Sandoz Private Limited 10/22/15

Department of Health and Human Services

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

Warning Letter

VIA UPS **WL: 320-16-01**

October 22, 2015

Mr. Richard Francis
Division Head
Sandoz International GmbH
Industriestrasse 25
83607 Holzkirchen
Germany

Dear Mr. Francis:

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

A. August 25-29, 2014: Sandoz Private Limited, MIDC Plot Nos. 8-A/2 & 8-B, TTC Industrial Area, Kalwe Block, Village Dinghe, Navi Mumbai 400 708, Maharashtra, India (Kalwe facility)

B. August 12-28, 2014: Sandoz Private Limited, Plot Nos. D31 & D32, MIDC, TTC Industrial Area, Turbhe, Thane-Belapur Road, Navi Mumbai 400 705 Maharashtra, India (Turbhe facility)

At both 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.

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 methods used in, or 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 conducted a detailed review of your firm's responses dated September 19 and September 22, 2014. We note that they lack sufficient corrective actions. We also acknowledge receipt of your firm's additional correspondence dated October 16,

November 5, November 25, December 18, and December 19, 2014; and February 25, March 16, May 6, May 21, June 30, and August 26, 2015.

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

A. Kalwe Facility (Finished Dosage Manufacturing Site FEI #3004944629)

1. Your firm failed to prepare batch production and control records for each batch of drug product that include documentation of the accomplishment of each significant step in the manufacture, processing, packing, or holding of the batch (21 CFR 211.188(b)).

On August 28, 2014, FDA investigators identified instances of non-contemporaneous documentation of batch production activities. Two uncontrolled Excel spreadsheets were used to record discrepancies and certain in-process drug quality data. This data was initially missing in the batch manufacturing record. Your firm later entered this data into batch records and backdated them.

For example, according to a March 2, 2013 entry in one spreadsheet, you did not perform **(b)(4)** testing as required after **(b)(4)** operations of **(b)(4)** mg batch **(b)(4)**. Despite this notation, the associated "In Process Sample Analysis Sheet" documents **(b)(4)** testing results from February 22, 2013.

In your response of September 22, 2014, you admitted that discrepancies noted during batch record review were documented in spreadsheets, and that batch records were backdated when missing data was added. Backdating CGMP records is unacceptable. You also stated that you have engaged the Auditing and Compliance group from **(b)(4)**, to audit and identify documentation issues across the site. However, you failed to demonstrate how widespread this practice is, and whether data recorded and reported for CGMP or other purposes in the past is reliable.

2. Your firm failed to maintain adequate written records of major equipment maintenance (21 CFR 211.182).

On August 25, 2014, FDA investigators found original preventive maintenance work orders in trash bags. A partially-completed document retrieved from the waste receptacle included handwritten notes about the condition of equipment observed during preventive maintenance. However, the corresponding official record did not include the same information. Your response did not sufficiently identify the scope of these practices at your facility.

3. Your firm failed to ensure that each person engaged in the manufacture, processing, packing, or holding of a drug product has the education, training, and experience, or any combination thereof, to enable that person to perform his or her assigned functions, and that training in current good manufacturing practice is conducted by qualified individuals (21 CFR 211.25(a)).

During interviews with our investigators, your contract employee who trains other contract employees on good documentation practices was unable to explain the

material he was required to present during training. In addition, while a significant number of your contract employees do not speak English, you only provided English training materials to these employees.

We also found an employee's failing equipment qualification training assessment form in the trash, yet that employee's official file showed passing results. According to your company policies, personnel with failing scores must be retrained, but your firm was unable to provide evidence of retraining in the employee's official record.

According to your response of September 22, 2014, department heads are now responsible for training their contractors. Your response is inadequate, as you failed to assess how critical operations were affected by unqualified personnel.

You have not demonstrated that you have provided employees with appropriate resources and training to make sure that they are qualified for the operations they performed. Falsification and manipulation of employee training records is unacceptable.

4. 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 was already distributed (21 CFR 211.192).

You failed to investigate an out-of-specification impurity result for the **(b)(4)** stability interval of **(b)(4)** Tablets USP, **(b)(4)** g, **(b)(4)** exhibit batch **(b)(4)**. Instead of fully investigating these results, your firm classified the result as "experimental." For the same out-of-specification impurity results, you found the **(b)(4)** equipment **(b)(4)** was not appropriately maintained during packaging, which caused the **(b)(4)** to be non-integral. Although this exhibit lot was not distributed, you did not evaluate the impact of this failure mode on the quality of other lots of product.

In addition, the inspection documented that your staff advised reporting the failure to the FDA. However, Regulatory Affairs determined not to inform us of the failure until the product was approved. Your decision to withhold information from the agency raises serious concerns.

In your response on September 22, 2014, your firm committed to investigate this out-of-specification result. However, your response did not identify whether there are other out-of-trend and out-of-specification incidents that were not investigated.

In your response to this letter, identify how other commercially-distributed products or stability batches were affected by the equipment failure that resulted in **(b)(4)** diversions and non-integral packaging.

5. Your firm failed to exercise appropriate controls over computer or related systems to assure that only authorized personnel institute changes in master production and control records, or other records (21 CFR 211.68(b)).

On August 25, 2014, we found there were no access restrictions to laboratory data generated by the **(b)(4)** instrument used to test and release raw materials and in-process drug products. Your laboratory computer systems lack necessary controls to prevent data tampering and to detect data that may have been compromised.

We acknowledge that you are in the process of qualifying a new **(b)(4)** instrument. However, your response is still inadequate; you failed to evaluate the effects of potentially compromised data on release decisions that rely on data generated by this uncontrolled system.

These examples are serious CGMP deficiencies and violations. They demonstrate that your quality system does not adequately ensure the accuracy and integrity of data generated and available at your facility. We strongly recommend that you hire a qualified third party auditor/consultant with experience in detecting data integrity problems to help you come into compliance with CGMP regulations and statutory authorities.

In your response to this letter, provide the following:

- A comprehensive investigation and evaluation. Describe your methodology. Results should include conclusions about the extent of data integrity deficiencies and their root causes, which may involve record control, contemporaneous recording, deletion of data, and other data integrity deficiencies.
- 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 management strategy that includes a detailed global corrective action and preventive action plan.

Describe the *corrective* actions you will take, such as contacting your customers, recalling product, conducting additional testing and/or adding lots to your stability programs to assure stability, monitoring complaints, or other steps to assure the quality of your products manufactured under the violative conditions discussed above.

Describe the *preventive* actions you will take, such as revising procedures, implementing new controls, training or re-training personnel, or other steps to prevent the recurrence of CGMP violations, including breaches of data integrity.

B. Turbhe Facility (Active Pharmaceutical Ingredient and Finished Dosage Manufacturing Site FEI #3003737804)

We are aware of your plan to shut down and/or divest the Turbhe facility. Nevertheless, because several CGMP violations at the Turbhe facility relate to aseptic process controls, and are similar to violations cited in Warning Letter 320-12-05 issued to Novartis International AG on November 18, 2011, we note the following violations at this site.

1. Your firm failed to establish and 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)).

a. You failed to perform adequate unidirectional airflow studies (smoke studies) on the aseptic filling line used to produce sterile finished drug products. Portions of a videotaped smoke study reviewed by the investigator did not adequately document airflow patterns during manual interventions. In some instances, airflow patterns could not be observed and evaluated. Insufficient smoke and poor camera angles made it impossible to determine unidirectional airflow.

b. Your firm failed to establish procedures to remove units following interventions, periodic adjustments, set-up, and end of fill. Furthermore, your firm rejected units with intact container/closure systems from media fills without written justification or explanation.

According to the SFDF/MF/12/07 media fill batch record (filling end date July 3, 2012), 359 media-filled vials were rejected after interventions due to machine set-up and periodic adjustments, and after the end of the filling process. None of these vials were incubated as part of the media fill.

According to the SFDF/MF/14/01 media fill batch record (filling end date May 13, 2014), 177 media-filled vials were rejected after interventions due to machine set-up and periodic adjustments, and after the end of the filling process. None of these vials were incubated as part of the media fill.

2. Your firm failed to establish an adequate system for monitoring environmental conditions in aseptic processing areas (21 CFR 211.42(c)(10)(iv)).

You have inadequate scientific justification for your environmental monitoring sampling plans in manufacturing areas for aseptically-filled injectable drug products. This includes the locations of viable airborne particulate sampling, settle plates, and contact surface monitoring.

We acknowledge your SOP/CB/QC/510, “Microbiological Monitoring of Air, Surfaces and Personnel in Production Area.” You used a chart contained in this SOP to justify your choice of environmental sampling locations. However, you did not supply data to support your current locations. In addition, neither your environmental monitoring procedures nor your sampling records clearly identify where environmental monitoring samples are taken.

Conclusion

The violations cited in this letter are not intended to be an all-inclusive list of violations that exist at your facility. You are responsible for investigating and determining the causes of these violations, for preventing their recurrence, and for finding and solving other potential violations.

If, as a result of receiving this warning letter or for other reasons, you are considering a decision that could reduce the number of finished drug products produced by your manufacturing facility, please contact CDER's Drug Shortages Staff immediately at drugshortages@fda.hhs.gov so that we 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 in the manufacture of your drug under 21 U.S.C. 356C(a)(1), and allows FDA to

consider what actions, if any, may be needed to avoid shortages and protect patients who depend on your products.

Until all corrections are completed and FDA confirms corrections of the violations and your firm's compliance with CGMP, FDA may withhold approval of any new applications or supplements which list your firm as a drug product manufacturer.

In addition, failure to correct these violations may result in FDA refusing admission of articles manufactured at the Turbhe facility and the Kalwe facility into the United States under Section 801(a)(3) of the Act, 21 U.S.C. 381(a)(3). Articles may be 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 CGMP within the meaning of Section 501(a)(2)(B) of the Act, 21 U.S.C. 351(a)(2)(B).

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 deviations. Provide supporting documentation. If you cannot complete corrective actions within 15 working days, state the reasons for your delay and your schedule for completion. If you no longer manufacture or distribute the drug products at issue, provide the date(s) and reason(s) you ceased production.

Please send your reply to:

Brooke K. Higgins, Compliance Officer
U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Office of Compliance
Office of Manufacturing Quality
Division of Drug Quality I
White Oak Building 51 Room 4235
10903 New Hampshire Avenue
Silver Spring, MD 20993

Identify your response with FEI #3004944629 for the Kalwe facility and FEI #3003737804 for the Turbhe facility**.**

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

Cc:
Mr. Joseph Jimenez
Chief Executive Officer
Novartis International AG

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