U.S. Food and Drug Administration
Protecting and Promoting *Your* Health

Frontida BioPharm Inc 8/15/16

Department of Health and Human Services

Public Health Service
Food and Drug Administration
PHILADELPHIA DISTRICT
900 U.S. Customhouse
2nd and Chestnut Street
Philadelphia, PA 19106
Telephone: 215·597·4390

WARNING LETTER
16-PHI-10

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

August 15, 2016

Dr. Song Li
CEO
Frontida BioPharm, Inc.
700 Pennsylvania Drive
Exton, PA 19341

Dear Dr. Li:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Frontida BioPharm, Inc., formerly known as Mutual Pharmaceutical Company, Inc., at 1100 Orthodox Street, Philadelphia, Pennsylvania, from June 15 to July 17, 2015.

This warning letter reviews significant violations of current good manufacturing practice (CGMP) 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 (the FD&C Act), 21 U.S.C. 351(a)(2)(B).

We reviewed your firm's August 7, 2015, response in detail and acknowledge receipt of your subsequent responses.

Our investigators observed specific violations including, but not limited to, the following.

1. Your firm failed to establish an adequate quality control unit with the responsibility and authority to approve or reject all components, drug product containers, closures, in-process materials, packaging material, labeling, and drug products; and the authority to review production records to assure that no errors have occurred or, if errors have occurred, assure that they have been fully investigated. (21 CFR 211.22(a))

Significant findings indicate that your quality unit is not fully exercising its authority and responsibilities. We detail three examples below. Your firm must provide the quality unit with the appropriate authority and sufficient resources to carry out its responsibilities and consistently ensure drug quality.

Release of potentially contaminated product

Your quality unit knowingly released 27 lots of various strengths of clonidine HCl tablets on or about March 5, 2015, despite evidence that active pharmaceutical ingredient (API) used in their manufacture (lot **(b)(4)**) was potentially contaminated. Your supplier recalled this lot of API based on **(b)(4)** inspectional findings that indicated inadequate controls to prevent cross contamination of the API. Your firm was notified of this recall as early as July 16, 2014.

Based on your supplier's recall notice, your firm initially placed 27 lots of clonidine HCl tablets on hold starting on July 16, 2014. You then hired a contract testing laboratory to analyze retain samples of the clonidine API lot for cross contamination. However, your contract laboratory provided documentation that its test method was not validated to detect low levels of cross contamination, and explicitly stated that the test results "may not be used for batch release." Despite this, your firm released the 27 lots of clonidine HCl in March 2015 without testing your finished products using a method that was both validated and sufficiently sensitive to detect cross contamination. On July 9, 2015, during our inspection, your firm recalled all 27 lots.

In your response you committed to engaging a third party to assess your supplier program to determine when you should take additional steps to assess your API supplier.

Inadequate investigation of stability failure

You did not adequately investigate the stability failure of lot **(b)(4)** of felodipine 2.5-mg tablets for an unknown impurity. The product specification for unknown impurities is **(b)(4)** percent, but your three-month stability test result for this lot was **(b)(4)** percent impurities. You opened an investigation into the stability failure on February 12, 2015. Your own records indicate that as of April 29, 2015, you were aware that benzophenone had leached into the tablets from the ink and varnish on the primary container label, but you did not recall this lot until July 16, 2015, during the FDA inspection.

In your response, you committed to developing a method to quantify benzophenone in your products as well as a method to screen labels prior to use.

Discrepancies in CGMP-related records

Your quality unit failed to ensure that CGMP-related records are accurate, contain appropriate documentation, and are consistent with your standard operating procedures (SOP). We found multiple discrepancies in quality unit-approved records, such as:

- investigation reports containing data and documentation from unrelated investigations
- records signed with only a first name

- records missing dates
- illegible entries in logbooks and laboratory notebooks

During the inspection, you attributed some of the documentation discrepancies to your practice of cutting and pasting between different investigation reports. You also committed to correcting other deficiencies.

In response to this letter:

- Provide a plan to ensure that your quality unit will adequately exercise its authority and perform its responsibilities.
- Describe how you ensure that your quality unit has rejected and will continue to reject all components and drug products that are not of adequate quality, purity, or safety.
- Describe improvements to your supplier qualification and auditing program and specify how you ensure that oversight of suppliers is commensurate with risk to your finished products.
- Provide the results of your audit of your clonidine HCl API supplier.
- Conduct a retrospective evaluation of your drug products within expiry to ensure they do not exceed specifications for any known or unknown impurities. Provide the results of this evaluation and indicate the steps you have taken to investigate any OOS results you identify as part of this retrospective evaluation.

Access to information during inspection

During the inspection, there were numerous instances where your firm failed to provide our investigators with information regarding investigations, corrective actions, and preventive actions in a manner that would allow the investigators to fully understand and evaluate your firm's internal processes and compliance with CGMP requirements. Your vice president of quality repeatedly denied any knowledge of your clonidine HCl API supplier's recall, even though e-mail evidence collected during the inspection showed that this individual had been notified of the recall as early as July 16, 2014. During the inspection, your firm removed this individual from his position.

In your response, you stated, "Mutual recognizes that the manner in which it provided information about this issue to the investigators during the inspection did not effectively convey Mutual's process for product disposition or the rationale for its decisions throughout the handling of the batch of Clonidine HCl API."

When an owner, operator, or agent delays, denies, limits, or refuses an inspection, the drugs may be adulterated under section 501(j) of the FD&C Act. We recommend that you review FDA's guidance for industry *Circumstances that Constitute Delaying, Denying, Limiting, or Refusing a Drug Inspection* at **http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM360484.pdf (http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM360484.pdf#_blank)**

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 in all your facilities.

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.

After you receive this letter, you have 15 working days to respond to this office in writing. 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 days, state your completion date and reasons for delay.

Correct the violations cited in this letter promptly. Failure to promptly correct these violations may result in legal action without further notice including, without limitation, seizure and injunction. Unresolved violations in this warning letter may also prevent other Federal agencies from awarding contracts.

Until these violations are corrected, we may withhold approval of pending drug applications listing your facility. We may also refuse requests for export certificates. We may re-inspect to verify that you have completed your corrective actions.

Send your reply to:

Yvette Johnson
Compliance Officer
U.S. Food and Drug Administration
U.S. Customhouse, Room 900
2nd and Chestnut Sts.
Philadelphia, PA 19106

Please identify your response with FEI 2523348.

Sincerely,
/S/
Anne E. Johnson
District Director
Philadelphia District

Cc:
Mr. James M. Scheirer
Vice President Manufacturing
Frontida BioPharm, Inc.
1100 Orthodox Street
Philadelphia, PA 19124

More in 2016 (/ICECI/EnforcementActions/WarningLetters/2016/default.htm)