Inspections, Compliance, Enforcement, and Criminal Investigations

ZaCh System S.A., 10/23/09

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
White Oak, Building 51
10903 New Hampshire Avenue
Silver Spring, MD 20993

Warning Letter

WL: 320-09-012

VIA FEDERAL EXPRESS MAIL

October 23, 2009

Mr. Bruno Michel, Deputy General Manager
ZaCh System S.A.
Zone Industrille La Croix Cadeau
B.P.10079
Avrille Cedex 49240
France

Dear Mr. Michel:

This is regarding a June 8 - 11, 2009 inspection of your active pharmaceutical ingredient (API) manufacturing facility, ZaCh System S.A., located at Avrille Cedex, France, conducted by Investigator Rebecca Parrilla. The inspection identified significant deviations from the Current Good Manufacturing Practice (CGMP) requirements for the manufacture of 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 requirements.

We have received your firm's response of July 24, 2009, and note that it lacks sufficient corrective actions.

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

1. Failure to have appropriate procedures (or practices) in place to prevent cross contamination.

In March 2008, your firm received a complaint regarding metallic foreign material found in Pioglitazone HCl (Lots **(b)(4)**). It was not until you initiated an investigation to identify the source of the metallic particles that you became aware of a cross-contamination problem involving three different APIs and one intermediate product. Approximately 0.40 g of Pioglitazone HCl, 0.07 g of **(b)(4) (b)(4),** 0.94 g of Venlafaxine HCl, and 0.01 g of **(b)(4)** (intermediate) were found present inside a **(b)(4)** of your **(b)(4)**. Metallic particles and residual solvent were also found inside the threads of a screw located inside the sealed box. You concluded that the possible root cause for the cross-contamination of APIs was the improper re-assembly of the **(b)(4)** that occurred during the last maintenance intervention of 2007.

We are concerned with your failure to take appropriate action against all potentially affected lots of APIs manufactured and released for distribution during the period of April 2007 (last maintenance date) to March 2008 (date cross-contamination was discovered). According to your response, a total of **(b)(4)** lots of four different products (**(b)(4)** Pioglitazone HCl, Venlafaxine HCl and Intermediate) were during this period in the **(b)(4)**.

We are also concerned that as of September 23, 2009, you have only tested a limited number of API batches manufactured between April 2007 and March 2008. We do not object to your decision to use a contract, or more specialized laboratory, to assist in the improvement of your analytical methods and testing of the affected products. However, we remain concerned that while your investigation remains open, your customers may still be manufacturing products with the affected API lots.

In the information you submitted to the agency after the inspection, and in comments made during the September 23,2009 meeting at CDER Office of Compliance, you suggested that because your process validation demonstrated homogeneity, the cross contamination would have been detected in your retain samples. We disagree with your assessment because process validation is not intended to evaluate the uniformity or homogeneity of a cross-contamination.

We note that the extent of the contamination remains unknown. You have been unable to clearly explain the presence of Pioglitazone HCl found in a retain sample of Venlafaxine HCL (Lot #**(b)(4)**). This is a concern because no Pioglitazone HCl was detected in the retain sample of the first batch of the Venlafaxine HCl campaign (Lot #**(b)(4)**) which was produced immediately after the product changeover from Pioglitazone HCl. There were several other manufacturing campaigns and cleaning operations conducted between Venlafaxine Lot # **(b)(4)** and contaminated Lot #**(b)(4)**

We are also concerned that you became aware of the cross-contamination problem in March 2008, but did not notify your customers of the problem until after the June 2009 FDA inspection. The corrective actions provided in your response lack assurance that the issue has been fully resolved.

Include in your response to this letter the action you intend to take regarding all API lots with detected cross-contamination that were shipped to the United States. Also include in your written response a copy of your Standard Operating Procedure that requires you to notify your U.S. customers of any quality problems at the time of occurrence.

2. Failure of your quality unit to exercise its responsibility to ensure the APIs manufactured are in compliance with CGMP, and meet established specifications for quality and purity.

During the inspection, Investigator Parrilla discussed several issues with your firm's management that were not addressed in the documentation related to the cross contamination investigation of March 2008. These included:

a. Your investigation failed to include direct evidence to support the indentified root cause of the cross-contamination (improper re-assembly of **(b)(4)**; product found inside the threads of a screw). The suspected source of the cross-contamination is not a product-contact surface.

b. Your investigation failed to recognize information in the impurity profile documentation for Pioglitazone HCl batches manufactured between April 2007 and March 2008. An unknown peak was detected, but reported as "0.00 %" due to the small amount detected and your

procedures for rounding results.

c. Your investigation failed to recognize that your rationale for establishing the worst case scenario for the cross-contamination, which dictated the sampling scheme used to detect contamination in retain samples, could not be supported based on the results from the samples tested. Specifically, you assumed that any cross-contamination would be more prevalent in the initial batches of each campaign. However, the results for testing of retain samples from Venlafaxine HCl Batch # **(b)(4)** included no traces of the previous product (Pioglitazone HCl). In contrast to your assumptions, the results for Venlafazine HCl Batch # **(b)(4)** (manufactured approximately 30 days later, after an API intermediate production campaign, and after five cleaning operations) were determined to be in the range of 50 ppm of Pioglitazone HCl. This indicates a flaw in your rationale for sample selection, or possible insufficient information from testing of Batch # **(b)(4)**

d. Your investigation failed to recognize that the cross-contamination is not uniformly distributed throughout a batch or campaign. Therefore, your testing of retain samples from suspect batches would not generate meaningful data to support a decision regarding the safety of the batches in question. Consequently, your proposed corrective actions regarding the development of a more sensitive method to better detect cross-contamination in your retain samples, cannot alone support your position related to the safety of the affected drug products.

Your response lacked any supporting documentation. Please provide additional information regarding your corrective actions for these specific deficiencies.

3. Failure to thoroughly investigate all Out-of-Specification (OOS) results.

Regarding Observation #3 on the Form FDA 483 Inspectional Observations (FDA-483), your firm's evaluation of the OOS results obtained for Related Substances testing of Pioglitazone HCl Lot #**(b)(4)** (reprocessed batch) was inadequate. We disagree with your decision to release this batch. Specifically, your firm's practice of injecting and reinjecting new preparations of the sample solution until a passing result is obtained is unacceptable. In addition, your initial conclusion that "a phenomenon causing the degradation of the product in solution" was not supported by the investigation.

Your response indicates that you have initiated "a study on the specific event." However, your response fails to provide supporting documentation related to how the study will be conducted or if the study will include an evaluation of the associated production operations.

Please provide details of the corrective actions you plan to implement to address this deficiency. We have concerns that other lots may have been released due to poor handling of OOS results.

4. Failure to monitor cleaning procedures, after validation, to ensure effectiveness.

Regarding FDA-483 Observation #2, the April 2007 - March 2008 cross-contamination incident indicates that your firm failed to adequately monitor the effectiveness of your validation for the cleaning procedures. Your response fails to provide specific details for how your firm will monitor the effectiveness of future cleaning operations.

The deviations cited in this letter are not intended to be an all-inclusive list of the 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 API's 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 CGMPs, this office will recommend withholding 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 denying entry of articles manufactured at ZaCh System S.A., Avrille Cedex, France 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 current good manufacturing practice within the meaning of Section 501(a)(2)(B) of the Act [21 U.S.C. § 351(a)(2)(B)].

We urgently need to discuss with you additional corrective actions related to the lots of APIs found with traces of cross-contamination that were shipped to the United States. Therefore, we recommend you contact Giuseppe Randazzo at Giuseppe.Randazzo@fda.hhs.gov or at (301)796-3277 within five days of receipt of this letter to arrange for a teleconference to further discuss this matter.

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 these 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 # 3002808164.

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

U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Division of Manufacturing and Product Quality
International Compliance Branch
White Oak, Building 51
10903 New Hampshire Ave
Silver Spring, MD 20993
Tel: (301) 796-3201
Fax: (301) 847-8741

Sincerely,

/s/

Richard L. Friedman
Director
Division of Manufacturing and Product Quality
Office of Compliance
Center for Drug Evaluation and Research

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