Longbow First Aid Products Manufactory 12/14/18

10903 New Hampshire Avenue
Silver Spring, MD 20993

Via UPS **Warning Letter** 320-19-09
Return Receipt Requested

December 14, 2018

Mr. Zhiyuan Dong
General Manager
Longbow First Aid Products Manufactory
2/F, A3 Building, Hantian Industrial Park, Guiping Road
Guicheng, Foshan 528200
CHINA

Dear Mr. Dong:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Longbow First Aid Products Manufactory at 2/F, A3 Building, Hantian Industrial Park, Guiping Road, Guicheng, Foshan, from April 16 to 20, 2018.

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 May 2, 2018, 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 does not have, for each batch of drug product purporting to be sterile and/or pyrogen-free, appropriate laboratory determination of satisfactory conformance to final specifications for the drug product (21 CFR 211.167(a)).

Your firm released your finished over-the-counter (OTC) **(b)(4)** drug products to the U.S. market without testing each batch for all appropriate quality attributes. For example, your firm distributed multiple batches of purportedly sterile **(b)(4)** without conducting sterility testing. Instead, you conducted microbiological enumeration tests with a specification of < **(b)(4)** CFU/mL. Microbiological enumeration testing is insufficient when testing for drug product sterility. Furthermore, you did not test your **(b)(4)** drugs for particulate matter before their release. Without appropriate testing for these physical and microbiological quality attributes, your quality unit lacks the essential safety information required to make suitable release decisions.

Your response stated that you did not conduct sterility testing because it was not a customer requirement, and that you will "take retention samples for sterility test and provide it to customer." Your response is inadequate because it lacked sufficient details, including who will test these retention samples and what specific test methods will be used on these drug products.

In response to this letter:

- Provide your newly established testing methods, such as your methods for particulate testing and sterility testing, and specifications intended for analysis of the physical properties of the drug products, for each batch of drug products before their release.
- Provide all sterility test results for your OTC **(b)(4)** drug products and indicate whether they conform to United States Pharmacopeia (USP) Sterility Tests <71>.
- For any drug product batch that failed to meet established quality criteria, provide your detailed corrective action plans, including notifying customers or recalling drug products.

2. Your firm failed to establish and follow appropriate written procedures that are designed to prevent microbiological contamination of drug products purporting to be sterile, and that include validation of all sterilization processes (21 CFR 211.113(b)).

You failed to demonstrate that your aseptic processes are capable of preventing microbial contami-nation of your ophthalmic drug products.

Inadequate Equipment Sterilization

Your firm has not demonstrated that your process is capable of ensuring the sterility of your **(b)(4)** equipment. You stated that you use an **(b)(4)** mixture that is intended to "sterilize" equipment before manufacturing. When our investigator asked for the concentration of **(b)(4)** used in this process, you could not provide this information, nor could you provide any documentation to support equipment "sterilization" before manufacturing. Furthermore, you lacked documentation and validation studies assessing the suitability and reproducibility of this method for sterilizing equipment. Your **(b)(4)** equipment must be sterilized using an appropriate and robust sterilization method to ensure that your **(b)(4)** drug products are safe for use by patients.

In your response, you stated that you will "validate the aseptic capacity of the **(b)(4)** equipment" by June 15, 2018. Your response is inadequate. You failed to provide data demonstrating use of appropriate and robust processes to sterilize the entire equipment path through which the drug product travels.

Your response also stated that "the final sterility warranty level is guaranteed by preservatives." You cannot rely on preservatives to ensure drug product sterility.

Lack of Media Fill Studies

Your firm has not performed aseptic process simulations (i.e., media fill studies). During the inspection, our investigator asked your firm if it had performed process simulations for the **(b)(4)** machine used to manufacture your OTC **(b)(4)** drug products. You stated that no media fill simulations had been conducted, but that you plan to perform media fill simulatons in the future. To ensure the sterility of products purporting to be sterile, aseptic filling and closing operations must be adequately validated before manufacture and distribution. Adequate media fill studies accurately simulate aseptic processing line practices and conditions, including any interventions that may be encountered during actual production. These studies should be conducted at least twice a year (for each shift) to evaluate whether each aseptic processing line remains in control and robustly yields sterile drugs that are safe for use by patients.

Your response lacks adequate details about the media fill program you will use to validate your **(b)(4)** operations. For example, your proposed media fill study does not incorporate all container sizes that you manufacture for the U.S. market. Media fill studies should be representative of all container sizes, filling speeds, and other parameters used in your production processes.

Refer to FDA's guidance document *Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice* for recommendations to help you meet CGMP requirements when manufacturing sterile drugs using aseptic processing. This guidance is on the FDA website at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070342.pdf.

In your response to this letter:

- Describe how you will sterilize the **(b)(4)** manufacturing equipment. Provide a detailed sterilization method, a list of all equipment sterilized using this method, validation protocols, and validation reports for your processes.
- Provide a comprehensive summary of your media fill program that ensures an appropriate simulation of the worst-case conditions of commercial manufacturing. In addition, describe in detail how you examine units for presence of growth and how you perform batch yield reconciliation. Include all related standard operating procedures (SOPs).

3. Your firm failed to conduct at least one test to verify the identity of each component of a drug product. Your firm also failed to validate and establish the reliability of your component supplier's test analyses at appropriate intervals (21 CFR 211.84(d)(1) and (2)).

Your firm failed to test your incoming raw materials, including **(b)(4)**, for identity, purity, strength, and other appropriate quality attributes. Instead, your firm relied on certificates of analysis (COA) from unqualified suppliers. During our inspection, you told our investigator that you consider a supplier qualified if they are registered and hold a certificate of GMP. FDA requires identity testing for each component lot used in drug product manufacturing, and

you can only rely on a COA for other component attributes by appropriately validating the supplier's test results at appropriate intervals.

In your response, you stated that you will "entrust a third party to examine each inspection item to confirm its authenticity." However, you failed to include details about this examination, and you do not describe what tests will be performed. Also, you have not described in detail how you will qualify

the third-party laboratory or how you will ensure that incoming raw materials meet USP testing requirements.

In response to this letter:

- Provide quality control release specifications for all incoming components, and the tests you perform for each lot.
- Provide a summary of test results obtained from comprehensive testing of all incoming components, to validate the COA from each manufacturer of raw material.
- Provide a summary of your procedures for qualifying and overseeing the adequacy of contract facilities that test incoming components and the drug products you manufacture.
- Provide a comprehensive, independent review of your material system to determine whether all containers, closures, and ingredients from each supplier are adequately qualified; whether they are assigned appropriate expiration or retest dates; and whether incoming material lot controls are adequate to prevent the use of unsuitable containers, closures, and components.

4. Your firm failed to ensure that its drug product bore an expiration date that was supported by appropriate stability testing 21 CFR 211.137(a).

You firm has not established a stability program. You lack data to demonstrate that the chemical, physical, and microbiological properties of your OTC **(b)(4)** drug products, including sterility, will remain acceptable throughout their labeled **(b)(4)** expiry period.

In your response, you stated that you will "establish the long-term stability testing of OTC **(b)(4)** drugs immediately," and that your laboratory needs to "acquire equipment for long-term stability testing." Your response is inadequate. You failed to include adequate stability protocols, including all relevant quality attributes and acceptance criteria, and provide assurance that your test methods will indicate adequate stability.

In response to this letter:

- Provide stability data to demonstrate that the chemical, physical, and microbiological properties of your **(b)(4)** drug products remain acceptable throughout their labeled expiry period.
- Provide a comprehensive assessment and CAPA to ensure the adequacy of your stability program. Your CAPA should include, but not be limited to, a remediated SOP describing your stability program; stability-indicating methods; stability studies to support each drug product in its container-closure system before distribution is permitted; an ongoing program that adds represen-tative batches of each product annually to determine if the shelf-life claim remains valid; and specific attributes to be

tested at each station.

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. We also recommend that the qualified consultant: (1) perform a comprehensive audit of your entire operation for CGMP compliance; and (2) evaluate the completion and effectiveness of corrective actions and preventive actions you have implemented, before you pursue resolution of your firm's compliance status with FDA.

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.

FDA placed your firm on Import Alert 66-40 on August 17, 2018.

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 Longbow First Aid Products Manufactory at 2/F, A3 Building, Hantian Industrial Park, Guiping Road, Guicheng, Foshan, 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:

Bryce Hammer
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 3006102089.

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