Inspections, Compliance, Enforcement, and Criminal Investigations

Aarti Drugs Limited 7/30/13

Department of Health and Human Services

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

Warning Letter

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

WL: 320-13-22

July 30, 2013

Mr. Harshit Savla
Joint Managing Director
Aarti Drug Limited
Mahendra Industrial Estate, Ground Floor
Plot No. 109-D, Road No. 29 Sion (E)
Mumbai 400 022 India

Dear Mr. Savla:

During our October 25-30, 2012 and November 1-5, 2012 inspections of your pharmaceutical manufacturing facilities, Aarti Drug Limited located at Plot No. E-22 M.D.I.C. Tarapur, Tal Palghar Thane District Maharashtra India (FEI 3006418686), and Aarti Drug Limited located at Plot No. G-60, M.D.I.C. Tarapur, Boisar District Thane, Maharashtra India (FEI 3009688205), investigator(s) from the U.S. 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 and identified deviations from current good manufacturing practice (CGMP) for the manufacture of active pharmaceutical ingredients (APIs). These deviations cause your APIs 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 conducted a detailed review of your firm's responses to both inspections and note that they lack sufficient corrective actions.

Our investigator(s) observed specific violations during the inspection, including, but not limited to, the following:

1. Failure to record all quality activities at the time they are performed.

At the Aarti facility (FEI 3006418686):

a. On October 26, 2012, the investigator noticed that during an inspection of the packaging area for **(b)(4)** # **(b)(4)** a production employee had recorded the final packed quantity of the batch in Step **(b)(4)**, even though the quantity was not yet known because the operator had not yet weighed the batch.

Immediately after observing the incident, the investigator requested a copy of page 6 of the batch record containing Step **(b)(4)** and was given a photocopy. A full batch record provided later that day did not include the original page 6. Instead it included a new version of page 6.

b. The investigator observed at least two examples when a manufacturing step was recorded in the batch record before it occurred:

i. The production operator had already recorded the start time for step **(b)(4)** for **(b)(4)** # **(b)(4)** as 12:15 PM on October 26, 2012, although it was still 11:00 AM when our investigator noticed this situation.

ii. For the **(b)(4)** # **(b)(4)**, at approximately 11:00 AM on the same date, a production officer had already recorded **(b)(4)** of **(b)(4)** used for **(b)(4)** the API **(b)(4)** in the **(b)(4)** at step **(b)(4)** in the batch production record, although the **(b)(4)** step had not yet occurred. The **(b)(4)** had not been pre-weighed or otherwise measured out in advance.

c. On October 27, 2012, our investigator noticed that a QC analyst was performing a Loss on Drying (LOD) analysis for **(b)(4)** Lot # **(b)(4)** and had recorded the completion time as "**(b)(4)**" and total time as "**(b)(4)**" in the usage log book for the LOD oven usage logbook although the step was not yet completed.

At the Aarti facility (FEI 3009688205):

d. The investigator observed that a QC analyst had recorded completion times of laboratory analyses that had not yet occurred. Specifically, a Loss on Drying (LOD) analysis was performed for **(b)(4)** Lot # **(b)(4)** and **(b)(4)** Lot #**(b)(4)** at approximately 10:55 AM. The investigator noted that the analyst had already recorded the completion time as "**(b)(4)**" for two **(b)(4)** samples and "**(b)(4)**" for one **(b)(4)** sample although the step was not yet completed. Our investigator asked the analyst why he recorded the completion time for each of the three samples if the step was still in progress. The analyst did not offer an explanation. Moreover, our investigator also found that weights for these three samples were recorded on blank pieces of paper and not directly onto the test data sheets.

Your response to this observation stated that a new SOP has been created to address this issue and that training on this SOP has occurred. Your response did not address the extent of this practice, the impact on the quality of the product and why your laboratory management failed to detect this practice. Your response also provided no actions to improve oversight by your quality unit (e.g., independence, authority, resources). The above practices observed during the inspection raise concerns regarding the reliability and accuracy of the data generated at your firm, including any other inappropriate data-related practices permitted by your firm when an inspection is not in progress.

In response to this letter, provide a summary of your full assessment of all the raw data recorded on each of the batch production and QC laboratory analytical records for the APIs intended for the US market to ensure their reliability.

2. Your firm failed to review and investigate production and QC laboratory deviations.

At the Aarti facility (FEI 3006418686):

a. The inspection revealed that more than 30 power outages occurred in 2012. The investigator was told that when a power failure occurs, the backup generator does not turn on automatically, but rather needs to be manually started by an employee. In each instance, your firm failed to conduct an investigation into the power outage's impact on quality of product(s) being manufactured at the time. The inspection documented that, despite the fact that your firm has an uninterrupted power supply used by the QC laboratories, power failures have impacted the QC stability chambers. However, in each case, no investigation was conducted to determine the impact of the power loss on the samples kept within the chambers.

b. Deviations pertaining to laboratory equipment failures were not investigated. During the review of the service report log books for HPLC and GC units, the investigator found many instances of servicing due to instrument problems that were not documented as deviations. As such, your firm failed to follow the SOP 1019 entitled "SOP for Deviation Management." According to this SOP, all service activities for equipment, including laboratory instruments, need to be documented as deviations. Your response stated that the SOP has been changed to require deviations only for

instances in which servicing was required to repair a problem with the instrument. Your response failed to address why no deviation was filed and investigated for the instances in which instrument problems were the cause of system maintenance (such as "system problem visit" on May 8, 2012, for Instrument QC/INST/067 or "needle motor stalled" on May 13, 2012, for Instrument QC/INST/022).

Please also note, as a general laboratory practice, any equipment malfunction that may have an impact on quality control testing should be appropriately recorded and investigated.

At the Aarti facility (FEI 3009688205):

c. The inspection at this facility found over 100 instances of power outages in 2012. Your firm did not conduct investigations into the impact of the power outages on the quality of products being manufactured, analyzed, or stored at the time of the outage. Moreover, your quality managers stated to our investigator that no procedure for this type of investigation exists at this facility. In response to this letter, please provide an assessment of the validity of the data generated during these documented power outages. We note that your response to the Form FDA 483 included procedures for investigating the impact of power outages on laboratory analyses; please provide a report documenting the power outages experienced since the date of that response and a summary of the resulting investigations with the product impact you have performed.

d. Your firm failed to conduct an investigation into unexplained discrepancies (atypical peaks) observed in the related substance assay results for multiple **(b)(4)** API batches (**(b)(4)**). During the inspection, the investigator noticed that the related substance chromatograms exhibited several peaks between **(b)(4)** of retention time. Your firm management did not know the source of these atypical peaks and had not initiated an investigation to document them. Your firm released those lots to the U.S. market despite the detection of atypical peaks during release testing. Your firm's response stated that you will begin integrating each peak and will conduct an investigation in the case of any peak anomaly. Your response did not address retrospective peak evaluation and risk assessment for these batches and other APIs. In response to this letter, describe the source of the atypical peaks detected in the related substance assays of the batches described above and in any other API distributed to U.S. market.

3. Failure to maintain laboratory control records with complete data derived from all tests conducted to ensure compliance with established specifications and standards, including examinations and assays.

At the Aarti facility (FEI 3006418686):

a. The inspection documented that HPLC processing methods (including integration parameters) and re-integrations are executed without a pre-defined, scientifically valid procedure. Your analytical methods are not locked to ensure that the same integration parameters are used on each analysis. A QC operator interviewed during the inspection stated that integrations are performed and re-performed until the chromatographic peaks are "good", but was unable to provide an explanation for the manner in which integration is performed. Moreover, your firm does not have a procedure for the saving of processing methods used for integration.

Your response did not include a description of the method by which chromatograph integrations are to be performed (e.g., what constitutes a chromatographic peak, how shoulder peaks are to be handled, etc.). In addition, your response did not include an audit of past chromatographic data to determine whether data used to support release and stability studies originated from appropriately integrated chromatograms.

At the Aarti facility (FEI 3009688205):

b. The inspection at this facility documented that there is no raw data for the related substance preparation of **(b)(4)** testing for lots **(b)(4)** of **(b)(4)** USP and there is no raw data for the standard and sample preparation for the residual solvent testing of the same lots. Your analysts informed the investigator that no raw data for standard and sample preparations are kept in the records. Your response states that your firm will begin maintaining the raw data used for the assays cited on the Form FDA-483 but makes no commitment to perform a laboratory-wide audit to determine whether other assays conducted in your laboratory also require procedural or

administrative changes to maintain all raw data generated during performance.

c. Additionally, as at the 3006418686 site, during the review of the chromatography data at the 3009688205 site, our investigator noticed that the raw data retained does not include the run sequence or the processing method used to perform the peak integrations. Your QC personnel perform peak integrations based on analysts' experience rather than by an approved procedure. Moreover, the chromatography raw data does not include the processing method used to produce the final analytical results; therefore, during the review of the analytical data, it would not be possible to detect any modification to the processing method. Your firm's response mentions that the QC operations are now under "direct control of administrator", but it does not define the roles and responsibilities of the administrator to ensure the integrity and reliability of all QC laboratory data.

d. The audit trail function for the chromatographic systems was disabled at the time of the inspection; therefore, there is no record for the acquisition of data or modifications to laboratory data. Your response to this deficiency did not discuss how you will ensure that data audit trails will not be disrupted in the future.

e. When weighing samples, reagents, and other laboratory materials, QC analysts write weight values on small pieces of paper, transcribe the values onto the analytical worksheets, and then destroy the original paper on which the weights are written. This was reported to be a normal practice within the laboratory. Our investigator also observed the practice of writing the weight values for samples on a small piece of paper and not on the analytical worksheet. This is an inappropriate documentation practice.

Your QC laboratory documentation practices do not support the reliability of the results reported. In response to this letter, provide a retrospective assessment of all the analytical data generated and used for the final API release shipped to U.S. market. Please explain the actions you are taking to prevent these unacceptable record-keeping practices, including but not limited to better defining the oversight role of QC management, as well as senior managers of your company, to ensure that all QC laboratory data is reliable.

4. Failure to implement access controls and audit trails for laboratory computer systems.

At both Aarti facilities (FEI 3009688205 and FEI 3006418686):

For example, your firm failed to have adequate procedures for the use of computerized systems used in the QC laboratory. At the time of the inspections, your QC laboratory personnel shared the same username and password for the operating systems and analytical software on each workstation in the QC laboratory. In addition, no computer lock mechanism had been configured to prevent unauthorized access to the operating system. The investigator noticed that the current QC computer users are able to delete data acquired. In addition, the investigator found that there is no audit trail or trace in the operating system to document deletions.

Additionally, at the Aarti Drug Limited facility (FEI 3009688205), the investigator noticed that the use of the Excel® spreadsheets in analytical calculations are neither controlled nor protected from modifications or deletion. The investigator noticed that the calculation for residual solvent for **(b) (4)** uses an Excel spreadsheet that has not been qualified. We are concerned about the data generated by your QC laboratory from non-qualified and uncontrolled Excel spreadsheets.

In response to this letter, provide a retrospective evaluation of the analytical values reported where such Excel spreadsheets have been used.

You are responsible for the accuracy and integrity of the data generated by your firm. A firm must maintain all raw data generated during each test from laboratory instruments. The authenticity of these records is critical, as they are used to demonstrate that each released batch was appropriately tested and met release specifications. Appropriate record retention policies should also be in place. The observation of premature data entries, when a manufacturing or QC laboratory step(s) has not been completed, into batch records and laboratory worksheets, and the modification and re-creation of batch records calls into question the accuracy and reliability of your firm's data. We remind you that all production-related and

laboratory-related activities are to be recorded at the time at which they are performed.

The items listed above, as well as other deficiencies our investigator found, lead us to question the effectiveness of your current quality system to achieve overall compliance with CGMP at your facility. It is apparent that you have not implemented a robust quality system at your firm. Be advised that corporate management is responsible for ensuring the quality, safety, and integrity of drugs manufactured by both Aarti facilities. FDA strongly recommends that your corporate management immediately undertake a comprehensive evaluation of global manufacturing operations to ensure compliance with CGMP regulations.

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

To ensure that your APIs meet the quality and purity characteristics that they purport, or are represented to possess, please reference the FDA-guidance entitled: Q7 *Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients* located at the following link: http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM129098.pdf[1]. In particular, we encourage you to reference the sections of this guidance pertaining to laboratory controls and validation of analytical procedures.

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 or active pharmaceutical ingredients produced by your manufacturing facility, FDA requests that you contact CDER's Drug Shortages Program immediately, as you begin your internal discussions, 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 Program 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, 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. In appropriate cases, you may be able to take corrective action without interrupting supply, or to shorten any interruption, thereby 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 an API manufacturer. In addition, your failure to correct these violations may result in FDA refusing admission of articles manufactured at Aarti Drug Limited located at Plot No. E-22 M.D.I.C. Tarapur, Tal Palghar Thane District Maharashtra India, and Aarti Drug Limited located at Plot No. G-60, M.D.I.C. Tarapur, Boisar District Thane, Maharashtra India into the United States under Section 801(a)(3) of the Act, 21 U.S.C. 381(a)(3). The 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 fifteen 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, and provide copies of supporting documentation. If you cannot complete corrective actions within fifteen working days, state the reason for the delay and the date by which you will have completed the corrections. Additionally, if you no longer manufacture or distribute the APIs at issue, provide the date(s) and reason(s) you ceased production. Please identify your response with FEI 3006418686 and FEI 3009688205.

Please send your reply to:

Rafael Arroyo
Compliance Officer
FDA/CDER/OC/OMPQ/DIDQ
10903 New Hampshire Ave.
White Oak Building 51, Room 4235
Silver Spring, MD 20993

Sincerely,

/S/
Michael D. Smedley
Acting Director
Office of Manufacturing and Product Quality
Office of Compliance
Center for Drug Evaluation and Research

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Note: If you need help accessing information in different file formats, see Instructions for Downloading Viewers and Players.

Links on this page:

1. http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM129098.pdf