GDUFA III Commitment Letter, your facility may be eligible for a Post-Warning Letter Meeting to obtain preliminary feedback from FDA on the adequacy and completeness of your corrective action plans.