Beijing Taiyang Pharmaceutical Industry Co Ltd 10/19/16

10903 New Hampshire Avenue
Silver Spring, MD 20903

Warning Letter: 320-17-03

Via UPS
Return Receipt Requested

October 19, 2016

Mr. Qi Hai Liang
Vice General Manager
Beijing Taiyang Pharmaceutical Industry Co., Ltd.
No. 1 Shuang Qiao East Road, Chaoyang District
Beijing, 100121
China

Dear Mr. Liang:

The U.S. Food and Drug Administration (FDA) arrived at your drug manufacturing facility, Beijing Taiyang Pharmaceutical Industry Co., Ltd., located at No. 1 Shuang Qiao East Road, Chaoyang District, Beijing, on November 16, 2015, to conduct an inspection.

Our investigators documented that your firm limited and/or refused an FDA inspection. Under the Federal Food, Drug, and Cosmetic Act (the FD&C Act), as amended by the Food and Drug Administration Safety and Innovation Act (FDASIA), section 707, 21 U.S.C. 351(j), your drugs are adulterated in that they have been manufactured, processed, packed, or held in an establishment where the owner or operator has limited inspection and refused inspection.

Our investigators also documented that your methods, facilities, or controls for manufacturing, processing, packing, or holding do not conform to current good manufacturing practice (CGMP). Accordingly, your drugs are adulterated within the meaning of section 501(a)(2)(B) of the FD&C Act, 21 U.S.C. 351(a)(2)(B).

We reviewed your firm's December 9, 2015, response in detail.

This letter summarizes your limitation of an inspection and significant deviations from CGMP for active pharmaceutical ingredients (API). Our investigators observed specific deviations including, but not limited to, the following.

1. Your firm delayed, denied, or limited an inspection, or refused to permit the FDA inspection.

On November 16, 2015, our investigators observed through a window a warehouse containing numerous drums bearing your company's label. When our investigators requested access to this warehouse, you barred them from entering the warehouse to examine the containers or the material in them without giving a reasonable explanation.

The following day, you gave our investigators access to the warehouse. However, upon entry they observed that a significant number of drums had been removed and were not available for inspection. When they asked about the drums they had observed the previous day, you provided no explanation of the whereabouts or contents of the drums.

You delayed FDA's access to the warehouse and limited FDA's inspection by removing the drums before our investigators could inspect them.

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

Our investigators observed systemic data manipulation across your facility. They documented unexplained deletions of laboratory test results. They discovered that you repeated tests until you obtained acceptable results and that you failed to investigate out-of-specification or otherwise undesirable test results. Your firm relied on these falsified and manipulated test results to support batch release and stability data. Your firm routinely re-tested high performance liquid chromatography (HPLC) samples and deleted previous chromatograms without justification. Your management acknowledged that employees in your quality control laboratory have access, authority, and the ability to delete and repeat HPLC injections when undesirable results were encountered prior to reporting final results.

Your response states repeated testing was due to quality control operators continuously injecting solvents until a stable baseline was achieved. The response also states the results of repeated tests were deleted to decrease the number of saved chromatograms on your hard drives. Any data created as part of a CGMP record must be evaluated by the quality unit as part of release criteria and maintained for CGMP purposes. In order to exclude data from the release criteria decision-making process, you must have valid, documented, scientific justification for its exclusion.

Reducing the number of records on your hard drives is not a sufficient justification for excluding data. Your response is inadequate because you have not shown how you

will correct the data manipulation and falsification practices discussed above, nor have you demonstrated how you will ensure that all CGMP test results are retained and considered by your quality unit as a part of batch release.

3. Failure to ensure that all quality-related activities are recorded at the time they are performed.

In the production area, our investigators witnessed an employee backdating production batch records for seven batches of **(b)(4)** (batches **(b)(4)** to **(b)(4)**) and transcribing data from a master template record. Furthermore, analysis of the transcribed data for these seven **(b)(4)** batches and for approximately 40 batches of **(b)(4)** API, indicated that you did not record data contemporaneously and that missing data was later falsified so the official records would appear complete.

In the laboratory area, our investigators observed a laboratory analyst attempting to remove a large pile of loose documentation from the HPLC instrumentation room. Upon reviewing the pile of documents, investigators found a significant number of partially completed quality control data worksheets and scratch-paper records containing sample weight values. Our investigators compared these to the official quality control data worksheets and found numerous discrepancies in weights and calculations.

Your response indicates that prior to this inspection you were operating without any document controls. You state that you revised procedures to ensure that distribution of all blank batch records and quality control documents would be done by the quality unit, and that controlled documents would now be identified with a “blue stamp.” However, unless the quality unit controls it by appropriate pagination and reconciliation or other appropriate means, a stamp system is insufficient to ensure that data is recorded contemporaneously. Your response also fails to investigate quality control worksheet and production batch record discrepancies to determine whether the data you relied on for drug release decisions was accurate.

4. Failure to maintain batch production and laboratory control records to determine compliance with established API specifications before a batch is released or distributed.

On November 16, 2015, you told our investigators that you had stopped manufacturing **(b)(4)** API in September 2015. However, during our inspection, our investigators reviewed HPLC and gas chromatogram electronic audit trails that indicated you conducted multiple HPLC and GC analyses on **(b)(4)** batches of **(b)(4)** API from November 5 to 6, 2015 (batch numbers **(b)(4)** to **(b)(4)**).

By your batch numbering system, these batch numbers correspond to batches manufactured in November 2015, two months past the date that you said you ceased production. During the inspection, you could not provide batch production records for these batches, nor did your instrument-use logbooks reflect the testing of these batches. Furthermore, the assay and related substance injection results for these **(b)(4)** batches had been deleted, according to your laboratory analyst, and could not be produced for review during the inspection.

Your response reiterates that your company did not manufacture **(b)(4)** API batches with batch numbers of **(b)(4)** through **(b)(4)** and the test results that our investigators reviewed and asked about during the inspections were from old samples and tests performed for training purposes. Your response is inadequate because you did not explain how analyses for non-existent batches could be labeled with official unique batch numbers, nor did you explain how your laboratory control system permits the exclusion of analytical results, whether for training or other reasons, without justification.

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 strongly recommend that you retain a qualified consultant to assist in your remediation. In response to this letter, provide the following.

A. A comprehensive investigation into the extent of the inaccuracies in data records and reporting. Your investigation should include:

- A detailed investigation protocol and methodology; a summary of all laboratories, manufacturing operations, and systems to be covered by the assessment; and a justification for any part of your operation that you propose to exclude.
- Interviews of current and former employees to identify the nature, scope, and root cause of data inaccuracies. We recommend that these interviews be conducted by a qualified third party.
- An assessment of the extent of data integrity deficiencies at your facility. Identify omissions, alterations, deletions, record destruction, non-contemporaneous record completion, and other deficiencies. Describe all parts of your facility's operations in which you discovered data integrity lapses.
- A comprehensive retrospective evaluation of the nature of the testing and manufacturing data integrity deficiencies. We recommend that a qualified third party with specific expertise in the area where potential breaches were identified should evaluate all data integrity lapses.

B. A current risk assessment of the potential effects of the observed failures on the quality of your drugs. Your assessment should include analyses 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. Your strategy should include:

- A detailed corrective action plan that describes how you intend to ensure the reliability and completeness of all of the data you generate, including analytical data, manufacturing records, and all data submitted to FDA.
- A comprehensive description of the root causes of your data integrity lapses, including evidence that the scope and depth of the current action plan is commensurate with the findings of the investigation and risk assessment. Indicate whether individuals responsible for data integrity lapses remain able to influence CGMP-related or drug application data at your firm.
- Interim measures describing the actions you have taken or will take to protect patients and to ensure the quality of your drugs, such as notifying your customers, recalling product, conducting additional testing, adding lots to your stability programs to assure stability, drug application actions, and enhanced complaint monitoring.

- Long-term measures describing any remediation efforts and enhancements to procedures, processes, methods, controls, systems, management oversight, and human resources (e.g., training, staffing improvements) designed to ensure the integrity of your company's data.
- A status report for any of the above activities already underway or completed.

Conclusion

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

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.

FDA placed your firm on Import Alerts 99-32 and 66-40 on April 28 and April 29, 2016, respectively.

Until you correct all deviations 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 deviations may also result in FDA continuing to refuse admission of articles manufactured at Beijing Taiyang Pharmaceutical Industry Co., Ltd., Beijing, 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 deviations 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:

Joseph R. Lambert, Consumer Safety 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 3003828267.

Sincerely,
/S/
Francis Godwin
Acting Director
Office of Manufacturing Quality
Office of Compliance
Center for Drug Evaluation and Research