Cadila Healthcare Limited 12/23/15

Department of Health and Human Services

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

Warning Letter

VIA UPS

WL: 320-16-05

December 23, 2015

Mr. Pankaj R. Patel
Chairman Managing Director
Cadila Healthcare Limited
Zydus Tower
Satellite Crossroads Road
Ahmedabad 380 015
India

Dear Mr. Patel:

The U.S. Food and Drug Administration (FDA) inspected the following two Cadila pharmaceutical manufacturing facilities in 2014:

A. August 28-September 5: Cadila Healthcare Limited located at Sarkhej-Bavla Road, N.H. No. 8A, Moraiya, Tal. Sanand, Ahmedabad, Ahmedabad City (FEI 3002984011)
B. December 1-6: Cadila Healthcare Limited India (Zyfine) located at Plots 265-266 B Zyfine Unit, Sarkhej-Bavla Road, N.H. No. 8A, Changodar, Tal. Sanand, Ahmedabad (FEI 3006595385)

At these two sites, we identified significant violations of current good manufacturing practice (CGMP) regulations for finished pharmaceuticals, Title 21, Code of Federal Regulations, Parts 210 and 211, and deviations from CGMP for the manufacture of active pharmaceutical ingredients (APIs).

These violations and deviations cause your drugs to be 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), 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 reviewed your firm's responses of September 26 and December 26, 2014 in detail. We note that they lack sufficient corrective actions.

We acknowledge receipt of your additional correspondence of November 29, 2014, January 1, January 31, February 28, April 2, June 1, July 2, August 1, September 1, and November 30, 2015 for FEI 3002984011; and correspondence of April 24, September 11, and September 23, 2015 for FEI 3006595385.

Our investigators observed specific violations and deviations during the inspections, including, but not limited to, the following:

A. Cadila Healthcare Limited (FEI 3002984011)

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).

Our inspection found that you did not adequately investigate out-of-specification (OOS) laboratory test results. For example, the following OOS investigation reports associated with potency and content uniformity specifications for warfarin sodium, a narrow therapeutic index drug, failed to identify a root cause or provide adequate corrective actions:

- Investigation #FI13/TS/US/004
- Investigation #OOS/US/022/14
- Investigation #OOS/US/065/14
- Investigation #OOS/US/029/13
- Investigation #OOS/US/037/13

In your September 26, 2014 response, you stated that you would temporarily suspend the manufacture of all strengths of warfarin sodium tablets USP (1, 2, 2.5, 3, 4, 5, 6, 7.5, and 10 mg) until completion of the investigation and implementation of corrective actions and preventive actions (CAPA).

On November 29, 2014, you informed the FDA that, based on protocols executed and various experiments performed, your firm decided to resume the manufacture of warfarin sodium tablets on November 24, 2014.

However, months later, in a meeting with FDA on June 8, 2015, you acknowledged that additional lots had failed since you resumed the manufacture of warfarin sodium tablets in November 2014.

This recurring quality problem was also identified in the FDA inspection of August 8-19, 2013, which revealed inadequate process controls and complaint and failure investigations related to warfarin tablets. In addition, on May 13, 2013, your firm initiated a recall of one lot of warfarin 2 mg tablets because of failed assay and oversized tablets.

The current inspection continued to find inadequate investigations into warfarin tablet failures. The recurrence of product quality failures following the completion of your

investigation indicates that your CAPA was ineffective. The recurrence of these failures is apparently due to inadequate identification of root causes and lack of action to resolve this manufacturing problem.

These persistent failures indicate that your manufacturing process is not in a state of control. Nevertheless, at this time, drugs from this facility are being released to the market.

In response to this letter, list all warfarin batches with out-of-specification and out-of-trend results, whether they were distributed to the United States or to other markets. Include all analytical testing results and investigations. Provide specific lot numbers and dates of manufacture of the warfarin tablets (retain samples) that you intend to test or have tested by a contract laboratory.

Your response to this letter should discuss any further work to remediate the process (such as improving process design) and quantify the reliability of equipment used in the manufacture of warfarin that can affect content uniformity, assay, thickness, or other relevant critical quality attributes. In evaluating equipment reliability, you should use methods such as rolled throughput yield and discrete process capability estimates. Also discuss your evaluation of other influential factors on manufacturing consistency. Include the role of particle size and the potential significance of **(b)(4)** particles on **(b)(4)**. Finally, provide your justification for continued production and explain how you have ensured that your marketed product is safe.

To learn more about FDA's current thinking on laboratory investigations, download our guidance for industry, *Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production*:http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm070287.pdf.

2. Your firm failed to establish and follow adequate written procedures describing the handling of all written and oral complaints regarding a drug product. You failed to maintain an adequate written record for each investigation conducted pursuant to 21 CFR 211.192 that included the findings of the investigation and follow-up (21 CFR 211.198(a) and (b)(2)).

Our inspection found that your firm did not adequately investigate and address consumer complaints on multiple occasions.

Over a three-year period, your firm received nine consumer complaints related to potential mix-ups among products produced at your facility. Complaints were reported by different pharmacies and distributors. During your investigations of these complaints, you documented that some of the mixed-up drugs were manufactured on adjacent equipment lines, but you never completed the root cause analysis. Thus, it remains unknown whether the mix-ups were caused by inadequate cleaning procedures, personnel flow, equipment suitability, material flow, line segregation, line-clearance documentation, or something else.

Additionally, during the inspection our investigator noted that you failed to file Field Alert Reports (FARs) with FDA in eight of these nine instances. Your own SOP/QA/029, Handling of Market Complaints, requires that you submit FARs when

"[a]ny incident that causes the drug product or its labeling to be mistaken for, product mix-up, or applied to another article."

Furthermore, the investigator reviewed SOP/QA/029 and found that this procedure was deficient because it did not require your complaint reviews to determine whether other products might be affected by confirmed complaints. SOP/QA/029 was also deficient because it did not require a documented review of manufacturing performance (e.g., deviations/discrepancy investigations, maintenance, and process control data) or quality data (e.g., other complaints) to rule out related issues.

Your firm's systems should be capable of detecting adverse trends. Your complaint review should determine whether other products and batches are potentially affected by the problem reported in a consumer complaint. Due to this deficient SOP and incomplete complaint handling practices, you did not ascertain the scope of quality defects, such that you could link consumer complaints to other potential quality problems.

As a result of FDA's inspection, you re-opened your investigations related to the nine consumer complaints about product mix-ups. You eventually identified manufacturing deficiencies that could have led to the product mix-ups. Also, as a result of our inspection and your subsequent re-opening of these investigations, you submitted FARs and initiated a product recall of several lots.

Your response indicated you planned to conduct a retrospective review of product complaints, deviations, and product failures from January 2013 to August 2014. This retrospective review appears to focus on your solid oral dosage products and is only conducted over a limited period. Your retrospective review period is insufficient and does not appear to address whether other dosage forms made at the site may also be vulnerable to mix-ups or other major defects.

In response to this letter, conduct and provide the details of your risk assessment to determine the adequacy of your firm's investigations into product complaints and effectiveness of the CAPAs you have taken in response to those complaints. Provide details of the specific changes you have made to ensure prompt identification, correction, and follow-up for all problems associated with your drug products. Significant problems must also be reported to FDA in accord with FDA field alert requirements. Include your revised SOP to remediate your systems for problem identification and trending, including but not limited to complaint handling.

B. Cadila Healthcare Limited India (Zyfine) (FEI 3006595385)

1. Failure to establish written procedures to monitor the progress and control the performance of processing steps that may cause variability in the quality characteristics of your APIs.

Our inspection found you obtained failing results for related compound analysis in four out of **(b)(4)** batches of **(b)(4)** API:

- **(b)(4)**
- **(b)(4)**
- **(b)(4)**
- **(b)(4)**

You did not identify the root cause of these failures, and reprocessed the failed batches without scientific justification.

In your December 26, 2014 response, your firm acknowledged repeated failures due to inadequate process controls. Your response is inadequate because you did not provide details about these repeated failures, your root cause analysis, or the CAPA implemented in response to your investigation of the failures.

In your response to this letter, summarize your investigation, root cause analysis and implemented CAPA. Specifically include your assessment of the effects of process control failures on the quality of the product, and any process controls you have modified or plan to modify in response to your investigation.

2. Your firm failed to exercise sufficient controls over computerized systems to prevent unauthorized access or changes to data.

a. Your firm failed to adequately control the use of computerized systems in the quality control laboratory. Our inspection team found that the laboratory manager had the ability to delete data from the Karl Fischer Tiamo software. During our limited review of your Karl Fischer data, we found that one file had been deleted. However, because the audit trail function for the Karl Fischer Tiamo software was not activated, and because eight different analysts share a single username and password, you were unable to demonstrate who performed each operation on this instrument system. You do not have a record of the acquisition of all data, nor do you have records of changes to or modifications of such data.

b. The inspection also found that a file containing the moisture content results for **(b)(4)** API batch **(b)(4)** had been deleted. This deletion was not identified and reviewed as part of your batch release decision. In your response, you indicated that the batch was within specifications according to raw data retrieved from the laboratory notebook. However, your response failed to address the deleted electronic record. You also did not indicate whether this deletion was an isolated incident or if other QC laboratory instruments and systems are configured to permit deletion of data.

In response to this letter, provide a comprehensive corrective action plan addressing the foregoing concerns. Include information regarding revised procedures, system upgrades, controls you have implemented, and appropriate retraining of employees to ensure that data generated and maintained on computerized systems is protected against unauthorized manipulation and deletion.

3. Your firm failed to ensure that all quality-related activities are recorded at the time they are performed.

Our inspection found that your firm's employees use "rough or unofficial notebooks" to document various CGMP activities. During their walk-through, our investigators found "unofficial" notebooks in the engineering office at your Zyfine **(b)(4)** plant, in the quality assurance office at your Zyfine **(b)(4)** plant, and in the scrap yard shared by **(b)(4)** plants.

a. For example, an “unofficial” notebook found in the engineering office stated, “Pseudomonas present in **(b)(4)** water system” on November 26, 2014 and “**(b)(4)** water system (Activity) investigation” on November 25, 2014. Your firm was unable to provide the investigators with any documentation regarding *Pseudomonas sp.* found in your water system and the related investigation.

In your response to the observation, you explained that this failure occurred during qualification of your water system, which was still in progress at the time of your response. Your response was deficient; the fact that your investigation into the presence of *Pseudomonas sp.* in your water system transpired during the qualification of that system is irrelevant. You must document all CGMP activities at the time you perform them, including equipment qualification and any deviations observed during such activities.

b. Our investigators found several plastic bags filled with paperwork and other scrapped items in the scrap yard. One item was a torn notebook of deficiencies recorded during review of your batch manufacturing records. For example, page 22 included a comment on batch **(b)(4)** “not mentioned any deviations of lower yield.” Our review of the batch record **(b)(4)** found that the yield reported was **(b)(4)**% (range: **(b)(4)**%), but the batch record did not indicate a deviation.

In your response of December 26, 2014, you stated that that these were personal notebooks intended only for meeting and other discussion notes. Your response did not explain why your production personnel used unofficial paper for documenting CGMP relevant data. Your response also did not explain whether the lower-yield event was investigated. Your batch records should include complete information related to the manufacture of each batch, including notation of any deviation, its evaluation, and investigation.

Your response is also inadequate in that the investigation you performed in response to FDA’s inspection was primarily limited to the discarded CGMP records cited in the Form FDA-483. Your investigation did not include a comprehensive review of all records in the waste area or a thorough review of your firm’s practice of destroying CGMP records.

In response to this letter, indicate the steps you have taken to ensure all CGMP activities are recorded at the time they occur and that the use of unofficial documentation (e.g., notebooks) has been discontinued. Describe how you will prevent this practice in the future. Also describe improvements to your systems for managing and retaining all CGMP records. Provide your revised record retention policy for all CGMP records. Demonstrate that you have implemented controls over record disposition that include, at a minimum, identification of appropriate documents, retention timelines, clear documentation of what record is destroyed, and names and signatures of those who witnessed the destruction.

c. On their December 1, 2014 walk-through of the Zyfine **(b)(4)** plant, our investigators reviewed AHU/HVAC filter cleaning records. Duplicate records were in the engineering office. One of your firm’s representatives stated that the records were rewritten for clarity. Our review of the original and rewritten records found discrepancies in cleaning dates and cleaning personnel.

Your December 26, 2014 response stated that poor documentation practices resulted from not operating under a corporate quality assurance structure until 2013.

In your response to this letter, describe your investigation into discrepancies in the filter cleaning records. Outline the extent of the lack of corporate quality assurance you described in your December 26, 2014 response and systems affected by this critical problem. Provide a summary of your findings, including instances of records that were duplicated or rewritten and any discrepancies found, and describe your CAPA.

These examples (B1 and B2) of our findings at your Zyfine facility raise serious concerns about the effectiveness of your manufacturing controls, the integrity of your computerized records, and the accuracy of your CGMP records.

In addition to the specific items requested above, in your response to this letter, provide the following:

- A comprehensive investigation and evaluation into the failures underlying these violations. Describe your methodology, including the role of an independent third party if you choose to engage one. Include detailed conclusions about the extent of your data integrity deficiencies and their root causes, which may involve lack of record control, non-contemporaneous recording, deletion of data, and other problems with the integrity of data.
- A risk assessment of how the observed deficiencies may affect the reliability and completeness of quality information available for your drug products. Also determine the consequences of your deficient documentation practices on the quality of drug products released for distribution.
- A comprehensive management strategy to address these serious breaches, including a detailed global CAPA. The CAPA should include:
- A description of the corrective actions you have taken or will take, such as contacting your customers, recalling product, conducting additional testing, adding lots to your stability programs to assure stability, monitoring complaints, reporting any issues affecting drug applications, and other steps to assure the quality of your products manufactured under the violative conditions discussed above
- A description of the preventive actions you have taken or will take, such as upgrading systems, revising procedures, implementing new controls, training or re-training personnel, and other steps to prevent the recurrence of CGMP violations, including breaches of data integrity.

The violations and deviations cited in this letter are not intended to be an all-inclusive list of violations and deviations that exist at your facilities. You are responsible for investigating and determining the causes of the violations and deviations identified above, for preventing their recurrence, and for preventing other violations and deviations.

If, as a result of receiving this warning letter or for other reasons, you are considering a decision that could reduce the number of active pharmaceutical ingredients or finished drug products produced by your manufacturing facilities, please contact CDER's Drug Shortages Staff immediately at drugshortages@fda.hhs.gov. We can work with you on the most effective ways 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 in your drug manufacture under 21 U.S.C. 356C(a)(1). As soon as possible, FDA must consider what actions, if any, may be

needed to avoid shortages and protect the health of patients who depend on your products. In appropriate cases, you may be able to take corrective action while avoiding or limiting drug shortages.

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 and an API manufacturer.

Under Section 801(a)(3) of the FD&C Act, 21 U.S.C. 381(a)(3), failure to correct these violations may also result in FDA refusing admission into the United States of articles manufactured at:

- Cadila Healthcare Limited, Sarkhej-Bavla Road, N.H. No. 8A, Moraiya, Tal. Sanand, Dist. Ahmedabad, Ahmedabad City
- Cadila Healthcare Limited India (Zyfine), Plots 265-266 B Zyfine Unit, Sarkhej-Bavla Road, N.H. No. 8A, Changodar, Tal. Sanand, Ahmedabad

Within 15 working days of receipt of this letter, please notify this office, in writing, of the specific steps that you have taken to correct and prevent the recurrence of violations and deviations. Provide supporting documentation.

If you cannot complete corrective actions within 15 working days, provide the date by which you will have completed the corrections. If you no longer manufacture or distribute the drug products and APIs at issue, provide the date(s) and reason(s) you ceased production. Send your reply to:

Rebecca Parrilla, M.S.
Compliance Officer/CSO
U.S. Food and Drug Administration
White Oak, Building Room 4359
10903 New Hampshire Ave.
Silver Spring, MD 20993

Please identify your response with FEI 3002984011 for the first site and FEI 3006595385 for the second site.

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