Guangzhou Baiyunshan Pharmaceutical Co., Ltd. 11/1/17

10903 New Hampshire Avenue
Silver Spring, MD 20993

Via UPS **Warning Letter** 320-18-05

November 1, 2017

Mr. Yanzhong Yang
General Manager
Guangzhou Baiyunshan Pharmaceutical Holdings Co. LTD
Baiyunshan Hejigong Pharmaceutical Factory
No. 52 Xiao Gang Dama Road, XinShi Street
Guangzhou, Guangdong 510410
China

Dear Mr. Yang:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Baiyunshan Hejigong Pharmaceutical Factory at No. 52 Xiao Gang Dama Road, XinShi Street, Guangzhou, Guangdong from May 22–25, 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 June 19, 2017 response in detail. Your response lacked a sufficient assessment of your operation and commitments to assure conformance to FDA requirements.

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

1. Your firm failed to clean, maintain, and as appropriate for the nature of the drug, sanitize and/or sterilize equipment and utensils at appropriate intervals to prevent malfunctions or contamination that would alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements (21 CFR 211.67(a)).

You manufacture over-the-counter (OTC) topical **(b)(4)**. Our investigator observed a **(b)(4)**, identified and approved as clean, that contained a significant amount of **(b)(4)** material and product residue. This particular **(b)(4)** is used for two different **(b)(4)** products. In your response, you blamed your employees for exercising poor discipline when cleaning the **(b)(4)**. While you acknowledge that this was also a management failure, your response was inadequate in that you failed to evaluate the adequacy of your cleaning procedures and did not perform a retrospective evaluation of past batches to determine if cross-contamination occurred.

2. Your firm failed to follow written procedures for production and process control designed to assure that the drug products you manufacture have the identity, strength, quality, and purity they purport or are represented to possess (21 CFR 211.100(b)).

Your validation protocol states that the time range for the **(b)(4)** step for the **(b)(4)** is **(b)(4)** to **(b)(4)**. However, your master batch record does not specify a **(b)(4)** time for this critical step.

In addition, a demonstration of your **(b)(4)** during the inspection revealed that it did not stop at the appropriate time because the timer malfunctioned.

3. Your firm failed to establish the reliability of the component supplier's analyses through appropriate validation of the supplier's test results at appropriate intervals (21 CFR 211.84(d)(2)).

For example, you were unable to identify the manufacturer of the **(b)(4)** raw material batch you had on site. **(b)(4)** is a critical material used in the manufacture of your **(b)(4)**. You also lacked sufficient systems to properly qualify raw materials.

4. Your firm failed to follow written procedures describing in sufficient detail the receipt, identification, storage, handling, sampling, testing, and approval or rejection of components and drug product containers and closures (21 CFR 211.80(a)).

For example, our investigator found uncontrolled component release stickers behind pallets of raw materials and on stairs in your warehouse. Uncontrolled storage of release stickers could lead to the use of unauthorized components in manufacturing your drug products.

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 consultant should perform a comprehensive assessment of your firm's operations to help you ensure systems and processes, and ultimately, the products manufactured, are remediated and conform to FDA requirements. Your use of a consultant does not relieve your firm's obligation to comply with CGMP. Your executive management remains responsible for fully resolving all deficiencies and ensuring ongoing CGMP compliance.

Formulation and Labeling Concerns

We note that your firm's drug products, **(b)(4)**, are labeled for use as **(b)(4)** drug products.

Drug products such as **(b)(4)** and **(b)(4)** intended for **(b)(4)** indications are being evaluated as part of the OTC Drug Review. They have been proposed to be classified as generally recognized as safe and effective and not misbranded under the Tentative Final Monograph (TFM) for **(b)(4)** Drug Products for Over-the-Counter (OTC) Human Use **(b)(4)** if they meet each condition in the TFM and each general condition in 21 CFR 330.1. Pending a final rule, FDA does not intend to pursue misbranding regulatory actions against products marketed in conformance with the conditions proposed in the TFM and each general condition in 21 CFR 330.1. Such marketing, however, is subject to the risk that a final rule may require reformulation and/or relabeling or FDA approval through the "new drug" procedures of the FD&C Act (section 505).

During the FDA inspection conducted on May 22–25, 2017, our investigator reviewed and directly observed your firm's microscopic analysis for identification of **(b)(4)** materials in a recently manufactured batch of **(b)(4)**. The label for **(b)(4)** does not declare these **(b)(4)** components. Your firm advised that the concentrations of these ingredients were low and medically ineffective. As you were advised during the inspection, all ingredients, whether active or inactive, must be declared on product labels. See Section 502(e)(1)(A) of the FD&C Act, 21 U.S.C. 352(e)(1)(A).

For your information, the TFM **(b)(4)** proposes allowable active ingredients for use in **(b)(4)** drugs such as **(b)(4)** and **(b)(4)**. You will note that there are no **(b)(4)** ingredients proposed in this TFM. In addition, to legally market an OTC **(b)(4)** drug product in the U.S., we remind you that it is your responsibility to ensure your product contains only suitable inactive ingredients that are safe in the amounts administered and do not interfere with the effectiveness of the preparation or with suitable tests or assays to determine if the product meets its professed standards of identity, strength, quality, and purity (21 CFR 330.1(e)).

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.

FDA placed your firm on Import Alert 66-40 on October 25, 2017.

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 continuing to refuse admission of articles manufactured at Baiyunshan Hejigong Pharmaceutical Factory, No. 52 Xiao Gang Dama Road, XinShi Street, Guangzhou, Guangdong, 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 (mailto:CDER-OC-OMQ-Communications@fda.hhs.gov)** or mail your reply to:

Brooke K. Higgins
Compliance 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 3004506176.

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

More in 2017 (/ICECI/EnforcementActions/WarningLetters/2017/default.htm)