Hetero Labs Limited Unit V 8/15/17

U.S. FOOD & DRUG ADMINISTRATION

U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov (http://www.fda.gov)

Via UPS

Warning Letter 320-17-46

August 15, 2017

Dr. Bandi Parthasarathy Reddy
Chairman and Managing Director
Hetero Labs Limited
7-2-A2, Hetero Corporate Industrial Estates
Sanath Nagar
Hyderabad 500 018, Telangana
India

Dear Dr. Reddy:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Hetero Labs Limited, Unit V at Polepally Village, Jadcherla Mandal, Mahaboob Nag, Telangana, from December 7–16, 2016.

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 January 10, 2017, response in detail and acknowledge receipt of your subsequent correspondence.

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

1. Your firm failed to thoroughly investigate any unexplained discrepancy or failure of a batch or any of its components to meet any of its specifications, whether or not the batch has already been distributed (21 CFR 211.192).

Your investigations into process deviations and out-of-specification (OOS) laboratory results are insufficient, and do not include scientifically-supported conclusions.

For example, you have acted as the contract manufacturer of **(b)(4)** mg **(b)(4)** tablets for multiple customers. In February 2016, you received a customer complaint that lot **(b)(4)** failed dissolution testing. During your investigation into this complaint, you noted that the **(b)(4)** used to manufacture lot **(b)(4)** was operating at up to **(b)(4)**% **(b)(4)**, although its specification was not more than (NMT) **(b)(4)**% **(b)(4)**. You also noted that the **(b)(4)** was recorded as "NMT **(b)(4)**," which does not indicate if the operating **(b)(4)** was maintained within the specification of **(b)(4)** ± **(b)(4)**.

Your March 2016 *Market Complaint Investigation Report* concluded, without scientific justification, that the **(b)(4)** and possible **(b)(4)** deviations during the **(b)(4)** process for this lot had no relationship to the dissolution test failure. Although the investigation also initially concluded that the failure could be a testing issue involving the use of **(b)(4)** µm filters, one of your customers found this explanation unacceptable. You subsequently acknowledged to another customer that you had not identified the root cause for the failing dissolution results.

Finally, in your April 2016 Closure Report to Market Complaint Investigation, you indicated that the dissolution failure was due to the **(b)(4)** and **(b)(4)** process.

Your response states that lot **(b)(4)** was the only lot manufactured during a **(b)(4)**-lot manufacturing campaign that appeared to be affected by these processing issues. This response is inadequate because it does not provide sufficient justification for this conclusion, and fails to fully investigate the scope and root causes of the reported dissolution failure.

In response to this letter, provide:

- Updated dissolution testing of all **(b)(4)** lot retains, and a commitment to add extra lots of the **(b)(4)**mg tablet to your annual stability program.
- Your detailed retrospective review of all complaint, manufacturing, and laboratory investigations associated with each product that you produce for the U.S. market, and all lots that are within expiry.
- Your detailed retrospective review of the manufacturing process validation for each product that can be exported to the U.S., including **(b)(4)**, to ensure your manufacturing processes are capable of consistently yielding finished products that meet quality attributes and manufacturing requirements. For each process, identify sources of variability in your raw materials and manufacturing process, and indicate the steps you have implemented to reduce variability or mitigate its potential effects on the quality of your products.
- Your plan to ensure that all future investigations are thorough, scientifically sound, and result in appropriate and effective CAPA.

2. 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)).

Our investigators observed multiple **(b)(4)**, which you identified as clean, containing colored residue and/or in poor condition.

For example, **(b)(4)** PDE-2095 had white **(b)(4)** residue on and around a white interior gasket. Our investigator documented a gap in the gasket that could allow processed materials to accumulate. The ends of the gasket were also in poor condition.

Your response states that you sampled and analyzed residues to identify and quantify chemical and microbiological contaminants, and the results met microbial attributes. You attributed the white residue to "… part of [the] overall finish of **(b)(4)** surface" and the "…drying of water drops after cleaning."

In response to this letter, provide:

- The sampling procedures and analytical methods you used to test the white residues. Include validation protocols and validation reports.
- Your procedures to install and maintain the "**(b)(4)** type" gasket in **(b)(4)** PDE-2095. Assess all **(b)(4)** that use similar gaskets in product contact areas. Justify the suitability and continued use of these gaskets in your **(b)(4)**.
- Your plan to ensure that personnel responsible for cleaning, verifying equipment cleanliness, and maintaining equipment are appropriately trained and capable of performing their assigned duties. Include cleaning validation studies for your **(b)(4)**.
- An overall assessment of the adequacy of your cleaning program for all equipment, with special emphasis on difficult-to-clean parts.

3. Your firm failed to establish adequate written responsibilities and procedures applicable to the quality control unit and to follow such written procedures (21 CFR 211.22(d)).

Your firm's procedures, QM001-04 Quality System Manual and CQA012-01 Product Recall, direct your firm to recall products that fail to meet specifications, but your quality control unit failed to follow your written procedures regarding the recall of failing products.

For example, on July 8, 2016, you received a complaint that one tablet in a bottle of 5 mg finasteride tablets, lot FIN16002, was approximately double the thickness of the others. You confirmed the defect after receiving the complaint sample on July 27, 2016, but did not initiate a product recall as directed by your own procedures until December 23, 2016. This was nearly a week after our investigators pointed out your failure to take action as directed by your own procedures regarding recalls of defective products.

Although you initiated a product recall in response to the discrepancy raised by our investigators, your response was inadequate because you did not explain why you failed to follow your own Quality System Manual and product recall procedure with respect to this product defect in the first instance.

In response to this letter, provide a list and summary explanation for all other instances in which product(s) distributed within the last five years failed to meet established specifications, but for which you failed to take actions prescribed by your Quality System Manual and recall procedure. Provide your planned corrective actions and preventive actions (CAPA) for each such instance and explain your CAPA for ensuring that you follow your own procedures regarding product quality and recalls.

Process Controls

Your firm does not have an adequate ongoing program for monitoring process control to ensure stable manufacturing operations and consistent drug quality. See FDA's guidance document, Process Validation: General Principles and Practices, for general principles and approaches that FDA considers appropriate elements of process validation, at **https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070336.pdf (https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070336.pdf)**.

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. 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.

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 (mailto: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 admission of articles manufactured at Hetero Labs Limited, Unit V at Polepally Village, Jadcherla Mandal, Mahaboob Nag, Telangana 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:

Jason F. Chancey
Consumer Safety 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 3008307735.

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