Inspections, Compliance, Enforcement, and Criminal Investigations

Canton Laboratories Pvt. Ltd. 2/27/14

Department of Health and Human Services

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

Warning Letter

WL: 320-14-04

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

February 27, 2014

Mr. Bhailalbhai Nathabhai Patel, Managing Director
Canton Laboratories Private Limited
110-A & B GIDC Estate
Makarpura Road
Vadodara 390 010, INDIA

Dear Mr. Bhailalbhai Nathabhai Patel:

During our April 01, 2013 through April 09, 2013 inspection of your pharmaceutical manufacturing facility, Canton Laboratories Private Limited located at 110-A & B GIDC Estate, Makarpura Road, Vadodara, India, investigators from the U.S. Food and Drug Administration (FDA) identified significant deviations from current good manufacturing practice (CGMP) for the manufacture of active pharmaceutical ingredients (APIs). These deviations cause your APIs 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.

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

1. Failure to perform laboratory testing of APIs to ensure conformance to specifications and to accurately report results on Certificates of Analysis (CoA).

Your firm reported microbial limits results on CoAs for three API batches without performing these tests. Specifically, your firm has no raw data for the microbial limits tests reported on the CoAs for **(b)(4)** USP lots **(b)(4)**, and **(b)(4)**. Your quality unit approved the release of these API batches without data to support that release specifications were met. While your CoAs state that microbial limits conformed to specifications, the inspection found that no testing was done. Multiple personnel confirmed that your firm did not perform the microbial tests reported on the CoAs.

Similarly, our inspection found other examples where your firm did not have raw data, yet reported testing as acceptable on your CoAs. For example, your firm released **(b)(4)** USP (for use in **(b)(4)**) and **(b)(4)** USP (for use in **(b)(4)**) without supporting documentation for metallic impurities testing.

Your firm's response to this observation stated that your firm has revised relevant SOPs and performed training on these SOPs. We note that the previous inspection in July 2008 found a similar observation. That inspection found that your firm did not retain raw data and documentation for Karl Fischer titration, Assay, Specific Gravity, solubility, clarity, and pH of **(b)(4)**, USP. Your firm's response to the 2008 observation, similar to your response to the current findings, was to correct this issue through retraining and document revision. It is very concerning that your firm has not taken the proper actions to address the underlying issues.

In your response, provide a complete corrective action plan that begins with a retrospective review of the analytical data and batch records for all products that remain within expiration. It is essential that this investigation includes all products manufactured at your site. In addition, provide details of the systemic actions taken to prevent recurrence of these fundamental deficiencies in laboratory data integrity and COA authenticity.

2. Failure to maintain complete data derived from all laboratory tests conducted to ensure compliance with established specifications and standards.

Your firm failed to prevent raw data from being deleted from the Atomic Absorption Spectrophotometer (AAS) used for elemental analysis testing. Specifically, our investigation found laboratory analysts had access to delete and overwrite AAS raw data. This instrument did not have sufficient controls to prevent unauthorized access to, changes to, or omission of data files and folders. This is especially concerning because our inspection uncovered only 38 raw data files on the hard drive of the AAS, while analysts stated that the AAS had been used for over 400 analyses. Your firm failed to store the raw data elsewhere. Therefore, all AAS testing results for which no raw data exists are in doubt. Your firm's improper control over the laboratory records raises concerns about the quality of the APIs your firm has released.

Your firm's response to this observation stated that the procedure governing use of the AAS has been updated to include the printing and attachment of AAS raw data to the test reports. However, this corrective action is not sufficient as it does not determine the extent and impact of the problem.

In your response, provide an action plan for an investigation into the extent of this practice, the impact on the quality of previously released product, and why your laboratory and quality management failed to detect this practice. Additionally, provide a clear and thorough procedure for the retention of your raw data for all laboratory instrumentation and equipment.

3. Failure to ensure equipment is cleaned in a reproducible and effective manner to prevent contamination of a material that would alter the quality of the APIs.

Your firm failed to ensure the non-dedicated **(b)(4)** was adequately cleaned after use. Specifically, during three separate walk-throughs of the facility taking place over five days, our inspection found what appeared to be product residue in the **(b)(4)** despite the "clean" label on the equipment. This represents a potential for cross-contamination of the APIs manufactured in this equipment.

In addition, your firm failed to perform adequate cleaning validation studies for your non-dedicated equipment. For example, your firm failed to perform recovery studies to ensure product residues could be detected during the cleaning validation studies.

Your firm's response to this observation stated that you are performing revised cleaning validation studies. We remain concerned that this corrective action is not extensive enough to determine the extent and impact of the problem.

In your response, provide a detailed action plan for an investigation into the impact on the quality of previously released product, along with your risk assessment. Additionally, provide an action plan for ensuring adequate cleaning in the interim, prior to completion of the validation studies, such as cleaning verification sampling with appropriate acceptance criteria. Furthermore, provide a report summarizing the revised cleaning validation studies that your firm has been conducting, addressing the issues discussed above. Your response should also include the establishment of a training program for operators, quality unit personnel, and managers to improve cleaning competencies.

4. Failure to ensure that APIs are produced according to pre-approved instructions and that batch production records include complete information pertaining to the production of each batch.

For example:

a. Your firm erroneously calculated and then used the incorrect amounts of starting materials on multiple occasions. The inspection found that your firm did not calculate correct proportions of starting materials that were released for the production of **(b)(4)** USP and **(b)(4)** USP. Your firm's Master Formula Records (MFRs) specify the proportions of raw materials, but your Batch Production Records (BPRs) do not include or describe calculations to appropriately adjust the amounts of starting materials to be used for a given batch size.
b. Your firm released APIs using BPRs that did not include the signatures of the production operators that performed each significant step or operation.
c. Your firm released API where production records contained missing information. For example, our inspection uncovered a Cleaning Report where the rinse sample pH was entered as "nil" despite the pH being a requirement to ensure the equipment is clean.

These gaps in your quality unit bring into question your firm's ability to properly evaluate the quality of your API batches before a disposition decision is made.

Your firm's response to this observation stated that SOPs pertaining to the relevant batch records have been revised and that training on these SOPs has occurred. We note that the previous inspection in July 2008 found a similar observation where your quality unit reviewed, released, and approved laboratory and batch records for **(b)(4)**, USP, that did not properly follow the MBR and did not include the signatures of the operators who performed the operations at the time of performance. Your firm's response to the 2008 observation was similarly retraining and document revision. It is concerning that your commitments in the previous response did not address the underlying issues.

Additionally, several other observations were of particular concern, such as your firm's:

- Failure to properly investigate customer complaints.
- Failure to properly investigate out-of-specification results.
- Failure to follow your Master Validation Plan for process validations or equipment calibrations.
- Failure to provide adequate resources to the quality unit.
- Failure of your quality unit to properly review production records and detect instances where testing was not performed to support your company's certifications on your COAs.
- Failure to perform appropriate stability studies for product currently in the market.
- Failure to establish an impurity profile for product currently in the market.

Our inspection revealed serious documentation practices and reported missing raw data. These deficiencies compromised the quality and accountability of your APIs in the supply chain by reporting that your APIs were in conformance to specifications on your CoAs, when tests were not being conducted. It is a basic responsibility of your quality unit to ensure that all API lots produced meet specifications that they are purported to possess.

The above examples raise serious concerns regarding the integrity, reliability and accuracy of the data generated and available at your facility. In your response to this letter, provide a comprehensive evaluation of the extent of the deletion and destruction of records, a risk assessment regarding the potential impact on the quality of products, and a comprehensive corrective and preventive action plan. Your response should include a summary of your investigation into missing, inaccurate or unreliable tests results with a description of these findings. Your investigation should assess the impact of all these incidents on the quality of the drug products produced with your APIs, and explain the systemic actions that will be instituted to prevent these fundamental breaches of data integrity and management oversight in the future.

Accordingly, you should include a detailed description of your plans to implement a robust quality system in your response to this letter. This remediation plan should describe the broader steps taken to ensure direct corporate oversight of the quality and operation functions of this facility. This system should ensure sustainable compliance with CGMP, including the basic capability to prevent data manipulation and destruction or deletion of records. The lack of reliability and accuracy of data generated by your firm's laboratory is a serious CGMP deficiency that raises concerns with all data generated by your firm.

Provide your corrective action plan that describes your commitment, procedures, actions, and controls to ensure data integrity. This

plan should include the corrective actions implemented to ensure that all managers, supervisors, and quality unit personnel are properly trained in detecting lack of data integrity and manipulation. The investigation should provide detailed descriptions of other incidents where your quality unit failed to ensure proper testing of materials and should include a retrospective review of all test results generated by your laboratory personnel. Also provide documentation of the specific training offered to all employees regarding the importance of following CGMP and ensuring that all required tests are performed.

In summary, you are responsible for having controls to prevent omissions of data, as well as recording any changes made to existing data, which should include the date of change, identity of person who made the change, and an explanation or reason for the change. All changes to existing data should be made in accordance with an established procedure. Your firm also needs to improve its procedures for analyzing complaints, out-of-specification results and investigations, deviations and investigations, validation, processes, work operations, monitoring systems, laboratory services, quality supplier audit reports, service records, and other quality records and sources of quality data to identify existing and potential issues that could cause the APIs not to have the identity, strength, quality, and purity they purport or are represented to possess. As well, your firm needs to improve its procedures that provide for investigation of the cause of out-of-specification results or other nonconformities relating to product, processes, and the quality system, and verifying and validating the corrective and preventive actions to ensure that such action is effective and does not affect the identity, strength, quality, or purity of the product.

Because of your failure to correct repeat violations and seriousness of the deficiencies found, we recommend you engage an independent third party with experience on CGMPs to assist you in developing and implementing a robust quality system, and with expertise in assessing breaches in data integrity, to ensure that all the APIs manufactured at your facility have the appropriate identity, strength, quality, and purity. Itis your responsibility to ensure that data generated is accurate and that the results reported are a true representation of the quality of your drug products. It is essential that your firm establishes a comprehensive ongoing training program for analysts, QC personnel, other quality unit personnel, operators, and management to address the fundamental issues discussed throughout this letter. Provide a list of all the lots of APIs shipped to the U.S. market that relied upon missing, inaccurate, or unreliable test data.

Please note that a guidance document entitled "Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients" (ICH CGMP guidance), prepared under the auspices of the International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use, describe current good manufacturing practice (CGMP) for the manufacture of APIs. The guidance is intended to help ensure that all APIs meet the standards for quality and purity they purport or are represented to possess. FDA considers the expectations outlined in ICH Q7, as well as alternatives intended to accomplish the same goals and provide an equivalent level of quality assurance, in determining whether a firm's APIs have been manufactured, processed, packed, and held according to current good manufacturing practice under section 501(a)(2)(B) [21 USC 351(a)(2)(B)] of the Act. To obtain the ICH CGMP guidance document for your reference, please refer to the following page of FDA's website: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073497.pdf[1]

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

If, as a result of receiving this warning letter or for other reasons, you are considering a decision that could reduce the number of 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 so that we can work with you on the most effective way to bring your operations into compliance with the law. Contacting the Drug Shortages Program also allows you to meet any obligations you may have to report discontinuances in the manufacture of your drug under 21 U.S.C. 356C(a)(1), 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 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 an API manufacturer. In addition, your failure to correct these violations may result in FDA refusing admission of articles manufactured at Canton Laboratories Private Ltd., Vadodara, 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 deviations, 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 manufacture or distribute the APIs at issue, provide the date(s) and reason(s) you ceased production. Please identify your response with FEI # 3003297374.

Please send your reply to: David S. Jones, Compliance Officer, White Oak Building 51, Room 4220, 10903 New Hampshire Ave, Silver Spring, MD 20993-0002.

Sincerely,
/S/
Michael Smedley Acting for Steve Lynn
Director
Office of Manufacturing and Product Quality
Office of Compliance
Center for Drug Evaluation and Research

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