Inspections, Compliance, Enforcement, and Criminal Investigations

Usv Limited 2/6/14

Department of Health and Human Services

Public Health Service
Food and Drug Administration
Silver Spring, MD 20993

Warning Letter

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

WL: 320-14-03

February 6, 2014

Mr. Prashant Kumar Tewari
Managing Director
USV Limited
Arvind Vithal Gandhi Chowk
BSD Marg, Govandi
Mumbai – 400088
India

Dear Mr. Kumar:

During our June 7-11, 2013 inspection of your control laboratory testing facility, USV Limited located at Arvind Vithal Gandhi Chowk, BSD Marg, Govandi, Mumbai India, investigators from the U.S. 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 products 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 conducted a detailed review of your firm’s response and note that it lacks sufficient corrective actions.

We acknowledge receipt of your firm’s correspondence dated July 1, 2013. We also acknowledge receipt of your firm's additional correspondence dated August 29, 2013 and December 5, 2013.

Our investigators observed specific violations during the inspection, including, but not limited to, the following:

1. Your firm failed to follow and document at the time of performance required laboratory control mechanisms (21 C.F.R. §211.160(a)).

Our investigators found that laboratory analysts did not document the balance weights at the time of sample weighing. Specifically, sample weights used in calculations were created after the chromatographic runs. The analyst admitted that the sample weights that were represented as raw data from the analysis actually were backdated balance weight printouts produced after the analysis and generated for the notebooks. These sample weights were used to calculate related compounds and impurities used in support of method validations submitted in FDA drug applications.

You submitted the data generated with the discrepancies above to the Agency in support of drug product application for **(b)(4)** Capsules USP **(b)(4)** mg and **(b)(4)** mg (**(b)(4)**). These data manipulation practices were also observed in data submitted for **(b)(4)** Tablets USP **(b)(4)** mg, **(b)(4)** mg and **(b)(4)** mg (**(b)(4)**) as well as **(b)(4)** Tablets USP **(b)(4)** mg, **(b)(4)** mg and **(b)(4)** mg (**(b)(4)**).

The lack of reliability and accuracy of data generated by your firm is a serious CGMP deficiency that raises concern for all data generated by your firm. While we acknowledge the commitment in your response that your staff is being interviewed to determine the extent of the problematic laboratory activities, we remain concerned about the capability and credibility of your quality unit. Specifically, in your response to your previous 2009 inspectional findings you stated that you audited all analytical method validation studies for all the **(b)(4)** submitted to the Agency since 2006. However, you failed to detect and investigate the inaccurate data found by our investigators during the recent inspection.

2. 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 C.F.R. §211.68(b)).

Your firm failed to have adequate procedures for the use of computerized systems in the quality control (QC) laboratory. Our inspection team found that current computer users in the laboratory were able to delete data from analyses. Notably, we also found that the audit trail function for the gas chromatograph (GC) and the X-Ray Diffraction (XRD) systems was disabled at the time of the inspection. Therefore, your firm lacks records for the acquisition, or modification, of laboratory data.

Moreover, greater than **(b)(4)** QC laboratory personnel shared **(b)(4)** login IDs for **(b)(4)** high performance liquid chromatographs (HPLC) units. In addition, your laboratory staff shared one login ID for the XRD unit. Analysts also shared the username and password for the Windows operating system for the **(b)(4)** GC workstations and no computer lock mechanism had been configured to prevent unauthorized access to the operating systems. Additionally, there was no procedure for the backup and protection of data on the GC standalone workstations.

In your response, you indicate that your firm performs periodic back-ups of data, however your firm lacks assurance that the periodic backed up data includes all of the original data generated. Your response to this deficiency does not discuss how you will ensure that data audit trails will not be disrupted in the future and lacked a computer life cycle approach to, for example, assure routine verification of access controls in computer systems.

In your response to this letter provide a comprehensive computer life cycle program to assure that appropriate controls are always exercised over computer or related systems to comply with 21 CFR 211.68.

The deviations listed above, as well as other deficiencies our investigator found, lead us to question the basic effectiveness of your current quality system to achieve overall compliance with CGMP at your facility. It is apparent that you have not implemented a robust quality system at your firm. Be advised that corporate management is responsible for ensuring the reliability of all data produced by your firm, including data submitted to FDA to support the safety, effectiveness, and quality of marketed products.

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 the violations identified above and for preventing their recurrence and the occurrence of other violations.

We acknowledge that you committed to hiring a third party auditor with experience in detecting data integrity problems, to assist you with this evaluation and to assist with your overall compliance with CGMP. It is your responsibility to ensure that data generated during operations is accurate and that all results reported are a true representation of the quality of your drug products. In response to this letter, provide a list of all the batches of drug products shipped to the U.S. market that relied upon missing, inaccurate, or unreliable test data.

Your data integrity consultant should:

1. Identify any historical period(s) during which inaccurate data reporting occurred at your facilities.
2. Identify and interview your current employees who were employed prior to, during, or immediately after the relevant period(s) to identify activities, systems, procedures, and management behaviors that may have resulted in or contributed to inaccurate data reporting.
3. Identify former employees who departed prior to, during, or after the relevant periods and make diligent efforts to interview them to determine whether they possess any relevant information regarding any inaccurate data reporting.
4. Determine whether other evidence supports the information gathered during the interviews, and determine whether additional facilities were involved in or affected by inaccurate data reporting.
5. Use organizational charts and SOPs to identify the specific managers in place when the inaccurate data reporting was occurring and determine the extent of top and middle management involvement in, or awareness of, data manipulation.
6. Determine whether any individual managers identified in item (5) above are still in a position to influence data integrity with respect to CGMP requirements or the submission of applications; and establish procedures to expand your internal review to any other facilities determined to be involved in, or affected by, the inaccurate data reporting.
7. As part of this comprehensive data integrity audit of your laboratory, your audit report also should include any discrepancies between data or information identified in approved applications, and the actual results, methods, or testing conditions submitted to the Agency. Include an explanation of the impact of all discrepancies. Provide a corrective action operating plan describing the specific procedures, actions and controls that your firm will implement to ensure integrity of the data in each application currently submitted to the Agency and all future applications. This should not only cover methods validation, but any other testing (e.g., stability tests, release tests) you have performed for customers that may have been used to support a drug application-related submission to the agency.

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 control testing laboratory. In addition, your failure to correct these violations may result in FDA refusing admission of articles tested at USV Limited, Arvind Vithal Gandhi Chowk, BSD Marg, Govandi, Mumbai, India into the United States under Section 801(a)(3) of the Act, 21 U.S.C. 381(a)(3). The articles may be 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 CGMP within the meaning of Section 501 (a)(2)(B) of the Act, 21 U.S.C. 351(a)(2)(B).

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 and prevent the recurrence of violations, and provide copies of supporting documentation. If you cannot complete corrective actions within fifteen working days, state the reason for the delay and the date by which you will have completed the corrections. Additionally, if you no longer validate the methods for testing or perform release testing of the drug products and APIs at issue provide the dates and reasons you ceased operation. Please identify your response with FEI # 3003255171.

Please send your reply to:

Milva Meléndez
Compliance Officer
Food and Drug Administration
CDER/OC/OMPQ/DIDQ/ICB2
10903 New Hampshire Ave.
Bldg 51, Room 4357
Silver Spring, MD 20993-0002

Sincerely,
/S/
Steven J. Lynn
Director
Office of Manufacturing and Product Quality
Office of Compliance
Center for Drug Evaluation and Research

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