Inspections, Compliance, Enforcement, and Criminal Investigations

CP Pharmaceuticals, Ltd. 10/29/10

Department of Health and Human Services

Public Health Service
Food and Drug Administration
Silver Spring MD 20993

Warning Letter

WL: 320-11-002

October 29, 2010

Mr. Sirjiwan Singh
Managing Director
CP Pharmaceuticals, Ltd.
Ash Road North
Wrexham Industrial Estate
Wrexham, LL13 9UF, United Kingdom

Dear Mr. Singh:

During our July 22-29, 2010 inspection of your pharmaceutical manufacturing facility, CP Pharmaceuticals, Ltd., located at Ash Road North, Wrexham Industrial Estate, Wrexham, LL13 9UF, United Kingdom, investigators from the Food and Drug Administration (FDA) identified significant violations of Current Good Manufacturing Practice (CGMP) regulations for Finished Pharmaceuticals, Title 21, Code of Federal Regulations, Parts 210 and 211. These violations cause your drug products to be adulterated within the meaning of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (the Act) [21 U.S.C. § 351(a)(2)(B)] in that the methods used in, or the facilities or controls used for, their manufacture, processing, packing, or holding do not conform to, or are not operated or administered in conformity with, CGMP.

We acknowledge your written responses, dated September 3, 2010, and September 24, 2010, to the Form FDA 483. However, because these responses were received more then 15 business days after the Form FDA 483 was issued, the responses have not been considered. We plan to evaluate your responses to the Form FDA 483, along with any other written material provided, as a direct response to this Warning Letter.

Specific violations observed during the inspection include, but are not limited, to the following:

1. Your firm has not established separate or defined areas or such other control systems to prevent contamination during aseptic processing [21 C.F.R. § 211.42(c)]. For example,

a. There is no documentary evidence of in-situ air pattern analysis (e.g., smoke studies) conducted at critical areas to demonstrate unidirectional airflow and sweeping action over and away from the product under dynamic conditions. Your firm failed to demonstrate that the appropriate design and controls are in place to prevent turbulence and stagnant air in the critical area. It is essential that you evaluate airflow patterns for turbulence that can act as a channel for air contamination. The studies should be well documented with written conclusions, and should include an evaluation of the impact of aseptic manipulations (e.g., interventions) and the equipment design.

b. Your aseptic processing control systems and operations do not provide assurance that the production rooms and equipment maintain aseptic conditions. Additionally, your environmental monitoring practices do not include adequate routine examination of the facilities and equipment to ensure that possible contaminants can be detected.

The inspection documented mold contamination in the class 100 production room and poor conditions of a wall in the freeze dryer room, even though maintenance is conducted on the freeze dryer every **(b)(4)** months. An incident report, initiated in November 2009, identifies holes in the ceiling and visible light coming from the roof near the ventilation system, bubbling of the vinyl and disintegration of the wall under vinyl in the freeze dryer room, visible black mold on the wall, a poor drain system for the freeze dryer steam venting system, and a soft (spongy) wall.

c. Operators involved in the filling operations for the sterile drug products manufactured at your facility do not practice adequate aseptic techniques to prevent product contamination. The environmental monitoring performed at the end of the production run consist of sampling the chest and the hand most frequently used (right or left) of the employee's gown. Also, this procedure is performed by the gowned operator and is not monitored by a second qualified person (e.g., supervisor; quality unit personnel) to ensure the proper techniques are being applied. This practice is unacceptable. We expect that all operators who conduct operations within aseptic processing areas be properly trained and monitored to ensure that proper techniques are utilized during all operations, including aseptic filling operations and personnel sampling.

2. Your firm has not thoroughly investigated the failure of a batch or any of its components to meet its specifications whether or not the batch has already been distributed [21 C.F.R. § 211.192].

For example, your firm's microbiology laboratory does not perform species identification on a routine basis of the yeast and molds detected in your production area. There was no identification raw data available for the media fill that failed in November 2009. Additionally, your firm does not perform challenge testing to the sterility media with environmental isolates from the environmental monitoring program.

3. Your firm has not established scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that components, in-process materials, and drug products conform to appropriate standards of identity, strength, quality, and purity [21 C.F.R. § 211.160(b)].

For example, at the time of the inspection the validation data for several laboratory methods was incomplete or unavailable (i.e. total viable aerobic count for the API, total viable aerobic plate count of raw materials, and bacterial endotoxin testing for (**(b)(4)**). However, you approved the validation for these methods without the complete data in place.

In addition to the items listed above, the inspection uncovered deficiencies that increase our concerns regarding the quality of the sterile drug products manufactured at your facility. These issues include, but are not limited, to:

☐ Your firm failed to adequately address the increased adverse trends observed in the environmental monitoring trends for the period of August 2009 to May 2010; and, therefore, did not recognize that the environment did not appear to be under control.

☐ Your firm did not establish a schedule for the cleaning with an agent designed to kill spores, although mold continued to be found in the class 10,000 area. Our investigators observed that the mold contamination had not been eliminated at the time of the inspection in July 2010, almost a year after the initial discovery.

We are concerned that your firm has not properly evaluated the risk these deviations pose to the products that have been released and distributed. Your firm has not provided a scientific justification to ensure the product available in the United States (U.S.) market is in compliance with CGMP standards. Please provide a list of all the products and lots shipped to the U.S. that remain within expiration, and any additional corrective actions you plan to initiate. It is important that you take appropriate actions to address these deficiencies and notify us if any actions are planned for lots of sterile drug products manufactured by your Wrexham facility, and include your rationale.

The violations cited in this letter are not intended to be an all-inclusive statement of violations that exist at your facility. You are responsible for investigating and determining the causes of the violations identified above and for preventing their recurrence and the occurrence of other violations. If you wish to continue to ship your products to the United States, it is the responsibility of your firm to ensure compliance with all U.S. standards for CGMP and all applicable U.S. laws and regulations.

Until all corrections have been completed and FDA has confirmed corrections of the violations and your firm's compliance with CGMP, FDA may withhold approval of any new applications or supplements listing your firm as a drug product manufacturer. In addition, failure to correct these violations may result in FDA refusing admission of articles manufactured at CP Pharmaceuticals, Ltd., Ash Road North, Wrexham Industrial Estate, Wrexham, LL13 9UF, United Kingdom, into the United States. The articles are subject to refusal of admission pursuant to section 801(a)(3) of the Act [21 U.S.C. § 381(a)(3)], in that, the methods and controls used in their manufacture do not appear to conform to Current Good Manufacturing Practice within the meaning of section 501(a)(2)(B) of the Act [21 U.S.C. § 351(a)(2)(B)].

Within fifteen working days of receipt of this letter, please notify this office in writing of the specific steps that you have taken to correct violations. Include an explanation of each step being taken to prevent the recurrence of violations and copies of supporting documentation. If you cannot complete corrective action within fifteen working days, state the reason for the delay and the date by which you will have completed the correction. Please identify your response with FEI # 3003369660.

If you have questions or concerns regarding this letter, contact Hidee Molina, Compliance Officer, at the below address and telephone number.

U.S. Food and Drug Administration
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Division of Manufacturing and Product Quality
International Compliance Branch
White Oak, Building 51, Room 4224
10903 New Hampshire Ave
Silver Spring, MD 20993
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Sincerely,
/Richard L. Friedman/
Richard L. Friedman
Director
Division of Manufacturing and Product Quality
Office of Compliance
Center for Drug Evaluation and Research

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