CP Pharmaceuticals 11/16/16

Department of Health and Human Services

Public Health Service
Food and Drug
Administration
Silver Spring, MD 20993

Via UPS
Return Receipt Requested

Warning Letter: 320-17-07

November 16, 2016

Dr. Habil Khorakiwala
Founder, Chairman & Group CEO
Wockhardt Limited
Wockhardt Towers
Bandra Kurla Complex, Bandra (East)
Mumbai, Maharashtra 400 051, India

Dear Dr. Khorakiwala:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, CP Pharmaceuticals, Ash Road North, Wrexham Industrial Estate, Wrexham, United Kingdom, from October 5 to 9 and October 12 to 13, 2015.

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 firm's November 3, 2015, response in detail and acknowledge receipt of your subsequent responses.

Our investigator observed specific violations during the inspection, including, but not limited to, the following.

1. Your firm failed to follow appropriate written procedures that are designed to prevent microbiological contamination of drug products purporting to be

sterile, and that include validation of all aseptic and sterilization processes. (21 CFR 211.113(b))

Our investigator observed poor practices during aseptic set-up and filling, including but not limited to the following examples.

- Multiple operators who had touched surfaces and items in the ISO-7 clean area failed to disinfect their hands before performing activities within the ISO-5 area. For instance, we observed operators touching the external control panel and push carts. Without disinfecting their gloved hands, these operators then opened the Restricted Access Barrier System (RABS) and performed activities in the ISO-5 area.
- We observed operators moving briskly and causing excessive movement of the **(b)(4)** located immediately adjacent to the RABS. This excessive movement occurred while the RABS **(b)(4)** were open.
- You do not routinely disinfect the cart used for holding **(b)(4)** items prior to use. This cart is stored in the Grade B area for an extended period, and is cleaned and disinfected only **(b)(4)**.
- We observed **(b)(4)** bags with sterile supplies coming in contact with the **(b)(4)** in the ISO-7 area when being transported to the RABS. These bags were not disinfected prior to entry into the RABS.

These deviations were neither documented in your batch production record, nor captured by the quality unit during their observation of videos of the operation as per your SOP #QAP-199-0-1704. This procedure requires quality unit personnel to review the acceptability of general techniques and behaviors of cleanroom personnel within classified areas (ISO 5 and ISO 7).

The ISO 5 is a critical area because sterile product is exposed and therefore vulnerable to contamination. Your aseptic filling process should be designed, and operations executed, to prevent contamination hazards to your sterile product.

Your firm's response is inadequate. Although your response includes a revised procedure (QAP-199-0-1704) on quality oversight of operations, you did not retrospectively evaluate video footage to identify poor aseptic practices and identify any batches produced under these conditions. In response to this letter, provide a third party's independent assessment of aseptic processing practices and affected batches.

2. Your firm failed to perform operations within specifically defined areas of adequate size and to have separate or defined areas or such other control systems necessary to prevent contamination or mix-ups in aseptic processing areas. (21 CFR 211.42(c)(10))

a. Environmental Monitoring

Your environmental monitoring program did not sufficiently cover personnel in your ISO-5 area during set-up, filling, and other activities in your aseptic processing rooms. For example, our review of the Class 100 entry/exit log and other production records for 9/16-17/15 showed that **(b)(4)** operators participated on the filling line. However, most of these operators were not monitored.

In your response, you committed to perform a risk assessment (RAS-088-3950) of the failure to sufficiently monitor all personnel conducting aseptic activities in the ISO-

5 area. Your response failed to describe any details of how this assessment will be conducted.

In response to this letter, provide a copy of your current risk assessment. Inform this office of all actions to be taken as a result of your risk assessment.

Also, explain whether production staff performing aseptic setup activities are part of your routine monitoring program.

Our previous warning letter (no. 320-11-002, dated October 29, 2010) also cited inadequate personnel monitoring. Your repeated failure to create a robust monitoring program indicates insufficient oversight of your aseptic production operation.

b. Disinfection Qualification
We observed that your firm did not adequately disinfect your RABS. For example, surfaces **(b)(4)** the RABS **(b)(4)** were not routinely disinfected, and your firm incompletely disinfected the bottom of the RABS **(b)(4)**.

In addition, you have not sufficiently established the efficacy of disinfectants you use in aseptic processing cleanrooms. Your disinfectant study only challenged **(b)(4)** and **(b)(4)** manufacturing surfaces. You did not provide an adequate scientific rationale for not challenging other representativesurfaces, such as glass windows, **(b)(4)**, **(b)(4)**, **(b)(4)**, **(b)(4)**, or other interior RABS surfaces.

In response to this letter, provide data to support the efficacy of your disinfection procedures on additional representative surfaces.

Aseptic processing guidance

See FDA's guidance document, *Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Practice*, to help you meet the CGMP requirements when manufacturing sterile drugs using aseptic processing. It is available online at *http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070342.pdf.*

Aseptic processing consultant recommended

Based upon the nature of the violations we identified at your firm and because you failed to correct repeat violations, we strongly recommend engaging a consultant qualified as set forth in 21 CFR section 211.34, to assist your firm in meeting CGMP requirements for aseptic processing. 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.

In response to this letter, provide the following:

- A comprehensive evaluation of the design, control, maintenance, and oversight of your aseptic processing lines, including but not limited to:

- o A thorough assessment of the adequacy of personnel behaviors and activities for all aseptic processing lines, including during both setup and processing.

- o A full review of the sufficiency of your RABS disinfection practices and procedures. This should include an evaluation of the adequacy of sporicidal disinfection of the interior prior to each RABS use. Also provide an evaluation of the adequacy of disinfection practices for operators' gloved hands and RABS surfaces during setup and batch operations.

- o An overall evaluation of CGMP compliance, including identification of additional contamination hazards in the operation, as well as any deficiencies in manufacturing design, systems, procedures, controls, maintenance, supervision, and training effectiveness.

- A risk assessment of the potential effects of the observed deficiencies on the quality of your drug products. Describe how these deficiencies may have impacted the quality of drug products released for distribution.
- An overall management strategy that describes how your executive management will oversee improvements in operations and ensure ongoing oversight to provide for sustainable quality assurance.

Conclusion

Violations cited in this letter are not intended as an all-inclusive list. You are responsible for determining the causes of these violations, for preventing reoccurrences, and for preventing other violations.

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.

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 product manufacturer.

Failure to correct these violations may also result in FDA refusing admission of articles manufactured at CP Pharmaceuticals, Ash Road North, Wrexham Industrial Estate, Wrexham, United Kingdom, 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:

Rafael Arroyo, 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 3003369660.

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