U.S. Department of Health & Human Services

U.S. Food & Drug Administration

Inspections, Compliance, Enforcement, and Criminal Investigations

UNAM, Facultad De Estudios Superiores Cuautitlan 3/27/12

Department of Health and Human Services

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

Warning Letter
WL: 320-12-014

VIA UPS MAIL

March 27, 2012

Dra. Alma Revilla Vazquez
Titular Professor
UNAM, Facultad De Estudios Superiores Cuautitlan
Campus 1, Laboratorio L-401
Avenida 1ro. De Mayo
Santa Maria La Torres
Cuautitlan, Izcalli
Mexico 54714

Dear Dra. Alma Revilla Vazquez:

During our September 13-14, 2011 inspection of your control testing laboratory, located in Cuautitlan Izcalli, Mexico, investigator(s) from the U.S. Food and Drug Administration (FDA) identified significant deviations from Current Good Manufacturing Practice (CGMP) for the manufacture (testing) of active pharmaceutical ingredients (APIs). These deviations cause the tested 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 acknowledge your written response to the Form FDA 483, submitted on December 19, 2011. However, because this response was received more than 15 business days after the Form FDA 483 was issued, the response has not been considered. We plan to evaluate your response to the Form FDA 483, along with any other written material provided, as a direct response to this Warning Letter.

We are concerned with the general lack of CGMPs at your firm, particularly in the fundamental area of documentation and record retention practices. Your firm serves as a contract testing laboratory for the APIs manufactured at **(b)(4)**. It is your responsibility to operate in full compliance with CGMPs and to promptly inform your customer of any significant problems you encounter during the testing of **(b)(4)**, API.

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

1. Failure to have laboratory records that include complete data derived from all tests conducted to ensure compliance with established specifications and standards.

For example, the usage logbook associated with the Varian Atomic Absorption Spectrophotometer (AA-800 ID# 1450219) did not include records of the **(b)(4)** API samples tested on this instrument between September 9, 1999 and September 8, 2011. Moreover, the laboratory notebook did not include the raw data from these tests.

In your response, include your remediation plans to ensure all raw data is recorded and maintained, including the written procedure describing the retention policy for all laboratory control records.

You should also include a summary of the results of a comprehensive review of your analytical data including a determination if all required analytical data is recorded and maintained, including but not limited to the date, time, product tested, lot number, complete details of the analysis and calculations, and the person(s) who performed the activities.

2. Failure to ensure laboratory instrumentation that is critical for assuring the quality of APIs is calibrated according to written procedures and an established schedule.

For example, you failed to provide evidence to demonstrate the routine calibration of your laboratory instrumentation, such as the Varian Atomic Absorption Spectrophotometer (ID# 1450219), the Shimadzu High Performance Liquid Chromatography (HPLC) (ID# 02228780), and the BOECO Analytical Balance (ID# 1780678). Moreover, our inspection found no records indicating that your laboratory instrumentation was qualified (Installation, Operation, and Performance Qualification) prior to placing your laboratory instrumentation into use.

Laboratory instrument qualification and routine calibration ensures that the instrument's individual components (e.g., pump flow rate, detector wavelength, column heater, injector precision in HPLC) are operating within acceptable limits and that the instrument, as a whole, meets the criteria for suitability for intended use.

In your response to this letter, please include a written copy of the procedures for the qualification and routine calibration of all laboratory instrumentation and the associated training documentation for these new procedures. Also, submit evidence of, or a schedule for, the qualification and calibration of the instrumentation within your laboratory in accordance with these new procedures.

3. Failure to appropriately prepare, identify, test, approve and store secondary reference standards.

For example, you failed to have documentation describing how the standards used for the testing of the APIs are obtained, prepared or qualified. No current standards (within expiry) could be located for conducting organic and inorganic impurity testing by atomic absorption for **(b)(4)** API manufactured by **(b)(4)**. Moreover, no other reference standard for **(b)(4)** could be produced during the inspection.

Your response to this letter should include a copy of your new procedure for the preparation of reference standards. This procedure should describe the steps followed to ensure appropriate handling, preparation, identification, testing, approval, and storage of reference standards and the associated training documentation. Additionally, include in your response a procedure describing the qualification and periodic re-qualification of secondary standards.

4. Failure of your quality system to have a written procedure to investigate out-of-specification results.

For example, you do not have a written procedure that describes how to investigate and document out-of-specification (OOS) results.

In your response, you should include a procedure describing the steps your laboratory staff will follow to investigate all OOS results, along with the associated training documentation for this new procedure. For example, this procedure should require initiation of an investigation without delay, an evaluation of the root cause of the result, justification of any re-sampling and/or retesting, conclusions, a system for assuring corrective actions are implemented, and notification of your client of any OOS result.

The following guidance should be of further assistance to your laboratory in creating an appropriate procedure, Guidance for Industry – Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production:

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070287.pdf [1]

5. Failure to ensure training is regularly conducted by qualified individuals and covers, at a minimum, the particular operations that the employee performs and CGMPs as it relates to the employee's functions.

Our inspection revealed basic CGMP deviations by your staff in assuring control of your laboratory. We note that employees who perform testing of drugs had not received training in either their specific job function or in CGMP. In your response to this letter, you should provide evidence of training on the methods required to test **(b)(4)** API for each employee that conducts analytical testing related to **(b)(4)** API manufactured by **(b)(4)**. In addition, your laboratory should establish a procedure for requiring, documenting, and periodically assessing all training.

We recommend that you seek the advice of a third-party consultant for assistance with a complete evaluation to determine the improvements that will be needed at your facility to meet the CGMP requirements for analytical testing of APIs. For more information on acceptable quality control laboratory practices, please see 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 [2]

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.

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 a contract testing laboratory.

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. Please identify your response with FEI # 3009132835.

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

U.S. Food and Drug Administration
Center for Drug Evaluation and Research
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
Fax: (301) 847-8741

Sincerely,

/s/

/Steven Lynn/
Steven Lynn
Acting 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/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070287.pdf
2. http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM129098.pdf

- Website Policies

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