U.S. Department of Health & Human Services

U.S. Food & Drug Administration

Inspections, Compliance, Enforcement, and Criminal Investigations

Wintac Limited 2/23/12

Department of Health and Human Services

Public Health Service
Food and Drug Administration
Silver Spring MD 20993

Warning Letter

VIA UPS MAIL

WL: 320-12-09

February 23, 2012

Mr. Jayaprakash Mady
Managing Director
Wintac Limited
#163 Reservoir Street
Basavanagudi, Bangalore 560004
India

Dear Mr. Mady:

During our September 12 to 20, 2011 inspection of your pharmaceutical manufacturing facility, Wintac Limited located at 54/1 Boodihal Village, Nelamangala, Bangalore 562 123, India, investigators from the Food and Drug Administration (FDA) identified significant violations of Current Good Manufacturing Practice (CGMP) regulations for Finished Pharmaceuticals, Title 21, Code of Federal Regulations, Parts 210 and 211. These violations cause your drug product(s) to be adulterated within the meaning of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (the Act) [21 U.S.C. § 351(a)(2)(B)] in that the methods used in, or the facilities or controls used for, their manufacture, processing, packing, or holding do not conform to, or are not operated or administered in conformity with, CGMP.

We have reviewed your firm's response dated October 11, 2011 and note that it lacks sufficient corrective actions.

Specific violations observed during the inspection include, but are not limited, to the following:

1. Your firm has not established or followed appropriate written procedures designed to prevent microbiological contamination of drug products purporting to be sterile. Such procedures shall include validation of all aseptic and sterilization processes [21 C.F.R. § 211.113(b)].
For example:

a. Your in *situ* air pattern analysis (smoke studies) does not demonstrate unidirectional airflow and sweeping action over and away from the critical processing areas under dynamic conditions.

Your response indicates that dynamic smoke studies for the **(b)(4)** filling area would be completed by the end of November, 2011. However, your response is inadequate because you failed to include a detailed interim plan describing additional steps taken in an effort to ensure that these areas were suitable for aseptic manufacturing of sterile drug products. Please provide a summary of the complete smoke studies (i.e., copy of video) conducted to evaluate whether the **(b)(4)** filling area is suitable for aseptic manufacturing of sterile drug products, and your firm's risk assessment of the product released to the market prior to your completion of the smoke studies.

b. Your firm demonstrates poor aseptic practices during the filling of sterile **(b)(4)** products including, but not limited to:

- An operator performing critical aseptic operations with exposed skin at the forehead, posing an unreasonable risk of the product becoming contaminated.
- Operators moving very quickly in the aseptic area, which may create unacceptable turbulence in the area, and disrupt the unidirectional airflow.
- Operators leaning halfway in and out of the class 100 area while performing interventions over opened bottles.

Your firm's response indicates that the operators are trained in aseptic practices. However, it fails to specifically address the observed deficiencies in the aseptic area during the inspection and the potential impact of these practices on drug products already distributed.

2. Your firm has not thoroughly investigated the failure of a batch or any of its components to meet its specifications whether or not the batch has already been distributed [21 C.F.R. § 211.192].

For example, during the aseptic filling of **(b)(4)** Solution lot **(b)(4)**, the batch record documented two dropper-plugging problems. The filling operation was stopped for 10 and 30 minutes, respectively, before this problem was rectified. There was no investigation or documentation of line clearance to remove potentially compromised bottles.

Your response indicates that the firm created a standard operating procedure (SOP) entitled, "Handling of Interventions During **(b)(4)** Filling," which includes appropriate investigation requirements for interventions due to manufacturing problems, and defining a method to segregate bottles potentially impacted during interventions. Your response is inadequate because you failed to include a risk assessment for the **(b)(4)** Solution lots already distributed prior to the implementation of this procedure.

3. Batch production and control records do not include complete information related to the production and control of each batch produced [21 C.F.R. § 211.188(b)].

For example,

a. Your firm failed to document in the batch record that **(b)(4)** Solution, lot **(b)(4)** had a 20-minute torque deviation during which the filling operation was interrupted. Problems with achieving proper torque are not infrequent. Six (6) out of **(b)(4)** (**(b)(4)**) batches had OOL (out-of-limit) results for in-process torque testing during packaging of **(b)(4)** Solution. Your firm failed to adequately investigate these results and implement adequate corrective actions to prevent recurrence.

Your response indicates that the torque value variation is due to inherent limitations of the machine and the variation in the size of the bottles and caps. Your proposed corrective action is to increase the torque limit range to **(b)(4)** oz/inch. However, this response is inadequate because you did not commit to enhanced monitoring of the modified torque range to ensure change effectiveness (i.e., confirm that physical integrity of the bottle is not compromised). Furthermore, you did not perform an evaluation or propose corrective actions to control your component supplier's variability

(bottles and caps), perform appropriate equipment qualification, and assure that technicians are adequately trained to effectively operate the packaging line.

We also note that your firm did not have an adequate system of recording torque non-conformances until recently, and a system is now in place following an evaluation by your firm's quality unit. It is important to note that in-process monitoring and testing results should be documented throughout your operations. In addition, adjustments and nonconformances need to be handled in accord with an appropriate operating procedure that provides for ongoing quality unit oversight.

> b. Your firm failed to document in the batch record that the sterilization cycle for **(b)(4)** Solution, lot **(b)(4)** was aborted due to a failure to reach the **(b)(4)** set point temperature during production.

This lot was ultimately rejected for confirmed out-of-specification (OOS) assays for **(b)(4)** of 56.6% (limit **(b)(4)**%-**(b)(4)**%) and **(b)(4)** of 55.5% (limit **(b)(4)**%-**(b)(4)**%). However, our inspection also noted multiple fundamental CGMP recordkeeping deviations. The sterilization cycle deviation was not documented in batch records or your firm's incident logs. Your firm also lacked any documentation, such as a printout, of the **(b)(4)** time and temperatures for the aborted load.

Your response indicates that **(b)(4)** failure events will now be handled through an incident reporting system to ensure appropriate documentation, traceability and controls. Your response is inadequate because it does not provide any specific details concerning the new incident reporting system. Please provide a copy of the new procedure for the incident reporting system.

Our inspection revealed several basic deficiencies in your firm's documentation of manufacturing operations and deviations. We urge you to perform a comprehensive evaluation and global remediation of your facility's documentation systems, including both manufacturing and laboratory operations.

The violations cited in this letter are not intended to be an all-inclusive statement of violations that exist at your facility. You are responsible for investigating and determining the causes of the violations identified above and for preventing their recurrence and the occurrence of other violations. If you wish to continue to ship your products to the United States, it is the responsibility of your firm to ensure compliance with all U.S. standards for CGMP and all applicable U.S. laws and regulations.

Until all corrections have been completed and FDA has confirmed corrections of the violations and your firm's compliance with CGMP, FDA may withhold approval of any new applications or supplements listing your firm as a drug product manufacturer. In addition, failure to correct these violations may result in FDA refusing admission of articles manufactured at Wintac Limited located at 54/1 Boodihal Village, Nelamangala, Bangalore 562 123, India into the United States. The articles are subject to refusal of admission pursuant to section 801(a)(3) of the Act [21 U.S.C. § 381(a)(3)], in that, the methods and controls used in their manufacture do not appear to conform to Current Good Manufacturing Practice within the meaning of section 501(a)(2)(B) of the Act [21 U.S.C. § 351(a)(2)(B)].

If, as a result of receiving this Warning Letter or in general, you are considering making a decision that will result in a decreased number of finished drug products or active pharmaceutical ingredients produced by your manufacturing facility, FDA requests that you contact CDER's Drug Shortages Program immediately, as you begin your internal discussions, at drugshortages@fda.hhs.gov in order to ensure that your action(s) does not adversely affect the public health.

Within fifteen working days of receipt of this letter, please notify this office in writing of the specific steps that you have taken to correct violations. Include an explanation of each step being taken to prevent the recurrence of violations and copies of supporting documentation. If you cannot complete corrective action within fifteen working days, state the reason for the delay and the date by which you will have completed the correction. Additionally, your response should state if you no longer manufacture or distribute **(b)(4)** Solution, **(b)(4)** and provide the date and reason you ceased production. Please identify your response with FEI # 3003821988.

If you have questions or concerns regarding this letter, contact Allison A. Aldridge, Ph.D., Compliance Officer, at the below address and telephone number.

> U.S. Food and Drug Administration
> Center for Drug Evaluation and Research
> Office of Manufacturing and Product Quality
> Division of International Drug Quality
> White Oak, Building 51, Room 2258
> 10903 New Hampshire Ave
> Silver Spring, MD 20993
> Tel: (301) 796-0483
> Fax: (301) 847-8741

Sincerely,

/s/

/Steven Lynn/
Steven Lynn
Acting Director
Office of Manufacturing and Product Quality
Office of Compliance
Center for Drug Evaluation and Research

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