

Inspections, Compliance, Enforcement, and Criminal Investigations

Cambrex Profarmaco Milano Srl 8/12/09



Department of Health and Human Services

Public Health Service
Food and Drug
Administration
CENTER FOR DRUG
EVALUATION AND
RESEARCH
Division of Manufacturing
and Product Quality
International Compliance
Branch

Warning Letter

VIA FEDERAL EXPRESS MAIL

WL: 320- 09-10

August 12, 2009

Dr. Paolo Russolo
President
Cambrex Profarmaco Milano S.r.l.
Via Cucchiari, 17
20155 Milano MI - Italy

Dear Dr. Russolo:

This is regarding a March 23 - March 31, 2009, inspection of your active pharmaceutical ingredient (API) manufacturing facility, Cambrex Profarmaco Milano S.r.l. ("Cambrex Profarmaco"), located at Via Cucchiari, 17, Milano, Italy, conducted by Kelly I. Anderson, Investigator, and Kim L. Thomas Cruse, Chemist. The inspection revealed significant violations from U.S. current good manufacturing practice (CGMP) in the manufacture of APIs. The CGMP violations

were listed on an Inspectional Observations (FDA-483) form issued to you at the close of the inspection.

These violations cause the APIs manufactured by your firm to be adulterated within the meaning of Section 501 (a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (the Act) [21 USC § 351(a)(2)(B)]. Section 501 (a)(2)(B) of the Act requires that all drugs, as defined in the Act, be manufactured, processed, packed, and held according to CGMP.

We have reviewed your April 30, 2009, written response to the FDA-483 observations. We acknowledge that some corrections appear to have been completed, or will soon be implemented. However, your response failed to adequately address the following violations:

1. Your quality unit failed to maintain complete laboratory control records for the analysis of your APIs (including graphs, charts, and spectra from laboratory instrumentation derived from all tests conducted) to ensure compliance with established specifications and standards. For example,

a. Raw data (e.g., chromatograms, standard and sample weights, calculations, standards, reagents, and instrument information) for the Albuterol Sulfate (June 2001) and Lorazepam (June 2006) related substances, method validation were not available during the inspection. The failure to have this data available during the inspection prevented the investigators from confirming the authenticity and reliability of data submitted to support drug application Nos. **(b)(4)**.

Your response regarding the failure to provide complete records of raw data for the Albuterol Sulfate, related substances, method validation states, in part:

"we recognise [sic] that, being that study quite old, the retrieval of the raw data was more difficult and incomplete."

In addition, your quality unit personnel informed the investigators that the computer software was upgraded and the raw data was lost during the software upgrade. We have serious concerns about your firm's implementation of changes to your computerized systems (e.g., software upgrade). It is your responsibility to provide the means of ensuring data protection (e.g., back-up system) for your computerized systems to prevent the permanent loss of records. Please provide corrective actions to prevent similar recurrences.

Note that the copies of analytical notebooks submitted in your response remain incomplete in that they lacked: laboratory equipment/instrument information (calibration/standardization status, conditions and parameters, system suitability test results); standards and reagents information (lot numbers, manufacturers, retest or expiry dates, grade or concentration, purity); filter information; dates and signatures of the persons who performed each test and reviewed the data; reference to the test method, version number, and effective date; and statement of how the test results compare with acceptance criteria. Please provide either complete analytical data packages for review, information that demonstrates that the validation test results are accurate and reliable, or other corrections (e.g. revalidation data).

In addition, your response addressing the failure to provide complete records of raw data for the Lorazepam, related substances, method validation indicates, in part:

"raw data were difficult to collect and found partially incomplete because recorded in different notebooks as the study was done by more analysts after a reorganization of the laboratory."

The recording of raw data in different notebooks by your analysts and the reorganization of your laboratory should have no effect on the traceability and accountability of your raw data. Please provide corrective actions (e.g., control system for the traceability and accountability of records) to prevent similar recurrences.

b. Evaluation of the laboratory, Karl Fischer (KF) raw data (i.e., instrument printouts and logsheet) corresponding to the December 11, 2007, and **(b) (4)** determination for **(b) (4)** lots of Hydrochlorothiazide (HCTZ) API, revealed that your quality unit attempted seven consecutive analyses (i.e., sample numbers 8 - 14). Your quality unit reported five analyses but could not find the raw data for the remaining two (i.e., sample numbers 9 and 11). The test results for **(b) (4)** lots of Hydrochlorothiazide (i.e.,) were used for release, stability, and validation purposes, and the lots were shipped to the U.S.

c. Evaluation of the laboratory KF raw data (i.e., instrument printouts and logsheet) corresponding to the April 9, 2008, **(b) (4)** determination for **(b) (4)** lots of Albuterol Sulfate API, revealed that your quality unit appeared to have standardized the KF instrument to obtain the **(b) (4)** factor that is required for KF **(b) (4)** determination. However, the laboratory data sheets containing the raw data did not include the instrument printouts for sample runs 6 and 7 (i.e.,

instrument standardization) in the sequence of analysis (i.e., sample numbers 6 - 22). These records could not be found by your quality unit during the inspection. The test results for **(b) (4)** lots of Albuterol Sulfate (i.e., **(b) (4)**) were used for release and stability purposes, and the lots were shipped to the U.S.

Your response regarding the failure to maintain complete laboratory records of KF raw data states, in part, "we were not able to find the four printouts of the Karl Fischer instrument...." and, "the missing printouts were probably aborted instrument runs that were not filed with the complete sequence of analysis."

The omission of the raw data (i.e., alleged aborted runs) from a complete sequence of analyses raises serious concerns regarding the integrity and reliability of your KF analytical results. It is well known that **(b) (4)** content is an attribute that is often detrimental to the chemical stability of drugs. Your quality unit personnel stated during the inspection that sample runs 6 and 7 should have been the instrument standardization data required before the actual KF sample analysis. Therefore, your premise (i.e., KF files were probably aborted runs) appears to be unjustified. Please provide supporting information to demonstrate that the December 11, 2007, and April 9, 2008, test results for HCTZ and Albuterol Sulfate APIs are accurate and reliable.

In addition, your response includes analyst training as a corrective action, and the revision of the KF and titration instrument, "History Log Sheets" as a preventive action. Your response does not address the failure of your quality unit to identify the deficiencies and prevent recurrence. Please provide assurance that both the Quality Assurance (QA) and Quality Control (QC) units have been included in your training program as part of your corrective and preventive actions. We recommend that you develop an internal audit program that will assist you in identifying and correcting similar incidents. We also recommend that you conduct a retrospective evaluation of other laboratory data to ensure that similar incidents have not occurred.

2. Your quality unit failed to ensure that all quality related activities are recorded at the time they are performed, and that instrument logsheet entries regarding the use of the KF instrument were made by laboratory personnel at the time the activities were performed. Specifically, on December 11, 2007, your laboratory personnel performed seven consecutive KF **(b) (4)** determinations (five for HCTZ API), but failed to record four of the seven on the instrument logsheet. You are responsible for ensuring that any deviation is documented and explained. Please identify and evaluate the root cause of the data omissions from the instrument logsheet and provide corrective actions that address your quality unit's failure to

identify this violation and prevent similar recurrences.

3. Your quality unit failed to establish controls for the issuance, revision, and withdrawal of all documents. Specifically, your quality unit did not establish a control system for the issuance, tracking, and maintenance of laboratory notebooks that are used to record raw data in the QC laboratory. Your firm's management was unaware of the total number of laboratory notebooks in inventory; and your QC personnel failed to maintain the laboratory notebooks, as well as the notebook numbering stamp, in a secure environment.

We acknowledge your response and commitment to implement a new procedure that introduces a tracking and control mechanism for the laboratory notebooks. Note that the tracking and control of the laboratory notebooks are fundamental to ensure the integrity of the laboratory data. Please ensure your QA and QC personnel are adequately trained.

The violations-cited above, or on the FDA-483 issued to your firm, are not an all inclusive list of the CGMP violations that may exist at your facility. FDA inspections are audits that are not intended to address all deficiencies from CGMP, or violations that may exist at a firm. 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 of CGMP and all applicable U.S. laws and regulations.

Until all corrections have been completed and FDA has confirmed corrections of the violations, as well as your firm's compliance with CGMPs, this office may recommend withholding approval of any new applications or supplements listing your firm as an API manufacturer. In addition, failure to correct these violations may result in FDA denying entry of articles manufactured at your facility (i.e., Cambrex Profarmaco) into the United States. The articles could 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)].

Please respond to this letter within thirty days of receipt and identify your response with FEI # 3003723076. If you have questions or concerns regarding this letter, contact Luis Dasta, Compliance Officer, at the below address and telephone number.

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Sincerely,

/S/
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Director
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Center for Drug Evaluation and Research