Inspections, Compliance, Enforcement, and Criminal Investigations

Trifarma S.p.A. 7/7/14

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: 320-14-10

July 7, 2014

Mr. Giulio Volante
President
Trifarma S.p.A.
Via G. Guarini Matteucci 1
20162 Milano
Italy

Dear Mr. Giulio Volante:

During our January 27 – 29, 2014 inspection of your pharmaceutical manufacturing facility, Trifarma S.p.A. located at Via Pavese 2, Rozzano, Italy, an investigator from the U.S. Food and Drug Administration (FDA) identified significant 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 response and note that it lacks sufficient corrective actions.

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

1. Failure to maintain complete data derived from all testing and to ensure compliance with established specifications and standards pertaining to data retention and management.

Your firm did not retain complete raw data from testing performed to ensure the quality of your APIs. Specifically, your firm deleted all electronic raw data supporting your high performance liquid chromatography (HPLC) testing of all API products released to the U.S. market. In addition, your firm failed to retain basic chromatographic information such as injection sequence, instrument method or integration method for the tests. Your firm's lack of data control causes us to question the reliability of your data.

In addition, your laboratory management was unaware of, and therefore did not follow, the written procedure detailing the review of analytical data. Furthermore, your management confirmed that the review of analytical data did not include evaluating the system suitability parameters to ensure proper column performance.

Your response states that your firm has been researching backup systems since July 2013 and will have a backup system online by the third quarter of 2014. Your response also states you have begun provisionally storing backup data on each computer, including the integration method as part of that

data. However, you do not address the backup of the injection sequence, the instrument method or audit trails. In addition, your response does not address how your firm will ensure that electronic files are not deleted prematurely from local computers.

In response to this letter, provide a comprehensive corrective action plan addressing the foregoing concerns. Include information regarding system-wide changes, revised procedures, and appropriate retraining of employees that will be implemented immediately to ensure retention of complete electronic raw data for all laboratory instrumentation and equipment.

2. Failure to prevent unauthorized access or changes to data and to provide adequate controls to prevent omission of data.

Your firm did not have proper controls in place to prevent the unauthorized manipulation of your laboratory's raw electronic data. Specifically, your laboratory systems did not have access controls to prevent deletion or alteration of raw data. The inspection noted that all laboratory employees were granted full privileges to the computer systems.

In addition, prior to January 7, 2014, HPLC and gas chromatograph (GC) computer software lacked active audit trail functions to record changes to data, including information on original results, the identity of the person making the change, and the date of the change.

Your response statesyour Agilent GC system and HPLC systems now have audit trails, with **(b)(4)** more GC systems to be upgraded by the second quarter of 2014. However, your response did not describe the audit trails for the processing of the data on your Agilent systems. Your response also states your firm has begun to retain electronic raw data on the local hard drive, but without proper safeguards to ensure they cannot be deleted prematurely. Such safeguards will not be implemented until the third quarter of 2014.

In response to this letter, provide your corrective action plan to prevent deletion and alteration of electronic data. In addition, describe with more detail your firm's new archival process and provide assurance that it will consistently function to prevent the types of failures described above from recurring in the future.

We also note that your firm lacked electronic raw data supporting cleaning, method and process validations. In response to this letter, provide a corrective action plan to review all related test methods associated with products distributed to the U.S. in light of the lack of supporting raw data.

3. Failure to ensure that employees receive appropriate and documented training on the particular operations that the employee performs.

Your firm did not document any training of production employees on the production operations they perform. Specifically, operators in Synthesis Plant **(b)(4)** did not have any documented on-the-job training associated with the production operations they perform. In addition, your management was unaware that they should follow the SOP for the issuance of CoAs, which provides for a review of relevant analytical data. Without documented training, there is a lack of assurance that your employees can reliably execute their API manufacturing responsibilities.

Your response states your firm had updated your training SOP in July 2013 to include on-the-job training along with CGMP training requirements. However, the current inspection revealed that your firm is not following this procedure.

In response to this letter, provide a corrective action plan to investigate the extent of this deficiency and to address the reasons why your manufacturing and quality management failed to detect these training deficiencies. In addition, this corrective action plan should include updated procedures and provisions for proper quality oversight to ensure that employees are adequately trained to perform all of their responsibilities with respect to CGMP.

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.

Our review of the significance of current findings indicates that your quality unit is not able to fully exercise its responsibilities. It is essential that you provide the quality unit with the appropriate authority and staff to carry out its responsibilities. We also recommend that you hire a qualified consultant to provide your firm's staff with guidance and training on CGMP and laboratory data integrity.

Finally, we note that the CGMP deviations listed in this letter include similar deficiencies to those cited in the Form FDA-483 from the November 2013 inspection of your Ceriano Laghetto, Italy plant (FEI 1000532829.) It is essential that your firm implement a robust global quality system. We remind you that you are responsible for ensuring that your firm's API manufacturing operations comply with all applicable CGMP requirements. FDA strongly recommends that your firm's executive management immediately undertake a comprehensive and global assessment of your manufacturing operations to ensure that your systems and processes, and ultimately, the APIs you manufacture, conform to FDA requirements.

Please note that a guidance document entitled "Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients" (ICH CGMP guidance), prepared under the auspices of the International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use, describes current good manufacturing practice (CGMP) for the manufacture of APIs. The guidance is intended to help ensure that all APIs meet the standards for quality and purity they purport or are represented to possess. FDA considers the expectations outlined in ICH Q7, as well as alternatives intended to accomplish the same goals and provide an equivalent level of quality assurance, in determining whether a firm's APIs have been manufactured, processed, packed, and held according to current good manufacturing practice under section 501(a)(2)(B) [21 USC 351(a)(2)(B)] of the Act. To obtain the ICH CGMP guidance document for your reference, please refer to the following page of FDA's website: http://www.fda.gov/downloads/regulatoryinformation/guidances/ucm129098.pdf[1]

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 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 Trifarma S.p.A., in Rozzano, Italy 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. In addition, 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 # 3002807260.

Please send your reply to:
David S. Jones
Compliance Officer
Office of Manufacturing and Product Quality
Office of Compliance
Center for Drug Evaluation and Research
Division of International Drug Quality
White Oak 51 Room 4220
10903 New Hampshire Ave
Silver Spring, MD 20993-0002.

Sincerely,
/S/
Thomas J. Cosgrove, J.D.
Acting Director
Office of Manufacturing and Product Quality
Office of Compliance

Center for Drug Evaluation and Research

Page Last Updated: 07/14/2014
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