Wuxi Medical Instrument Factory 9/7/17

10903 New Hampshire Avenue
Silver Spring, MD 20993

Via UPS

Warning Letter 320-17-49

September 7, 2017

Mr. Chongjiu Li
General Manager
Wuxi Medical Instrument Factory
No. 86, East Street, Zhangjing, Xibei Town,
Wuxi City, Jiangsu, 214194, China

Dear Mr. Li:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Wuxi Medical Instrument Factory at No. 43 Xixin Road, Zhangjing, Xibei Town, Wuxi City Jiangsu, from March 6 to 10, 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 March 31, 2017, response in detail and acknowledge receipt of your subsequent correspondence. Your response failed to commit to comprehensive actions to address the violations observed during the inspection.

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

1. Your firm failed to establish written procedures for production and process controls 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(a)).

You failed to adequately validate the process used to manufacture your sterile **(b)(4)**. During the inspection, you could not provide process qualification batch records and quality control test documentation. You provided only a protocol and a summary report with insufficient data. Batch records for your commercial product also failed to document all significant process parameters (e.g., **(b)(4)** times), order of ingredient addition, sampling frequency, and sample size. You lacked assurance that in-process materials and finished drug products met predetermined manufacturing and quality requirements.

The purpose of validation is to determine whether your processes can operate within established parameters to assure consistent batch uniformity, integrity, and drug quality. Reliable and well-documented batch operations are essential to ensuring process control and drug quality.

See FDA's guidance document, *Process Validation: General Principles and Practices*, at https://www.fda.gov/downloads/drugs/guidances/ucm070336.pdf.

In response to this letter, provide:

- A data-driven and scientifically sound program that identifies and controls all known sources of variability, such that your production and packaging processes will consistently meet appropriate parameters. This includes, but is not limited to, evaluating suitability of equipment for its intended use, assuring quality of input materials, and determining the capability and reliability of each manufacturing process step and control.
- Revised procedures that establish an ongoing program for monitoring process control and detecting variation throughout the product lifecycle.
- An updated master batch record for manufacturing sterile **(b)(4)** that requires specific processing details in order to fully document each significant manufacturing step.

2. Your firm failed to establish laboratory controls that include scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that components, drug product containers, closures, in-process materials, labeling, and drug products conform to appropriate standards of identity, strength, quality and purity (21 CFR 211.160(b)).

You did not perform growth promotion testing on each batch of microbiological growth media you prepare for settle plate, bioburden, and sterility testing. In addition, you do not have a written procedure to ensure that prepared media consistently meets appropriate standards of quality and purity.

In response to this letter, provide your procedures to ensure that media used for settle plate, bioburden, and sterility testing is prepared consistently and promotes microbial growth.

3. 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)).

On March 7, 2017, our investigator observed that your firm had stored clean **(b)(4)** tubing in an open container in your Apparatus Storage room. It was to be used to transfer **(b)(4)** during batch manufacture. The exposed tubing ends were not covered to protect against dust or other contamination of your terminally sterilized drug product. You lacked procedures for maintaining, cleaning, and sanitizing this tubing to prevent contamination.

In response to this letter, provide your procedures for maintaining, cleaning, and sanitizing all equipment used in manufacturing your drugs.

4. Your firm failed to maintain adequate written records of major equipment maintenance (21 CFR 211.182).

During the inspection, you provided our investigator with records documenting **(b)(4)** sanitization of your **(b)(4)** loop. The records, covering January to March, 2017, were signed by two employees, and indicated that sanitization had been completed and verified contemporaneously throughout this period. However, our investigator found that these operations were not documented at the time of their actual performance, but were instead created and completed on March 7, 2017, the second day of the inspection.

Your response acknowledges this data integrity issue and indicates that you have taken some remediation steps. In response to this letter, provide:

A. A comprehensive investigation into the extent of the inaccuracies in data records and reporting. 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, and provide an evaluation of the nature of the data integrity deficiencies.

B. A current risk assessment of the potential effects of the observed failures on the quality of your drugs.

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 comprehensive description of the root causes of your data integrity lapses, the interim measures you have taken or will take to protect patients and to ensure the quality of your drugs while remediation is ongoing, and the long-term measures you

will take to ensure the integrity of your company's data. Include a status report for any of the above activities already underway or completed.

CGMP Consultant Recommended

Based upon the nature of the violations identified at your firm, we strongly recommend engaging a consultant qualified as set forth in 21 CFR 211.34, to assist your firm in comprehensively meeting CGMP requirements. 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.

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 admission of articles manufactured at Wuxi Medical Instrument Factory, No. 43 Xixin Road, Zhangjing, Xibei Town, Wuxi City, Jiangsu, 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:

Joseph Lambert, Pharm.D.
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 3006851654.

Sincerely,

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