USV Limited 3/10/17

U.S. FOOD & DRUG
ADMINISTRATION

10903 New Hampshire Avenue
Silver Spring, MD 20993

Via UPS
Return Receipt Requested

Warning Letter 320-17-29

March 10, 2017

Mr. Prashant K. Tewari
Managing Director
USV Private Limited
Arvind Vithal Gandhi Chowk, B.S.D. Marg,
Govandi, Mumbai 400 088
India

Dear Mr. Tewari:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, USV Private Limited at H-17/H-18, OIDC, Mahatma Gandhi Udyog Nagar, Dabhel, Daman from June 1 to 10, 2016.

This warning letter summarizes significant violations of current good manufacturing practice (CGMP) regulations for finished pharmaceuticals. See 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 July 1, 2016 response 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 establish laboratory controls that include scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that components, drug product containers, closures, in-process materials, labeling, and drug products conform to appropriate standards of identity, strength, quality, and purity (21 CFR 211.160(b)).

For example, during inspection of the QC microbiology testing laboratory, our investigators observed:

A. No growth on the positive control plate for media used to test microbiological **(b)(4)** samples. When a positive control fails to yield growth, test results cannot be considered valid due to the potential for false negatives.

B. Desiccation of a contact media plate used during environmental monitoring of the sterility testing area. Desiccated, cracked, or otherwise damaged **(b)(4)** compromises microbial growth promotion and accurate enumeration, and can lead to artificially low microbiological counts and false negatives. Using deficient media compromises the validity of your microbiological test results.

Also, you did not appear to routinely identify (i.e., to species level) bacterial and fungal isolates recovered during environmental monitoring of your aseptic processing room.

C. Air bubbles between filtration **(b)(4)** and **(b)(4)** plates in 13 out of **(b)(4)** microbiological **(b)(4)** system sampling plates. Inadequate contact between the filter **(b)(4)** and the **(b)(4)** plate may compromise recovery.

Your response indicates that you evaluated the impact of these laboratory deviations and believe they pose a low risk. The response lacks a commitment to perform a comprehensive evaluation of your microbiology laboratory controls and practices.

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)).

During review of your 2014 smoke studies, our investigators observed turbulent air flow in the ISO 5 area on the **(b)(4)** vial filling and capping production line at approximately 09:53 and 10:39 minutes.

In your response, you state that you have performed new smoke studies and that these new studies demonstrate unidirectional airflow during manual interventions. However, your response is inadequate because you did not assess past occurrences of deficient airflow in smoke studies or provide corrective actions to your process

design to resolve these issues. You also did not provide copies of the recent dynamic smoke studies.

In response to this letter, include a thorough retrospective review of smoke studies and a CAPA plan to address all deficiencies.

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 http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070342.pdf.

3. Your firm failed to exercise appropriate controls over computer or related systems to assure that only authorized personnel institute changes in master production and control records, or other records (21 CFR 211.68(b)).

For example, during inspection of the sterile manufacturing and QC microbiology areas, our investigators observed:

A. Deletion of at least six **(b)(4)** and **(b)(4)** tests in the audit trails for two instruments used to test sterile **(b)(4)**. Your systems allowed operators to delete files. You had no procedure to control this practice or to ensure a backup file was maintained. When you reviewed the audit trail data further, you identified a total of 25 deleted **(b)(4)** test results. In your response, you state that the production staff now only have "view and print" privileges. However, your response is inadequate because it lacks details of how appropriate oversight will be exercised over data backup to ensure it is appropriately retained.

B. No restricted access to the microbial identification instrument. Further, you lacked restricted access to the external hard drive used for backup of this instrument. All users could delete or modify files. In your response, you commit to limit access to the system and external hard drive. However, your response is inadequate because you did not provide a retrospective risk assessment of the impact and scope of inadequate system controls at your firm.

4. Your firm failed to ensure that laboratory records included complete data derived from all tests necessary to assure compliance with established specifications and standards (21 CFR 211.194(a)).

(b)(4) failed identity testing. You accepted a passing retest result without any investigation of the failed result.

In your response, you state that you attempted to conduct a retrospective investigation of the analysis which occurred more than a year earlier, and tentatively concluded that the out-of-specification (OOS) result might have been caused by analyst error. Also, your investigation recommends replacement of the polarimeter on which the OOS result was obtained.

Your response did not include a commitment to revisit the adequacy of your OOS procedures. When an OOS result is obtained, initiation of a prompt laboratory

investigation is critical. In addition, you must provide all data obtained during testing to the quality unit for batch record review. If the laboratory invalidates an OOS result, it is essential that the batch record include the relevant investigation. Only a scientifically sound and conclusive investigation can justify the exclusion of an OOS result from the final certificate of analysis.

For more information about the proper handling of OOS results and documentation of your investigations, see FDA's guidance document, *Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production,* at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070287.pdf

Data Integrity Remediation

Your quality system does not adequately ensure the accuracy and integrity of data to support the safety, effectiveness, and quality of the drugs you manufacture. We acknowledge that you are using a consultant to audit your operation and assist in meeting FDA requirements.

In response to this letter, provide the following.

A. A comprehensive retrospective investigation into the extent of the inaccuracies in data records and reporting.

B. A current risk assessment of the potential effects of the observed failures on the quality of your drugs. Your assessment should include analysis of the risks to patients caused by the release of drugs affected by a lapse of data integrity, and risks posed by ongoing operations.

C. A management strategy for your firm that includes the details of your global corrective action and preventive action plan.

Reference USV Private Limited, Mumbai, Warning Letter 320-14-03 for additional details to provide on data integrity remediation.

Repeat violations at multiple sites

FDA cited similar CGMP violations at other facilities in your company’s network. Warning Letter 320-14-03 was issued to USV Private Limited at Arvind Vithal Gandhi Chowk, BSD Marg, Govandi, Mumbai in February 2014. These repeated problems at multiple sites demonstrate that your company’s oversight and control over the manufacture of drugs is inadequate.

Your executive management remains responsible for fully resolving all deficiencies and ensuring ongoing CGMP compliance. You should immediately and comprehensively assess your company’s global manufacturing operations to ensure that systems and processes, and ultimately, the products manufactured, conform to FDA requirements.

Conclusion

Violations cited in this letter are not intended as an all-inclusive list. You are responsible for investigating these violations, for determining the causes, for preventing their recurrence, and for preventing other violations in all your facilities.

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) and 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 applications or supplements listing your firm as a drug manufacturer.

Failure to correct these violations may also result in FDA refusing admission of articles manufactured at USV Private Limited at H-17/H-18, OIDC, Mahatma Gandhi, Udyog Nagar, Dabhel, Daman into the United States under section 801(a)(3) of the FD&C Act, 21 U.S.C. 381(a)(3). Under the same authority, articles 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 or mail your reply to:

Lynnsey Renn, Ph.D.
Compliance Officer
U.S. Food and Drug Administration
White Oak Building 51, Room 4359
10903 New Hampshire Avenue
Silver Spring, MD 20993
USA

Please identify your response with FEI 3004086192.

Sincerely,
/S/
Thomas J. Cosgrove, J.D.
Director

Office of Manufacturing Quality
Office of Compliance
Center for Drug Evaluation and Research