Taiwan Biotech Co., LTD. 5/31/18

10903 New Hampshire Avenue
Silver Spring, MD 20993

Via UPS
Return Receipt Requested

Warning Letter 320-18-56

May 31, 2018

Dr. George Ko
Chairman
Taiwan Biotech Company, Ltd.
22, Chieh-Shou Road
Taoyuan District, Taoyuan City
Taiwan R.O.C.

Dear Dr. Ko:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Taiwan Biotech Company, Ltd at 22, Chieh-Shou Road, Taoyuan District, Taoyuan City, from September 1 to 11, 2017.

This warning letter summarizes significant violations of current good manufacturing practice (CGMP) regulations for finished pharmaceuticals. See 21 CFR, parts 210 and 211.

Because your methods, facilities, or controls for manufacturing, processing, packing, or holding do not conform to CGMP, your drug products are adulterated within the meaning of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 351(a)(2)(B).

We reviewed your November 2, 2017, response in detail and acknowledge receipt of your subsequent correspondence.

During our inspection, our investigator observed specific violations including, but not limited to, the following.

1. Your firm failed to establish an adequate system for monitoring environmental conditions in aseptic processing areas (21 CFR 211.42(c)(10)(iv)).

During the inspection, our investigator found the following issues related to your sterile over-the-counter **(b)(4)**: **(b)(4)** and **(b)(4)**.

Environmental and Personnel Monitoring Alert Investigations

Our investigator identified several environmental monitoring plates from the ISO 5 (Class A) and the surrounding ISO 8 (Class C) clean areas which exceeded action limits and for which investigations were not initiated.

On September 6, 2017, our investigator found containers storing environmental and personnel monitoring microbiological samples, dated August 30 and 31, 2017. Numerous samples lacked basic documentation, including missing colony-forming unit (CFU) counts and the identity of the person who collected the sample. At the request of our investigator, your firm enumerated CFU for these plates. While several plates exhibited counts outside of action limits, your firm had not initiated investigations. As an example, a sample taken for **(b)(4)** lot **(b)(4)** yielded an extremely high count of 140 CFUs in your ISO 5 area. The action limit for this critical area is < **(b)(4)** CFU.

Due to our investigator's findings, you initiated investigations during the inspection regarding the undocumented microbial growth. On September 7, 2017, you provided a copy of these initial investigations.

Notably, when asked by the investigator to provide all deviations from environmental monitoring limits, your firm had reported no results outside limits for over a year prior to the inspection date. This reported level of environmental control is dubious, in that during the current FDA inspection, several environmental monitoring samples were found to have significant growth, and these results had not been enumerated and recorded.

Your failure to accurately account for numerous environmental monitoring plates, enumerate the results, and fully investigate the systemic flaws that led to the unreported data raises questions regarding the integrity of data generated by your firm.

Insufficient surface monitoring

On September 6, 2017, our investigator determined that your microbiology technician had not collected required surface samples since September 1, 2017. Further, our inspection revealed that your firm lacked environmental sampling during your **(b)(4)** and **(b)(4)**. Your management acknowledged that deficient environmental monitoring on these production **(b)(4)** had been occurring for approximately 1–2 years.

In your response, you stated that you created a standard operating procedure (SOP) to track your environmental monitoring samples, and committed to hiring more personnel to supervise activities. However, your response was inadequate. You did not provide the SOP or indicate plans to fully remediate your environmental monitoring program. You also did not indicate whether all unaccounted samples identified by our investigator were enumerated, and if investigations and risk assessments were initiated in response to any results outside established limits. In addition, you did not indicate whether a comprehensive review of all laboratory practices and controls was conducted to ensure reliable laboratory operations, including but not limited to accurate reporting of all laboratory data.

In response to this letter, provide the following.

- Further details on additional microbiological plates that were not initially enumerated and the results that your firm ultimately obtained for these plates. Also, summarize all lots made without sufficient environmental

monitoring on the **(b)(4)** and **(b)(4)**. Provide risk assessments for any potentially affected products marketed to the United States.

- Your investigations of multiple deviations from action limits for ISO 5 and other clean areas.
- A thorough, independent assessment with corrective actions and preventive actions (CAPA) for your environmental monitoring and personnel monitoring programs. For instance, your remediation should include adequate sampling procedures, media suitability, sample accountability (e.g., identification, storage, logging, analysis dates/times), appropriate locations and frequencies, proper responses to alert and action limits, routine identification of microbes isolated from cleanroom and personnel samples, and various other elements of an effective program.
- A comprehensive, independent review of your laboratory practices, methods, equipment, and analyst competencies. Based on this review, provide a detailed CAPA plan to fully remediate your laboratory system. Your plan should also include the process you will use to evaluate the effectiveness of the implemented CAPA.
- A comprehensive identification of all contamination hazards in your aseptic processes, equipment, and facilities. Provide an independent risk assessment that covers, among other things, all human interactions with the ISO 5 area, equipment placement and ergonomics, air quality in the ISO 5 area and surrounding room, facility layout, personnel flow, and material flow.

2. Your firm failed to follow an adequate written testing program designed to assess the stability characteristics of drug products (21 CFR 211.166(a)).

Your firm failed to conduct on-going stability testing of **(b)(4)** and **(b)(4)** at various time intervals, as specified in your stability program. For example, in September 2016, you failed to perform testing at the 12-month stability time interval for **(b)(4)** batch **(b)(4)**. Further, you performed the scheduled 6-month stability testing of **(b)(4)** batch **(b)(4)** four months late (in March 2017). You lacked an investigation to address the missed and delayed stability testing.

In your response, you indicated that you revised the SOP QOP-046, *Receiving/Using/ Destroying*, and you committed to ensure all future stability testing is conducted in a timely manner. However, you failed to provide the revised SOP and a retrospective analysis to determine the root cause of all missing and delayed testing.

In response to this letter, provide the following.

- A retrospective review into all missing or delayed stability testing that is intended to support the shelf-life of each of your U.S. products.
- An impact assessment for the missed or delayed stability testing, and an updated summary of all stability data (i.e., data obtained for each testing) supporting each of your U.S. products.
- A comprehensive assessment and CAPA to ensure the adequacy of your stability program. Your CAPA should include, but should not be limited to, correcting the root causes of the missed and delayed stations, ensuring adequate number of qualified quality control personnel, improved procedures, and comprehensive personnel training.

3. Your firm failed to maintain written records so that data therein could be used for evaluating, at least annually, the quality standards of each drug product to determine the need for changes in drug product specifications or manufacturing or control procedures (21 CFR 211.180(e)).

Your annual product reviews (APR) only included batches shipped to the United States and the associated deviation investigations. The APR did not include batches shipped to countries other than the United States, but manufactured under the same conditions.

For example, your 2016 APR of **(b)(4)** mL included only **(b)(4)** batches and two deviation investigations. However, in 2016, you manufactured **(b)(4)** batches of this product for all markets at your facility and conducted 16 investigations of which 15 were related to product yield failures. Because all the batches were manufactured using the same manufacturing operation, each of these batches should be included in your APR to allow meaningful trends to be detected.

Your firm did not provide a sufficient response to this violation. For example, there was no indication that you are remediating your APR program or retrospectively reviewing trends by incorporating batches not shipped to the United States into annual reviews.

In response to this letter, provide an assessment of manufacturing and quality data associated with each drug marketed to the United States. Include remediated procedures and retrospective trending to identify any adverse findings and determine the need for changes to manufacturing, control, or specifications.

Quality Control Unit

Significant findings in this letter indicate that your quality unit is not able to fully exercise its authority and/or responsibilities. Your firm must provide the quality unit with appropriate authority and sufficient resources and staff to carry out its responsibilities and consistently ensure drug quality.

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. In response to this letter provide the following.

A. A comprehensive investigation into the extent of the inaccuracies in data records and reporting, including results of the data review for drugs distributed to the United States. Include a detailed description of the scope and root causes of your 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. The detailed corrective action plan should describe how you intend to ensure the reliability and completeness of all data generated by your firm, including microbiological and analytical data, manufacturing records, and all data submitted to FDA.

CGMP Consultant Recommended

Based upon the nature of the violations we identified at your firm, we strongly recommend engaging a consultant qualified as set forth in 21 CFR 211.34 to assist your firm in meeting CGMP requirements. The third-party consultant should comprehensively audit and assist with remediating your operations, including but not limited to data integrity, environmental monitoring, investigations of deviations, container-closure defects, aseptic processing, laboratory systems, quality unit authorities and resources, equipment and facilities, and all other elements of your quality system.

Your use of a consultant does not relieve your firm’s obligation to comply with CGMP. Your firm’s executive management remains responsible for fully resolving all deficiencies and ensuring ongoing CGMP compliance.

Conclusion

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

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.

Until you correct all violations 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 violations may also result in FDA refusing of articles manufactured at Taiwan Biotech Co., Ltd at 22, Chieh-Shou Road, Taoyuan District, Taoyuan City 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 violations 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:

LT Loan Chin
Pharmacist
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 3003598505.

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

More in Warning Letters (/ICECI/EnforcementActions/WarningLetters/default.htm)