U.S. Department of Health & Human Services

U.S. Food and Drug Administration

Inspections, Compliance, Enforcement, and Criminal Investigations

Cadila Healthcare Limited 6/21/11

Department of Health and Human Services

Public Health Service
Food and Drug Administration
Silver Spring MD 20993

Warning Letter

VIA UPS MAIL

WL: 320-11-015

June 21, 2011

Mr. Pankaj R. Patel
Chairman and Managing Director
Zydus Group
Zydus Tower
Satellite Cross Roads
Ahmedabad 380 015 India

Dear Mr. Patel:

During our January 17 - February 3, 2011 inspection of your pharmaceutical manufacturing facility, Cadila Healthcare Limited, located at Sarkhej Bavla N.H. No.8 A, Moraiya, Tal: Sanand, Dist. Ahmedabad, Gujarat, India, 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 have reviewed your firm's response of February 10, 2011, and note that it lacks sufficient corrective actions.

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

1. Your firm's laboratory records fail to include complete data derived from all tests necessary to assure compliance with established specifications and standards [21 C.F.R. § 211.194].

For example,

a. Your microbiologists reported the MA 5 and MA 6 microbiological plates as "nil" while each plate contained one (1) colony forming unit (CFU).

On January 21, 2011, the FDA investigator observed the microbiological plates, MA 5 and MA 6, from air sampling locations in the Class 100/Grade A laminar air flow cabinet in the Microbiology Lab. Each microbiological plate contained one (1) CFU/m3. Your microbiologists reported these microbiological plates as "nil" on your form FM/QC/252-9 Quality Control Department Record of Environmental Monitoring of Microbiology Laboratory. However, the action limit for these sample locations is **(b)(4)** CFU/m3 which requires an investigation per your procedure SOP/QC/049 entitled Environment Monitoring of Aseptic Area by Settle Plate, Air Sampling, Surface Sampling (RODAC Plate) and Personnel Hygiene for Viable Count. The results as originally reported on your form FM/QC/252-9 would not have prompted an investigation.

b. The microbiological growth found on settle plate MS 4 was incorrectly identified and reported as a typical microorganism when compared against your firm's library/photographs of typical environmental flora.

Your microbiologists identified the growth on the MS 4 plate as typical flora. However, the FDA investigator found that when compared with your normal environmental flora, the growth should have been reported as atypical since the microorganism identified is not included in firm's library/photographs of typical environmental flora. Your written procedure SOP QC/049 requires further identification of microbial growth not included in your firm's library/photographs. The results originally reported on your form FM/QC/252-9 (typical flora) would not have prompted further identification.

Your response recognized that the microbiologists should have classified the MS 4 microorganism as atypical. Moreover, your response indicated that an investigation was performed and microbiologists were retrained. You stated that as part of your corrective actions two microbiologists will observe counts for three months to "rule out any possibility of erroneous reporting." However, during the inspection, the FDA investigator observed two microbiologists reading plates and recording data. Therefore, your corrective action plan does not adequately address the observation, nor does it appear to improve on current practices for reading plates and recording data. Additionally, the revised form used to document the microbiologist observation lacks appropriate identification of the microbiologist performing the task at the time of the final reading of the plates.

You are responsible for the accuracy and integrity of the data generated by your firm. We are concerned that trained microbiologists employed by your firm were unable to accurately identify microbial growth on environmental monitoring plates. Additionally, there is no assurance that such errors have not occurred previously (during the manufacture of exhibit batches for application products pending with FDA). Provide a more comprehensive corrective action plan to ensure the integrity of all data used to assess the quality and purity of all drugs manufactured at your facility, including any registration lots.

Accurate and reliable microbiological data is essential to support the aseptic processing operations used during the manufacturing of sterile finished drug products intended for distribution in the United States. Your response includes retraining documentation related to identifying environmental isolates as typical/atypical and observation of microbial growth, as well as retraining on SOP QC/049. According to information provided to the FDA investigators during the inspection, the Microbiology Laboratory is staffed by **(b)(4)** microbiologists. The training attendance sheets in your response do not include the same individuals. For example, 10 QC personnel attended the training on observation and counting of colonies on environmental monitoring plates held on January 22, 2011; and, only 8 QC personnel attended the training on identifying typical/atypical environmental isolates during environmental monitoring plate observation. Explain this discrepancy and provide documentation confirming that all employees have been retrained. Additionally, provide documentation of specific training offered to all employees regarding the importance of following CGMP, and ensuring that they accurately report all required tests.

2. Your firm has not established or followed appropriate written procedures designed to prevent microbiological contamination of drug products purporting to be sterile [21 C.F.R. § 211.113(b)].

For example,

a. Your firm's environmental monitoring is inadequate in relation to personnel monitoring.

Our investigators found that gowns worn by operators working in the aseptic processing areas are only monitored **(b)(4)** per week. Additionally, gloves are only monitored at the **(b)(4)** the shift. We are concerned with the fact that operators performing critical operations may not be adequately monitored. Therefore, there is no assurance that your environmental monitoring program is capable of detecting all microbiological contaminants.

Since personnel can significantly affect the quality of the environment, a robust personnel monitoring program should be in place in order to be compliant with CGMPs. Your response indicates that SOP/QC/049 was revised to require additional monitoring of gloves after **(b)(4)** for personnel involved in aseptic connections on filling line and filtration activities apart from regular monitoring at the **(b)(4)** of the shift. It is your responsibility to ensure that all personnel involved in aseptic

processing are properly monitored on a daily basis, or in association with each lot. We acknowledge that SOP/QC/049 has now been revised to require sampling of gowns per **(b)(4)**/per **(b)(4)**.

b. The technician performing the air sampling held the probe close to the HEPA filter face rather than **(b)(4)** as specified in section 4.5 of your written procedure SOP/QC/049.

During the inspection, the investigators were provided with retraining records for technicians performing active air sampling.

Your responses and corrective actions related to items 2a and 2b of this letter failed to indicate the disposition of exhibit batches that were manufactured during the time when personnel and air sampling monitoring was inadequate. Provide information on the disposition of these batches.

The violations cited in this letter are not intended to be an all-inclusive statement of violations that exist at your facilities. 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 Cadila Healthcare Limited located at Sarkhej Bavla N.H. No.8 A, Moraiya, Tal: Sanand, Dist. Ahmedabad, Gujarat, India, 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 #3002984011.

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

U.S. Food and Drug Administration
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Sincerely,
/Steven J. Lynn/
Steven J. Lynn
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