Micro Labs Limited 1/9/15

Department of Health and Human Services

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

Warning Letter

WL: 320-15-05

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

January 9, 2015

Mr. Anand Surana
Director
Micro Labs Limited
27, Race Course Road
Bangalore 560 001 India

Dear Mr. Surana:

During our inspection between May 5-10 and 12-13, 2014, of your pharmaceutical manufacturing facility, Micro Labs Limited, located at Plot No. S-155 to S-159, Phase III, Verna Industrial Estate, Verna, 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.

In addition, our investigators identified significant violations of Section 505(k) of the Act, 21 U.S.C. 355(k), and Title 21, Code of Federal Regulations, Section 314.81, promulgated in accordance with Section 505(k)(1) of the Act, 21 U.S.C. 355(k)(1), which require applicants to establish and maintain records, and to report data relating to clinical experience, along with other data or information. Failure to comply with regulations promulgated under Section 505(k) is a prohibited act under Section 301(e) of the Act, 21 U.S.C. 331(e).

We have conducted a detailed review of your firm’s response dated June 3, 2014, and note that it lacks sufficient corrective actions. We also acknowledge receipt of your firm's additional correspondence dated June 17, July 22, and December 4, 2014.

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

Current Good Manufacturing Practice Observations

1. 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)).

Our inspection identified laboratory test records that you did not review and evaluate in making batch release decisions. These records contained uninvestigated, out of specification (OOS) data. You did not include the data described below when calculating test results that you used to release finished product. You also failed to identify, investigate, and determine the significance of the OOS results discussed below until our investigators identified the excluded records during our inspection.

a) During the inspection, your management admitted that employees in both of your Quality Control (QC) laboratories had frequently conducted unauthorized "trial" High Performance Liquid Chromatography (HPLC) injections prior to additional injections that were used in the reported test results. Although your management stated that this practice ended in February 2014, FDA investigators discovered evidence that this practice continues. The inspection found that the names assigned to each sequenced injection were often changed during testing, obscuring the traceability of repeated injections. The data from "trial" injections was not reviewed or considered in determining batch quality. For example,

1) For the related substances analysis of **(b)(4)** USP **(b)(4)** mg Tablets batch **(b)(4)** conducted on February 25, 2013, there were three sample injections of vial 1_8, all named "TEST," which were run prior to the reported sample injections. The "TEST" injection data was stored in the "Trial" folder located on a personal computer (PC) with no audit trail linked to the HPLC instrument.

During the inspection, the calculations that you performed using the target sample weight showed that the "TEST" injections were OOS (**(b)(4)** as compared to the specification of NMT **(b)(4)**) for the highest unknown impurity.

The "TEST" injections were not reviewed and evaluated when making the batch release decision.

2) For the dissolution analysis of **(b)(4)** USP **(b)(4)** mg Capsules batch **(b)(4)** conducted on July 13, 2013, two sets of six sample preparations each were run on the HPLC system as trial sample injections. The trial injection data was stored in the "Trial" folder located on a PC with no audit trail linked to the HPLC instrument.

During the inspection, the calculations that you performed using the target sample weight for three of the injections performed on July 11th, 2013, showed that some of the trial injections produced low dissolution test results (Sample-4 **(b)(4)**%, Sample-5 **(b)(4)**%, and Sample-6 **(b)(4)**%, as compared to the Q-value criteria of NLT **(b)(4)**% of dissolved active ingredient in 45 minutes).

The trial sample injections were not reviewed and evaluated by your firm when making batch release decisions.

3) For the assay analysis of **(b)(4)** USP **(b)(4)** mg Capsules (**(b)(4)** drug product) batch **(b)(4)** conducted on May 15, 2013, two trial HPLC sample injections were run before the reported sample injections. The trial injection data was stored in the "Trial" folder located on a PC with no audit trail linked to the HPLC instrument.

During the inspection, the calculations that you performed showed that one of the extra injections was OOS (**(b)(4)**%, as compared to the specifications of NLT **(b)(4)**% and NMT **(b)(4)**% of label claim).

The trial sample injections were not reviewed and evaluated as part of the batch release decision.

4) HPLC sequence GSTA130522-DS showed **(b)(4)** single injections, in addition to the sequenced injections, during dissolution testing of **(b)(4)** Tablets (**(b)(4)** drug product) submission stability batch **(b)(4)**. Two of the extra single injections were from vial 15, labeled as "STD," indicating that the lab may have injected standard solution and not the test sample solution. Notably, the vial 15 contents were then injected a third time and used as the "Sample 6" test result.

The trial sample injections were not reviewed when assessing batch quality and product stability.

5) The audit trail for the dissolution analysis of the 9-month long-term stability sample of **(b)(4)** USP **(b)(4)** mg Tablets batch **(b)(4)** conducted on March 22, 2014, showed a single manual injection that was not included in the official test results package. A manual "trial" sample injection from vial position **(b)(4)** at 12:29 pm was injected between the Set **(b)(4)** and Set **(b)(4)** analytical sequences. No deviation was documented regarding the extra sample injection. In addition, the original injection data obtained for vial position **(b)(4)** was overwritten and not saved. Because the original data was overwritten, you did not review and evaluate it as part of your batch release decision.

Examples (1) through (5) are examples of unreported extra data that FDA investigators observed on the analytical systems in your QC laboratories. The inspection also identified **(b)(4)** unexplained extra HPLC sample injections for the four stability batches that define the stability characteristics of your **(b)(4)** formulation.

b) The inspection also found similar unreported and unexplained sample data acquired during your gas chromatography (GC), ultra violet (UV) spectroscopy and **(b)(4)** analyses. The extra GC data was stored in the "Trial" folder located on a PC with no audit trail linked to the GC instrumentation. The extra UV and **(b)(4)** data was stored on the instrument hard drives. This unreported and unexplained data was not reviewed when assessing batch quality and making product disposition decisions. For example,

1) For the **(b)(4)** analysis of the 9-month long-term stability sample of **(b)(4)** USP **(b)(4)** mg Capsules (**(b)(4)** drug product) batch **(b)(4)** conducted on January 10, 2014, three extra analyses that were run prior to the reported sample were found on the instrument hard drive. During the inspection, the calculations that you performed showed that two of the extra analyses were OOS (**(b)(4)**% & **(b)(4)**%, as compared to the specification of NMT **(b)(4)**%).

Notably, there were no test sample weight records for the three extra **(b)(4)** tests. The extra sample data was not reviewed when assessing batch quality and product stability.

2) For the dissolution analysis of **(b)(4)** USP **(b)(4)** mg Tablets batch **(b)(4)** conducted on February 21, 2013, a set of test samples was run 14 minutes prior to the reported test samples. The extra data, named slightly differently than the reported test results, revealed several low dissolution test results (**(b)(4)**%, and **(b)(4)**%, as compared to the Q-value criteria of NLT **(b)(4)**% of dissolved active ingredient in 45 minutes).

This trial sample data was not reviewed and evaluated when making the batch disposition decision.

Your response states that you have initiated investigations into such extra data, together with data integrity audits. We note that your response does not address the testing you have

performed on active pharmaceutical ingredients, in-process goods, and validation samples tested by your QC laboratories. Please address these other drugs in your response to this letter. In addition, your response does not include a complete review of all "trial" data (including samples and standards) generated by your firm to ensure that all of the OOS results have been identified and investigated. As part of your response discussed below under "Summary," please include the results of such a review, including steps taken to fully understand the scope and significance of this practice.

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 CFR 211.68(b)).

FDA investigators discovered a lack of basic laboratory controls to prevent changes to electronically stored data. The following examples show that you lack effective control of the integrity of instrument output data:

a) The ten Shimadzu HPLC instruments in the QC "commercial" laboratory were configured to send acquired injection data to PCs without audit trails.

b) There was a lack of controls to prevent substitution or overwriting of data. The **(b)(4)** audit trail dated January 6, 2014, for HPLC MLG/QC/12/026 and the **(b)(4)** audit trail dated January 15, 2014, for HPLCs MLG/QC/12/031 and MLG/QC/12/027 each showed sample injections marked with the same small graphic symbol. For each of these entries, you replaced the original injection sequence data with data from a single manual injection and failed to save the original sequence data.

In your response to this letter, include a chronology of Chromeleon audit trail information that shows all single manual sample injections that replaced data collected during HPLC testing.

c) A "File Note" dated February 10, 2014, signed by the QC Head, established that the printed data used for batch disposition decisions from the Metrohm Titrando Instrument MLG/QC/12/048 hard drive was not necessarily the complete data for a batch. Our inspection found that data on the instrument was selected for use and was not protected from change and deletion. Notably, the audit trail capability of this QC "commercial" laboratory instrument was not enabled, even aftercreation of the "File Note."

3. Your firm failed to record and justify any deviations from required laboratory control mechanisms (21 CFR 211.160(a)).

According to your management, a new standard operating procedure (SOP) was approved in February 2014, in order to eliminate your "trial" sample injection practices. However, during our inspection, we observed that your analysts continued these "trial" injection practices after the approval of your new SOP, and that your quality system and your management failed to detect and correct these deviations from the new procedure (*see, e.g.,* Example 1(a)(5) above).

Post-Market Reporting Requirements Observation

4. Your firm failed to submit NDA/ANDA Field Alert Reports within three working days of receipt of information concerning any significant chemical, physical, or other change or deterioration in the distributed drug product, or any failure of one or more distributed batches of the drug product to meet the specification established for it in the application (21 CFR 314.81(b)(1)(ii)).

You failed to file a Field Alert Report (FAR) within three working days for the failing unknown impurity results observed for **(b)(4)** Tablets USP batches **(b)(4)** (12 months @ 25˚C/60% Relative Humidity (RH)) and **(b)(4)** (6 months @ 25˚C/60% RH and 6 months @ 40˚C/75% RH). We note that in response to our inspection, you ultimately submitted the required FAR on May 12, 2014, which was 26 days late.

The NDA/ANDA field alert reporting requirements in 21 CFR 314.81(b)(1)(i) and (ii) require holders of NDAs and ANDAs to submit certain information about distributed drug products to the appropriate FDA district office within three working days of receipt by the applicant. Field Alert Reports help to ensure that significant problems are brought to the Agency's attention by applicant holders in order to prevent potential safety hazards from drug products already in distribution and also to prevent potential safety hazards with drug products manufactured in the future. When you become aware of a product quality defect that is likely to pose a risk to patients, such as the unknown impurity failure discussed above, you must submit a FAR within the required time period.

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.

Summary

The above examples are of serious CGMP deficiencies and violations demonstrating that your quality system does not adequately ensure the accuracy and integrity of the data generated and available at your facility to support the safety, effectiveness, and quality of the drug products you manufacture. We strongly recommend that you hire a qualified third party auditor/consultant with experience in detecting data integrity problems to assist you with coming into compliance with CGMP regulations and statutory authorities. In your response to this letter, provide the following to the Agency:

1. A comprehensive investigation and evaluation, including a description of the methodology for such investigation and evaluation, of the extent of deficiencies relating to record control, contemporaneous recording, deletion of data, and any other data integrity deficiencies at your firm, such as those identified above;

2. A risk assessment of the potential effect of the observed deficiencies on the quality of your drug products. As part of your risk assessment, determine the effects of your deficient documentation practices on the quality of the drug products released for distribution; and

3. A management strategy for your firm that includes a detailed global corrective action and preventive action plan.

a) As part of your corrective action and preventive action plan, describe the *corrective* actions you will take, such as contacting your customers, recalling product, conducting additional testing and/or adding lots to your stability programs to assure stability, monitoring of complaints, or other steps to assure the quality of the products manufactured under the violative conditions discussed above.

b) In addition, as part of your corrective action and preventive action plan, describe the *preventive* actions you will take, such as revising procedures, implementing new controls, training or re-training personnel, or other steps to prevent the recurrence of CGMP violations, including breaches of data integrity.

If, as a result of receiving this warning letter or for other reasons, you are considering a decision that could reduce the number of finished drug products 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 a drug product manufacturer. In addition, your failure to correct these violations may result in FDA continuing to refuse admission of articles manufactured at Micro Labs Limited, Verna, 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 manufacture or distribute the drug product(s) at issue, provide the date(s) and reason(s) you ceased production. Please identify your response with FEI # 3005210225.

Please send your reply to: Regina T. Brown, Senior Policy Advisor, Food and Drug Administration, Center for Drug Evaluation and Research, OC/OMPQ/DIDQ/ICB-2, Bldg. 51 Room 4248, 20903 New Hampshire Avenue, Silver Spring, Maryland 20993 U.S.A.

Sincerely,
/S/
Thomas Cosgrove, J.D.
Director
Office of Manufacturing and Product Quality
Office of Compliance
Center for Drug Evaluation and Research