# Sharp Global Limited 10/15/14

Department of Health and Human Services

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

**Warning Letter**

**WL: 320-15-01**

**CERTIFIED MAIL**
**RETURN RECEIPT REQUESTED**

October 15, 2014

Mr. Sanjay Sinhal
Managing Director
Sharp Global Limited
Sharp House, Plot No. 9, 1st Floor, Part 1, Sagar Centre
Gujranwala Town, New Delhi, 110009
India

Dear Mr. Sanjay Sinhal:

During our March 6, 7, and 10, 2014 inspection of your pharmaceutical manufacturing facility, Sharp Global Limited located at Sharp House, Plot No. 9, 1st Floor, Part 1, Sagar Centre, Gujranwala Town, New Delhi, India, an investigator 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.

Your firm failed to fulfill its registration obligations under Section 510(i)(1) of the Act and its listing obligations under Sections 510(i)(2) and 510(j), which is prohibited under Section 301(p), 21 U.S.C. 360(i)(1) and (2), 360(j), and 331(p).

For example, in 2014, your firm offered for import into the United States drugs manufactured or otherwise processed at plants **(b)(4)** and **(b)(4)** located in New Delhi, India. All drug-manufacturing facilities producing drugs intended for the U.S. must be registered before importation.

Please note that a drug offered for import into the United States may be refused admission under Section 801(o) of the Act if the importer, owner, or consignee is not able to provide a statement of the registration of the establishment that manufactured it. In addition, if a drug is not listed in accordance with Section 510 of the Act, including if the listing for the drug references a manufacturing establishment that does not maintain a current establishment

registration, the drug appears to be misbranded under Section 502(o) and subject to refusal of admission under Section 801(a)(3), 21 U.S.C. 352(o).

Your response did not address this issue. Information on how to register and list is available at the following internet website: **http://www.fda.gov/cder/drls/registration_listing.htm**. If you continue to produce drugs that are offered for import into the U.S., you must complete the required registration and listing. You should provide evidence that you have fulfilled these requirements in your response to this letter.

We have conducted a detailed review of your firm's response dated March 25, 2014 and note that it lacks sufficient corrective actions.

Our investigator observed specific deviations during the inspection, including, but not limited to, the following:

1. Failure to prevent unauthorized access or changes to data and to provide adequate controls to prevent omission of data.

Your firm did not have proper controls in place to prevent manipulation of your laboratory's electronic raw data. Specifically, your NuCon 5700 gas chromatographs (GCs) did not have access controls that would prevent the deletion or altering of raw data files. In addition, the GC software lacked active audit trail functions to record any changes to the data, including the previous entries, who made the changes, and when the changes were made. The use of audit trails for computerized analytical instrumentation is essential to ensure the integrity and reliability of the electronic data generated.

During the inspection, your management explained that the laboratory practice was to delete the raw data files once the chromatograms were printed. As such, your firm did not retain complete raw data from testing to ensure the quality of your APIs. Specifically, electronic raw data files, supporting your GC testing for release (assay) were deleted.

Your response indicates you issued a standard operating procedure (SOP) entitled "Security of GC Data" (SGL-SOP-QC-079) to prevent unauthorized access or changes to data. Your response is inadequate because it does not address the audit trail functions referenced above.

In your response to this letter, provide a copy of your action plan to prevent deletion and alteration of electronic data. Include your timeline for ensuring that all applicable computerized systems are equipped with audit trail functions. In addition, describe the archival process your firm has implemented to address these issues and how you will evaluate the effectiveness of these corrections. Provide a detailed summary of the steps taken to train your personnel on the proper use of computerized systems.

Your response should also address your firm's procedure for the establishment, issuance, and control of passwords used to access your GC instrumentation. All access levels for computerized systems should be clearly defined and documented in a written procedure. Your response to the FDA-483 appears only to address access to the Windows operating software and not for access to the GC data acquisition system.

2. Failure to have appropriate controls for issuance of batch records.

Our inspection found that batch records were uncontrolled in that operators had the ability to print batch records from their personal computers. In addition, various uncontrolled blank manufacturing batch records were found in a binder located in the production office.

We acknowledge the revisions made to SOP No. SGL-IMS-04 (section 2.3), “Control of Records,” however, your firm provided no evidence demonstrating that all operators have been trained on the revised procedure. Provide documentation to ensure that all personnel have been trained on the revised procedure.

3. Failure to have appropriate documentation and record controls.

a. Critical information necessary to assure the traceability of all the raw materials used during the production of **(b)(4)** USP was not maintained. Our inspection found that your firm placed correction tape over multiple entries of raw material batch numbers in a logbook used to track crude **(b)(4)**(raw material) used for the manufacture of **(b)(4)** USP. In addition, you used correction fluid on a recurring basis to make corrections in a logbook used to record various details of **(b)(4)** within the **(b)(4)** USP manufacturing process. Corrections to entries should be dated and signed, and the original entry must remain legible for review.

In addition, your current SOP SGL-SOP-GEN-001 “Correct Way of Making Monitoring Records,” prohibits the use of white ink for corrections of *any written matter*; however, operator training records did not show training on this procedure.

It is your responsibility to ensure that all applicable operators are trained on your procedures. Please provide assurance that this procedure is fully implemented and provide a corrective action plan that prevents the recurrence of this deficiency.

b. We also note that the authorizing production official did not sign as required the in-process batch record BP/USP #U2-167/13-14 for **(b)(4)** USP even though the entry was dated 1/20/14.

3. Failure to validate non-compendial analytical test methods.

Your firm failed to validate the non-compendial analytical test method used to analyze **(b)(4)** USP for chromatographic purity. The inspection documented that your firm could not demonstrate that the method in place was suitable for its intended purpose. In addition, the system suitability for this test method was inadequate because it did not comply with the official United States Pharmacopoeia (USP) monograph for **(b)(4)**. Specifically, the inspection documented that system suitability was performed **(b)(4)**, and following an instrumentation error, despite use of the method throughout the **(b)(4)**.

In your response, you indicate that your method has been validated for chromatographic purity and that you are now completing system suitability **(b)(4)** batch sample analysis. Please note that the USP monograph for **(b)(4)** was revised to include assay and related compounds effective May 1, 2014. Provide your revised validation protocol and timeline for completing the validation of your method for assay and related compounds. In addition, confirm that all **(b)(4)** USP lots manufactured prior to May 1, 2014 met the appropriate specifications for chromatographic purity and provide a summary of your assessment. It is also your responsibility to ensure that all lots manufactured after May 1, 2014, comply with the current official monograph requirements for assay and related compounds.

General Comments:

The inspection found that batch records related to non-US products were not completed at the time key operations were performed for batches that were subsequently distributed for use. For example,

The authorizing QC and QA officials did not sign the **(b)(4)** blend production review and release order page of batch records USP #MU-048/13-14 and USP #MU-047/13-14 for **(b)(4)** USP even though the entries were dated 11/22/13 and 11/24/13, respectively. In addition, there were a number of manufacturing sections within the batch records that were completely blank; specifically, pages 3, 4, and 6. Moreover, Batch records USP #MU-014/13-14, #MU-022/13-14, #MU-023/13-14, #MU-025/13-14, #MU-027/13-14, and #MU-033/13-14 were found to be missing production and QC signatures; specifically, in sections **(b)(4)** of the batch records. Please note that signatures of personnel performing the manufacturing steps, directly supervising, or verifying the completion of the manufacturing steps are required.

Your response is inadequate in that the batch record submitted as an example of the corrective actions implemented continues to be deficient. In your response, you state that all records regarding batches of **(b)(4)** USP are complete. However, the **(b)(4)** *Log* page of batch record U2-174/13-14 for **(b)(4)** USP is missing the required signatures for **(b)(4)** listed.

We also note that the label included in your batch record is incomplete in that it fails to indicate the **(b)(4)** form, **(b)(4)** or **(b)(4)**, of **(b)(4)** USP.

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 deviations 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 deviations may result in FDA refusing admission of articles manufactured at, Sharp Global Limited, Gujranwala Town, New Delhi, 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 dates and reasons you ceased production. Please identify your response with FEI # 3004161432.

Please send your reply to:
Christina Alemu-Cruickshank
Consumer Safety Officer

Division of International Drug Quality
Office of Manufacturing and Product Quality
Office of Compliance
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Building 51 Room 4233
Silver Spring, MD  20993-0002.

Sincerely,
/S/
Thomas Cosgrove, J.D.
Acting Director
Office of Manufacturing and Product Quality