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Inspections, Compliance, Enforcement, and Criminal Investigations

Ercros S.A. 6/20/12



Department of Health and Human Services

Public Health Service
Food and Drug Administration
Silver Spring MD 20993

Warning Letter

VIA UPS MAIL

WL: 320-12-021

June 20, 2012

Dr. Maria Carmen Cruzado
Manager
Ercros S.A.
Paseo del Deleite, S/N
28300 Aranjuez
Madrid Spain

Dear Ms. Cruzado,

During our July 11-15, 2011 inspection of your active pharmaceutical ingredient (API) manufacturing facility, Ercros S.A. located at Paseo del Deleite, 2803 Aranjuez, Madrid, Spain, investigators from the 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 have reviewed your firm's response of August 05, 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 validate that your water system is capable of consistently producing purified water suitable for its intended use.

Your API, **(b) (4)**, is used in the manufacture of sterile drug (medicinal) products. Your firm failed to validate the performance of the purified water system that provides water for the **(b) (4)**. It is essential that this water system consistently produces water that meets an appropriate endotoxin limit, in order to prevent contamination of the **(b) (4)** API. Your firm began to use the purified water system in November 2004 but did not perform a validation of the system until January 2010. The 2010 validation conducted was retrospective and included very limited sampling data. Significantly, this 2010 study included data from only one point of use per month over a period of eleven months. The validation failed to include a thorough assessment of elements critical to the performance of the system such as an evaluation of the quality of the water at each step in the **(b) (4)** process, a thorough evaluation at all points of use, and a complete microbial and endotoxin analysis.

In your response, you indicate that you plan to perform a retrospective validation of the system. However, your response lacks specific methods, acceptance criteria, and does not address whether adequate retrospective data is available to establish that the system maintains daily control.

In your response to this letter, please describe more fully the validation of the purified water system that you will perform, and describe how the current water monitoring program (including but not limited to frequency of monitoring) ensures the system produces water appropriate for its intended use for each batch produced by your facility.

2. Failure to document complete raw data derived from tests conducted to ensure compliance with the established specifications.

For example, your firm could not provide complete raw data derived from the endotoxin tests performed on purified water samples, including a complete description of the sample, test method used, record of all raw data generated during the test, and signatures of the person who performed the task and the person who reviewed it. We note that you intend to use these unsupported endotoxin results in your proposed retrospective water validation detailed in the previous section.

In your response you stated that you will revise the endotoxin laboratory procedure. Your response failed to include data to support the actual conditions of the tests performed and an evaluation of all other laboratory operations for which an insufficient record of raw data exists.

Your response to this letter should include an updated procedure regarding endotoxin testing, as well as an evaluation of all test procedures and documentation/retention of associated raw data.

This is a recurrent observation from the 2002 FDA inspection at your facility.

3. Failure to maintain buildings and equipment used in the manufacture of intermediates and active pharmaceutical ingredients.

For example, during the inspection an FDA investigator observed accumulation of dirt on top of **(b) (4)** tanks #DF0094-00 and #DF-0091-00 near the tanks' hatches. A product transfer pipe connected to a **(b) (4)** tank appeared to have a leak with resulting material build up around and under the hole.

Additionally, **(b) (4)** tanks #DF-0094-00 and #DF-0091-00 and **(b) (4)** #JL-011-00, used in the **(b) (4)** of **(b) (4)** API, had not been cleaned since the last campaign, approximately **(b) (4)** months prior. The interior of the equipment had accumulated approximately half an inch of a white substance and contained a shallow pool of liquid at the bottom.

Furthermore, Building #**(b) (4)** was observed in a state of disrepair with multiple large openings that provided a point of entrance for pests. The presence of pests was confirmed by an FDA investigator who observed bird feathers in the plant and spiders residing near the hatch of the **(b) (4)** tank #DF-0094-00.

In your response, you promised to revise the procedure for cleaning and maintenance and to "improve pest control nearby the **(b) (4)** tanks." Your response lacks specific corrective and preventive actions regarding maintenance, and you did not improve your pest control program for your entire facility.

Your response to this letter should provide data to assure adequacy of cleaning methods to prevent cross-contamination. Your response should also include specific details of the repairs to your facility and an augmented pest control program.

4. Inadequate or lack of any investigation of critical deviations or a failure of a batch to meet its specifications or quality standards.

For example, the IR spectra of **(b) (4)** API lots **(b) (4)**, and **(b) (4)** did not match the IR spectrum of the standard. The quality unit released these lots. The quality unit failed to document and investigate the presence of bands in the IR spectra that did not match the spectrum of the standard.

In your response, you indicate that the quality unit did not investigate because it believed the additional peaks in the IR spectra were due to ambient **(b) (4)**. Your response failed to explain why ambient **(b) (4)** bands appear to only affect the spectra for the above-mentioned lots but not the reference standard spectrum. Your response also did not address under what conditions analysts could potentially perform background corrections to remove the **(b) (4)** bands.

In your response to this letter, please provide specific actions that will be taken to ensure any differences between sample and reference standard spectra are identified, documented, and investigated.

Additionally, your firm failed to investigate excursions of temperature and relative humidity in your stability chambers and sample retention room, and failed to investigate incorrect labeling of laboratory samples that led to laboratory errors.

In your response your firm promised to revise the procedures for each of these issues. Your response lacks specific corrective and preventive actions to ensure that future out of specification results (OOS) and deviations are thoroughly investigated and documented. In your response, please describe how this concern will be addressed for all laboratory and quality oversight procedures.

5. Failure to verify and document the suitability of testing methods under actual conditions of use.

Specifically, your firm failed to conduct and document a verification under actual conditions of use of the following laboratory testing methods: related substances method (HPLC) used for release and stability testing of **(b) (4)** API, identification (IR) method for release testing of **(b) (4)** API, microbial and endotoxin testing methods used to monitor the quality of the purified water, and assay (titration) method for release and stability testing of **(b) (4)** API. In addition, during the inspection your firm could not provide forced degradation data to support suitability of the HPLC test method for stability testing of **(b) (4)** API. Review of the chromatograms from the release testing of related substances for **(b) (4)** API lots **(b) (4)** and **(b) (4)** show peaks that do not separate, suggesting the method is not capable of detecting all related substances present.

In your response, you propose to perform a verification of the methods according to your firm's requirements. Your response fails to provide the procedures and acceptance criteria for the verification studies and failed to determine the impact of the inadequately validated/verified methods on previously released materials.

In your response to this letter, please address these issues and provide a risk assessment for possible impurities present in **(b) (4)** lots **(b) (4)** and **(b) (4)**. You are responsible for ensuring that all analytical methods are verified prior to continuing manufacture and release of API lots to US. You are also responsible to ensure that the methods used for releasing product to U.S. comply with CGMP requirements for U.S. (i.e., use of USP methods).

This is a recurrent observation from the 2002 FDA inspection at your facility.

6. Failure to evaluate the potential impact of changes in the manufacturing process on the quality of the intermediates and API.

Specifically, your firm performed changes to the steps in the manufacturing process of **(b) (4)** in April 2008, included **(b) (4)**. You intended these changes to directly impact the purity profile of the API. Your firm classified these changes as minor and did not notify manufacturers of finished drug products that use your API of the changes from established production and process control procedures until the FDA investigators pointed out this discrepancy.

In your response, you state that the changes were minor, "since they affect to intermediate stages" and had no impact on the product specifications. Your response indicates there was no change in the API attributes other than a **(b) (4)**, but you did not provide any data as to whether these changes affect established retest or expiry dates. Additionally, your response lacks sufficient corrective and preventive actions to assure that the change management system will adequately document, evaluate, classify, and notify customers of changes based on the potential impact on product quality, process validation, and regulatory status.

Your response to this letter should include a reevaluation of all changes made to your processes

both "minor" and "major". The review should be used to update your drug master file(s) accordingly as per 21 CFR 314.420, and your customers should be notified of the summation of changes you have performed to your processes and your supporting evidence that each of these changes have had no negative impact on the quality, identity, purity, efficacy or stability of the APIs you manufacture.

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 supplement: listing your firm as an API manufacturer. In addition, failure to correct these deviations may result in FDA refusing admission of articles manufactured at Ercros S.A. located at Paseo del Delite, 28300 Aranjuez, Madrid, Spain 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. Please identify your response with FEI # 3003562118.

If you have questions or concerns regarding this letter, contact Milva E. Meléndez, 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) 796-0662
Fax: (301) 847-8741

Sincerely,

/Steven Lynn/
Steven Lynn
Director
Office of Manufacturing and Product Quality
Office of Compliance
Center for Drug Evaluation and Research

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