U.S. Department of Health & Human Services

U.S. Food & Drug Administration

Inspections, Compliance, Enforcement, and Criminal Investigations

Farma Quimia S.A. de C.V. 3/9/12

Department of Health and Human Services

Public Health Service
Food and Drug Administration
Silver Spring MD 20993

Warning Letter

VIA UPS MAIL

WL: 320-12-011

March 9, 2012

Mr. Gustavo Berea
Director General
Farma Quimia S.A. de C.V.
Andre Marie Ampere No. 11
Parque Industrial Cuamatla
Cuautitlan Izcalli, Mexico 54730

Dear Mr. Gustavo Berea:

During our September 12-15, 2011 inspection of your active pharmaceutical ingredient (API) manufacturing facility, Farma Quimia S.A. de C.V., located in Cuautitlan, Izcalli, Mexico, investigators from the U.S. Food and Drug Administration (FDA) identified significant deviations from Current Good Manufacturing Practice (CGMP) for the manufacture of APIs. These deviations cause your API(s) 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 are concerned with the lack of quality oversight and CGMP documentation practices at your facility. Our investigators were unable to confirm that your quality unit performs review and approval of GMP-related documentation. Additionally, evidence of the following could not be provided to our investigators during our inspection: analyst training, sample preparation, raw data for stability testing, which equipment was used for batch manufacturing, etc. We remind you that you are responsible for ensuring your facility complies with applicable CGMP requirements associated with the manufacturing and analytical testing of **(b)(4)** API.

We have reviewed your firm's response of October 4, 2011, and note that it lacks sufficient corrective actions.

Specific deviations observed during the inspection include, but are not limited, to the following:

1. Failure to ensure batch production records are prepared for each of your APIs and include complete information relating to the production and control of each batch.

For example, neither your procedures nor your master batch production records require documentation of basic information such as the identity of manufacturing equipment used in the production of your API, sampling amounts, the identity of the person taking samples, or the time the samples were taken. Similarly, actual batch production and control records fail to document the completion of each significant manufacturing step, the signature of the persons performing manufacturing steps, equipment used, and sampling information.

Additionally, your firm uses a log sheet to document the **(b)(4)** temperature of the batch during the **(b)(4)** step of the manufacturing process. This **(b)(4)** log sheet is ultimately included as part of the batch record, however, the data recorded does not support the entire **(b)(4)** step of the manufacturing process. Your **(b)(4)** log sheet only records the temperature of the batch being **(b)(4)** once (at the **(b)(4)** of the process step) during the entire **(b)(4)** step which, according to your process, is approximately a **(b)(4)** hour **(b)(4)** step for a **(b)(4)** batch size of **(b)(4)** USP API. Furthermore, your batch record is not completed by the individual who performed the processing steps.

Your response indicates that you will write and implement new procedures addressing our observations. Your response is unacceptable as you have not provided any specific instructions that will be included in these new procedures, copies of these procedures, or any associated training for these new procedures, nor does your response address your quality unit's lack of involvement in all quality related matters. Your firm should perform a comprehensive review of the adequacy of your batch records. Your response to this letter should include a copy of an updated batch record that addresses deficiencies identified as part of your comprehensive review. The letter should also address the batch production record deficiencies identified during the inspection, including but not limited to assuring your firm identifies all manufacturing equipment used during the manufacturing process and records all individuals involved in the batch operation (e.g., performing and supervising critical steps). Finally, your response should contain a list of all new procedures and the associated training documentation for those procedures.

2. Failure of your quality unit to review and approve all appropriate quality related documents.

For example, your quality unit failed to review and approve the analytical release testing and the executed production batch records for **(b)(4)** USP (API) prior to batch release. Furthermore, your quality unit did not approve the master batch production or production batch records prior to their execution.

Your response indicates that you will write and implement new procedures for the "approval and checking of analytical data," "for releasing the product," and for "inspection" of all manufacturing documents. Your response is unacceptable as you have not provided any specific instructions that will be included in these new procedures, copies of these procedures, or any associated training to demonstrate that quality related documents are properly reviewed by your quality unit. In your response to this letter include copies of these procedures and your rationale for the release of material to date without quality approval and evidence to support assurance of the quality and purity of the released product currently on the U.S. market and within your distribution chains.

3. Failure of your quality unit to establish written procedures for monitoring the progress and controlling the performance of processing steps that cause variability in the quality characteristics of intermediates and APIs.

For example, your firm performs no in-process testing of the API intermediate **(b)(4)** **(b)(4)** used in the production of the **(b)(4)** API. The

corrective action listed within your response states, "Determine specification and analysis techniques for **(b)(4)**." We interpret your response to mean that your firm has not yet established specifications for the critical quality attributes required for **(b)(4) (b)(4)** or the analytical methods to test them. Your response is inadequate as it does not include your proposed in-process controls and acceptance criteria, or scientifically sound sampling plans and procedures.

In your response to this letter please include the in-process controls for **(b)(4) (b)(4)** intermediate. In addition, include the specifications and the analytical methods, along with their associated method validation summaries, for **(b)(4) (b)(4)** intermediate. Finally, you should describe your sampling plan and procedures for the **(b)(4)** intermediate.

4. Failure to validate those operations critical to the quality and purity of your API.

For example, your API manufacturing processes for **(b)(4)** USP (API) and **(b)(4)** (API intermediate) is not validated. Your firm has released more than **(b)(4)** batches of **(b)(4)** USP (API), consisting of more than **(b)(4) (b)(4)**, to the U.S. market since 2009.

Your response consists of "Validation process / Validation report" as your corrective action with an expected completion date of January 2012. This response is unacceptable as you provided no details as to how you will conduct process validation, such as a validation plan or protocol. In addition, you did not: define your API in terms of its critical quality attributes, identify process parameters that could affect the critical quality attributes of your API, or determine the appropriate operating ranges for each critical process parameter to be used during routine manufacturing.

In response to this letter, provide the validation protocols and the results for the validation studies for **(b)(4)** USP (API) and **(b)(4)** (API intermediate). Additionally, include a summary of your review of the manufacturing process for all previously manufactured batches of **(b)(4)** USP (API), released to the U.S. market, against the newly validated process for **(b)(4)** USP (API) to determine if there were potential gaps in the quality and consistency of released API that was manufactured by the previous process.

5. Failure of your quality unit to ensure that control, weighing, measuring, monitoring and test equipment that is critical for assuring the quality of intermediates and APIs is calibrated according to written procedures and an established schedule.

For example, our inspection revealed manufacturing equipment and laboratory instrumentation were past due for re-calibration or had never been calibrated. Specifically, the manufacturing scale (BE-01) used to weigh finished **(b)(4)** API into commercial containers had not been calibrated since October 28, 2009. Additionally, no record of calibration existed for the autoclave and incubator used for conducting microbiological analyses for **(b)(4)** API. In addition, no record of calibration existed for your UV spectrophotometer (#EF-01) and pH meter (#MH-02) used in the analytical testing of **(b)(4)** API. Furthermore, analytical balances within your laboratory are not being verified prior to their daily use.

In your response, you state that you will author calibration programs for instruments and autoclaves and implement use logs for your balances and pH meters. Your response is inadequate as you have not included a review of the calibration status of all equipment and instrumentation used in the production or testing of API intended for the U.S. market.

Your response to this letter should include a plan for the implementation of procedures and a formal schedule that provides for a robust equipment and instrumentation calibration program.

Moreover, your October 4, 2011 response does not address marketed API batches within expiry that were manufactured using an un-validated manufacturing process, had no quality unit review of manufacturing batch records or analytical test results, were manufactured and tested on non-calibrated equipment and instrumentation, and which lacked testing to ensure conformance with USP requirements for **(b)(4)**, USP.

In addition to the items listed above, the inspection revealed inadequate oversight of your contract testing laboratory, **(b)(4)**. We remind you that you are responsible for ensuring that drug manufacturing operations (including laboratory testing) for your API comply with applicable requirements, including the CGMP regulations. Please note that any facility contracted to perform a function is an extension of your own operation, and must conform with CGMP. FDA expects Farma Quimia S. A., to undertake a comprehensive and global assessment of the manufacturing operations including adequate oversight of your contracted facilities to ensure that your processes and laboratory controls, and ultimately, the drugs you manufacture, meet FDA requirements.

To ensure that your APIs meet the quality and purity characteristics that they purport, or are represented to possess, please reference the FDA issued ICH guidance entitled "Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients" at http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM129098.pdf [1].
We also recommend that you hire a qualified consultant to provide CGMP evaluation and training in major areas of deficiency, such as the responsibilities and procedures applicable to the quality unit.

The deviations detailed in this letter are not intended to be an all-inclusive statement 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. If you wish to continue to ship APIs to the United States, it is the responsibility of your firm to ensure compliance with all U.S. standards for CGMP and all applicable U.S. laws and regulations.

Until all corrections have been completed and FDA has confirmed corrections of the deviations 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, failure to correct these deviations may result in FDA refusing admission of articles manufactured at Farma Quimia S.A. de C.V. located in Cuautitlan, Izcalli, Mexico into the United States. The articles are 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 Current Good Manufacturing Practice within the meaning of section 501(a)(2)(B) of the Act [21 U.S.C. § 351(a)(2)(B)].

If, as a result of receiving this Warning Letter or in general, you are considering making a decision that will result in a decreased 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 in order to ensure that your action(s) does not adversely affect the public health.

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 deviations. Include an explanation of each step being taken to prevent the recurrence of deviations and copies of supporting documentation. If you cannot complete corrective action within fifteen working days, state the reason for the delay and the date by which you will have completed the correction. Additionally, your response should state if you no longer manufacture or distribute **(b)(4)** USP API, and provide the date(s) and reason (s) you ceased production. Please identify your response with FEI # 3003887583.

If you have questions or concerns regarding this letter, contact An Vu Compliance Officer, at the below address and telephone number.

U.S. Food and Drug Administration
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Office of Manufacturing and Product Quality
Division of International Drug Quality
White Oak, Building 51
10903 New Hampshire Ave
Silver Spring, MD 20993
Tel: (301) 796-3251
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Sincerely,

\Steve Lynn\
Steven Lynn
Acting Office Director
Office of Manufacturing and Product Quality
Office of Compliance
Center for Drug Evaluation and Research

Links on this page:

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

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