FACTA Farmaceutici S.p.A. 1/13/17

Department of Health and Human Services

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

Via UPS
Return Receipt Requested
January 13, 2017

Warning Letter: 320-17-17

Mr. Carlo Vergani
President
FACTA Farmaceutici S.p.A
Viale Addetta 4/12
20067 Tribiano, Milan
Italy

Dear Mr. Vergani:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, FACTA Farmaceutici S.p.A at Zona Industriale Sant Atto, San Nicolo a Tordino, Teramo 64100, from January 11 to 19, 2016.

This warning letter reviews significant violations from current good manufacturing practice (CGMP) regulations for finished pharmaceuticals. See 21 CFR, parts 210 and 211.

Because your methods, facilities, or controls for manufacturing, processing, packing, or holding do not conform to CGMP, your drug products are adulterated within the meaning of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 351(a)(2)(B).

We reviewed your February 8, 2016, response in detail and acknowledge receipt of your subsequent correspondence.

During our inspection, our investigators observed specific violations including, but not limited to, the following.

1. Your firm failed to ensure that laboratory records included complete data derived from all tests necessary to assure compliance with established specifications and standards (21 CFR 211.194(a)).

For multiple sterile drug product lots, your original data showed failing results, but data you reported showed passing results. This discrepancy was not adequately explained.

You stored original data in an “unofficial” and uncontrolled electronic spreadsheet on a shared computer network drive. Your analyst stated that original data was first recorded in this “unofficial” spreadsheet and transcribed later to an “official” form. This spreadsheet showed failing results above the limits you established in your procedure, PCH 035 *Visible Particle Determination* in use prior to September 1, 2014.

For example, the spreadsheet showed glass, metal, fibers, and other particles that were out-of-specification (OOS) in **(b)(4)** finished code **(b)(4)**, lot **(b)(4)**. The spreadsheet showed five glass particulates (100-200 microns) in the **(b)(4)** sample. However, your reported data stated zero glass particulates.

According to your analyst, a second reviewer may have determined that the number and type of particles originally recorded for glass, metal, fibers, and other particles were incorrect. However, no documentation showed that a second reviewer evaluated the results.

According to your response, the procedure PCH 035 “was for internal information purposes only” and the analyst did not follow this procedure. All results were “preliminary” until a second chemist “with much more experience” reviewed them. When “an experienced analyst” tested the retained samples, passing results were obtained and recorded. Your response is inadequate because you did not include details to support your assertion that the original analyst lacked the necessary experience, nor did you provide supporting documentation for the secondary review.

In response to this letter:

- Evaluate training in your quality control laboratory, specifically for your procedure PCH 035.
- Specify how you assign tasks so that qualified and experienced personnel review and document critical test results.
- Comprehensively evaluate test samplesperformed by other analysts from January to September, 2014, when the unofficial spreadsheet was in use.
- Evaluate the extent of uncontrolled spreadsheets at your facility.
- Indicate which visual inspection procedure was utilized for release of drug products to the U.S. prior to implementation of procedure PCH 047 on September 1, 2014.

2. Your firm failed to establish an adequate quality control unit with the responsibility and authority to approve or reject all components, drug product containers, closures, in-process materials, packaging materials, labeling, and drug products (21 CFR 211.22(a)).

Our investigator observed many copies of uncontrolled blank and partially-completed CGMP forms (e.g., environmental monitoring recordings, OOS forms, water testing sheets, and clean room entry and exit logs) without any accountability or oversight of your quality unit.

For example, a supervisor said he photocopied a blank OOS form and transcribed the information because he had made mistakes in the original document. Although your procedures required correcting mistakes on the original form, he made a new copy of a blank OOS form and rewrote the data.

Our investigator documented that your employees used paper shredders to destroy critical laboratory and production records without the appropriate controls and procedures. Shredded documents included High Performance Liquid Chromatography (HPLC) chromatograms and a partially-completed OOS form.

Your quality unit is responsible for reviewing and approving these critical production records to ensure that, if an error occurred, a comprehensive investigation is conducted. Uncontrolled destruction of CGMP records also raises concerns, because retention of CGMP records must follow established procedures approved by your quality unit.

These findings raise questions about the effectiveness of your quality unit and the integrity and accuracy of your CGMP records.

In your response, you stated that you "do not consider this OOS form to be an official document until it is initiated into the QA system" and that "OOS forms…are not intended to collect raw data… [but] are used to create the narrative which contains transcriptions of the details in order to described the event."

Your response is inadequate. For more information about proper handling of OOS results and documenting your investigations, refer to the FDA guidance for industry *Investigating Out-of Specification (OOS) Test Results for Pharmaceutical Production* at **www.fda.gov/downloads/Drugs/.../.../ucm070287.pdf (http://www.fda.gov/downloads/Drugs/.../.../ucm070287.pdf)**.

In response to this letter:

- Evaluate all OOS test reports from January 2014 to January 2016 associated with the release of your products. Document the associated HPLC and gas chromatography data. Include your detailed action plan and schedule to fully investigate the extent of your deficient handling of OOS test results.

Data Integrity Remediation

Your quality system does not adequately ensure the accuracy and integrity of data to support the safety, effectiveness, and quality of the drugs you manufacture. We strongly recommend that you retain a qualified consultant to assist in your remediation.

In response to this letter, provide the following.

A. A comprehensive investigation into the extent of the inaccuracies in data records and reporting. Your investigation should include:

- A detailed investigation protocol and methodology; a summary of all laboratories, manufacturing operations, and systems to be covered by the assessment; and a justification for any part of your operation that you propose to exclude.
- Interviews of current and former employees to identify the nature, scope, and root cause of data inaccuracies. We recommend that these interviews be conducted by a qualified third party.
- An assessment of the extent of data integrity deficiencies at your facility. Identify omissions, alterations, deletions, record destruction, non-contemporaneous record completion, and other deficiencies. Describe all parts of your facility's operations in which you discovered data integrity lapses.
- A comprehensive retrospective evaluation of the nature of the manufacturing and laboratory data integrity deficiencies. We recommend that a qualified third party with specific expertise in the area where potential breaches were identified should evaluate all data integrity lapses.

B. A current risk assessment of the potential effects of the observed failures on the quality of your drugs. Your assessment should include analysesof the risks to patients caused by the release of drugs affected by a lapse of data integrity, and risks posed by ongoing operations.

C. A management strategy for your firm that includes the details of your global corrective action and preventive action plan. Your strategy should include:

- A detailed corrective action plan that describes how you intend to ensure the reliability and completeness of all of the data you generate, including analytical data, manufacturing records, and all data submitted to FDA.
- A comprehensive description of the root causes of your data integrity lapses, including evidence that the scope and depth of the current action plan is commensurate with the findings of the investigation and risk assessment. Indicate whether individuals responsible for data integrity lapses remain able to influence CGMP-related or drug application data at your firm.
- Interim measures describing the actions you have taken or will take to protect patients and to ensure the quality of your drugs, such as notifying your customers, recalling product, conducting additional testing, adding lots to your stability programs to assure stability, drug application actions, and enhanced complaint monitoring.
- Long-term measures describing any remediation efforts and enhancements to procedures, processes, methods, controls, systems, management oversight, and human resources (e.g., training, staffing improvements) designed to ensure the integrity of your company's data.
- A status report for any of the above activities already underway or completed.

Conclusion

Violations cited in this letter are not intended as an all-inclusive list. You are responsible for investigating these violations, for determining the causes, for preventing their recurrence, and for preventing other violations.

If you are considering an action that is likely to lead to a disruption in the supply of drugs produced at your facility, FDA requests that you contact CDER's Drug Shortages Staff immediately, at drugshortages@fda.hhs.gov, so that FDA 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 or interruptions in your drug manufacture under 21 U.S.C. 356C(b) 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.

Until you correct all violations completely and we confirm your compliance with CGMP, FDA may withhold approval of any new applications or supplements listing your firm as a drug manufacturer.

Failure to correct these violations may also result in FDA refusing admission of articles manufactured at FACTA Farmaceutici S.p.A., Zona Industriale Sant Atto, San Nicolo a Tordino, Terramo, into the United States under section 801(a)(3) of the FD&C Act, 21 U.S.C. 381(a)(3). Under the same authority, articles may be subject to refusal of admission, 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 FD&C Act, 21 U.S.C. 351(a)(2)(B).

After you receive this letter, respond to this office in writing within 15 working days. Specify what you have done since our inspection to correct your violations and to prevent their recurrence. If you cannot complete corrective actions within 15 working days, state your reasons for delay and your schedule for completion.

Send your electronic reply to **CDER-OC-OMQ-Communications@fda.hhs.gov (mailto:CDER-OC-OMQ-Communications@fda.hhs.gov)** or mail your reply to:

Cesar E. Matto, Compliance Officer
U.S. Food and Drug Administration
White Oak, Building 51, Room 4359
10903 New Hampshire Ave
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Please identify your response with FEI 3006028606.