WARNING LETTER

Wintac Limited

MARCS-CMS 606700 — AUGUST 13, 2020

Delivery Method:

Via Email

Reference #:

320-20-43

Product:

Drugs

Recipient:

Dr. Veerappan Subramanian

President and CEO

Wintac Limited

300 Franklin Square Drive
Somerset, NJ 08873
United States

Issuing Office:

Center for Drug Evaluation and Research | CDER

United States

Warning Letter 320-20-43

August 13, 2020

Dear Dr. Subramanian:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Wintac Limited, FEI 3003821988, at 54/1 Bodhihal Village, Nelamangala, Bangalore, from February 10 to 19, 2020.

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 response to our Form FDA 483, received March 10, 2020, 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 the batch has already been distributed (21 CFR 211.192).

Your investigation into contaminated media fill units is inadequate in that it did not include scientifically supported conclusions, it lacked corrective actions and preventive actions (CAPA), and it failed to address all potentially compromised lots.

In November 2019, you conducted a media fill on the **(b)(4)** line. On the **(b)(4)** of incubation, you observed more than **(b)(4)** contaminated units. Your investigation into this media fill failure was inadequate. You considered a limited portion of the **(b)(4)** processing train to be the potential source of the *Ralstonia picketti* contamination. However, your investigation lacked scientific justification for its narrow focus and for ruling out other meaningful failure modes. Your investigation did not identify any CAPA to resolve the potential root causes, and you closed the investigation without sufficiently assessing how other batches manufactured on the line may have been or will be compromised. Instead, you concluded that there was no impact to product quality, citing the passing results of subsequent 2019 media fill runs.

Your firm's response is inadequate. Your response stated you did "not formally document" CAPA for this investigation "because they weren't connected to a definitive root cause and therefore not addressed."You further stated that only a "most probable" root cause had been identified in your investigation. It is essential that your investigations identify areas for improvement even when only possible root causes are identified. Without such risk mitigation, there is no assurance that you can prevent recurrence of failures from the same sources of excessive variation that led to the original failure. Your response did not include a retrospective evaluation of investigations to ensure CAPA have been identified and implemented when you do not find a definitive root cause.

Similar deficiencies were observed with your investigation into another failing media fill used to qualify your new aseptic filling line in June 2019. This investigation also did not thoroughly investigate potential root causes, include appropriate CAPA, and specify the number of contaminated units. We note this new filling line has not been used to manufacture commercially distributed products for the U.S. to date.

In response to this letter, provide:

• A comprehensive, independent assessment of your overall system for investigating deviations, discrepancies, complaints, out-of-specification 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 unit oversight, and written procedures. Address how your firm will ensure all phases of investigations are appropriately conducted.

• Your updated media fill failure investigations, which include a detailed, independent, retrospective evaluation of your media fills. Your third party should oversee your investigations to-date and provide their independent evaluation of these and other investigations which should include, but not be limited to:

o Events of all sterility positives and out-of-specification endotoxin results for the past four years, regardless of whether the batch was shipped to the U.S.
o Media fill failures for the past four years
o Identification of all potential failure modes associated with these events
o A detailed description of each aseptic connection made **(b)(4)** of the **(b)(4)** for line **(b)(4)**, including but not limited to the connections made before and after the **(b)(4)** tank and on the filling line

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)).

Inadequate Smoke Studies

Smoke studies performed for your **(b)(4)** aseptic processing operation lacked simulation of interventions and other related activities that occurred during aseptic manufacturing operations.

We also note that there were multiple aspects of both your cleanroom and aseptic processing line design which represent fundamental contamination risks. Your smoke studies demonstrated that:

• There is minimal protection of the aseptic processing line.
• There are extensive manual interactions with the aseptic processing line and its exposed sterile drug product and containers/closures.
• There is non-unidirectional airflow within the **(b)(4)** area, and limited space around the critical **(b)(4)** processing area.
• Personnel are inadvertently in contact with the interior of the **(b)(4)** used to access the area which houses the **(b)(4)** aseptic processing area.
• When these **(b)(4)**, there is a profound change in airflow that causes excessive turbulence.

While we have noted these deficiencies and the lack of adequate qualification, it is unclear whether your firm has undertaken efforts to remediate your cleanroom and processing line design.

Your firm's response is inadequate. You noted in your response that you performed additional smoke studies and concluded that airflow patterns were unidirectional. These smoke studies are inadequate. For example:

• Smoke studies did not provide adequate visualization of airflow of the aseptic processing operation.
• Smoke studies were not performed under dynamic conditions, as incorrectly identified in your report.
• You did not address smoke which travels along the gaps between the ceiling HEPA filters and mixes with first air.

The **(b)(4)** 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 **(b)(4)** processing area.

Inadequate Media Fills

Media fills should accurately simulate commercial operations. Our inspection found that interventions and other operations simulated during media fills were not sufficiently representative of commercial aseptic manufacturing.

We disagree with your initial response that indicated your media fills studies have been representative of commercial manufacturing operations. You did not provide a comprehensive retrospective review of all interventions and activities performed proximal to the aseptic processing line during commercial operations to fully remediate your media fill simulations.

If a media fill program fails to incorporate contamination risk factors and closely simulate actual drug product exposure, the state of process control and sterility assurance cannot be accurately assessed.

In response to this letter, provide:

• 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 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 **(b)(4)** area
o Equipment placement and ergonomics
o Air quality in the **(b)(4)** area and surrounding room
o Facility layout
o Building management systems (e.g., address insufficiencies in differential pressure recording frequency)
o Personnel flows and material flows throughout all rooms used to conduct and support sterile operations

• A detailed remediation plan based on review and recommendations by a third party, with timelines, to address the findings of the contamination hazards risk assessment. Describe how you will significantly improve aseptic processing operation design and control. In particular, 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.

• An update on the third-party assessment of your media fill program. Provide your third party's assessment of the updated media fills, and your plan for implementing the recommendations in the assessment.

• An update on the media fills you committed to perform on your **(b)(4)** manufacturing lines, and your assessment of frequency and duration of interventions performed. Describe improvements made to more accurately and appropriately simulate interventions and activities next to the **(b)(4)** zone that occur during production.

Additional Guidance on Aseptic Processing

See FDA's guidance document Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Practice to help you meet the CGMP requirements when manufacturing sterile drugs using aseptic processing at https://www.fda.gov/media/71026/download.

CGMP Consultant Recommended

Based upon the nature of the violations we identified at your firm, we strongly recommend engaging a consultant qualified as set forth in 21 CFR 211.34 to assist your firm in meeting CGMP requirements.

Your use of a consultant does not relieve your firm's obligation to comply with CGMP. Your firm's executive management remains responsible for resolving all deficiencies and systemic flaws to ensure ongoing CGMP compliance.

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 these 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.

Until you correct all violations completely and we confirm your compliance with CGMP, FDA may withhold approval of any new drug applications or supplements listing your firm as a drug manufacturer.

Failure to correct these violations may also result in the FDA refusing admission of articles manufactured at Wintac Limited, FEI 3003821988, at 54/1 Bodhihal Village, Nelamangala, Bangalore 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 may be subject to refusal of 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).

After you receive this letter, respond to this office in writing within 15 working days. Specify what you have done since our inspection to correct your violations and to prevent their recurrence. 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 3003821988 and ATTN: Brooke K. Higgins.

Sincerely,
/S/

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

cc: Sunil Gundewar, Chief Operating Officer

More Warning Letters (/inspections-compliance-enforcement-and-criminal-investigations/compliance-actions-and-activities/warning-letters)