U.S. Department of Health & Human Services

FDA U.S. Food and Drug Administration

Inspections, Compliance, Enforcement, and Criminal Investigations

Ningbo Smart Pharmaceutical Co. Ltd. 3/30/11

Department of Health and Human Services

Public Health Service
Food and Drug Administration
Silver Spring MD 20993

Warning Letter

VIA UPS MAIL

WL: 320-11-010

March 30, 2011

Mr. Grant Wu
Chairman
Ningbo Smart Pharmaceutical Co. Ltd.
#1 Yicheng Road, Xiaogang
Beilun District
Ningbo, China 315803

Dear Mr. Wu:

During our October 25-29, 2010 inspection of your active pharmaceutical ingredient (API) manufacturing facility, Ningbo Smart Pharmaceutical Co. Ltd. located at #1 Yicheng Road, Xiaogang, Beilun District, Ningbo, China 315803, an investigator 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 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.

We have reviewed your firm's response of November 19, 2010, and note that it lacks sufficient corrective actions.

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

1. Failure of your quality unit to ensure that materials are appropriately tested and the results are reported.

For example, your Quality Control Unit (QCU) approved the release of four **(b)(4)** USP batches (#**(b)(4)**) without data to support that the test for organic volatile impurities (OVI) met release specifications.

While your Certificates of Analysis state that OVI levels conformed to specifications, the inspection found that no testing was done.

It is essential that your firm only report results to customers when you have actually performed the analysis.

This serious CGMP deviation raises concerns regarding the reliability and integrity of other data generated by your firm. While we acknowledge the commitment in your November 19, 2010 response to improve the QCU, we remain concerned that your investigation is not comprehensive enough to determine the extent and impact of the problem. A review of the **(b)(4)** OVI records of batches that were not previously tested is not sufficient. In your response, provide a complete corrective action plan that includes a retrospective review of the analytical data and batch records for all products manufactured at your facility that remain within expiration. In addition, provide the actions taken to prevent recurrence of the problem. Your investigation should be expanded to all other products manufactured at this site and include the establishment of a comprehensive training program for analysts and QC personnel.

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

For example, the inspection revealed that your QCU released API lots to the U.S. without assuring that all required tests are performed. It is a basic responsibility of your QCU to ensure that all API lots produced meet specifications for quality and purity prior to being released. Your QCU also failed to detect that your COAs stated that OVI results conformed to specifications, although the test was not performed.

In addition to your failure to test **(b)(4)**, USP, your QCU approved the release of **(b)(4)**, USP batch # **(b)(4)** with no testing for OVI. This test is required under DMF **(b)(4)**, submitted by your firm in 2005.

In your response, you stated that your former Head of Quality Control thought it was sufficient to test the organic volatile impurity in three (3) **(b)(4)** batches and then discontinue testing of future batches. We acknowledge that your firm has begun testing for organic volatile impurities.

Within fifteen (15) days of receipt of this letter please send us a list of all APIs (include lot numbers and dates) that were not tested. Also provide a copy of a complete investigation and retrospective review of all test results generated by your laboratory, and corrective actions to prevent recurrence.

Your response also indicates that you revised the procedure for releasing batches and trained the Quality Control and Quality Assurance personnel. Your response is inadequate in that it does not address the failure of your QCU to detect inaccurate reporting of laboratory results. It also lacks a description of any training program provided to prevent recurrence of the problem.

Please provide a comprehensive corrective action plan that describes your commitment, procedures, actions, and controls to ensure data integrity. This plan should include training to all managers, supervisors, and quality unit personnel in detecting data manipulation and questionable practices.

3. Failure to perform at least one identity test of each batch of incoming material.

For example, the starting material **(b)(4)** lot **(b)(4)**, used for the production of **(b)(4)** USP, API lots **(b)(4)**, was not tested for identity.

Please include a copy of your incoming raw material testing procedure and explain how your firm will assure all raw materials are tested prior to release for production in the future.

You are responsible for the accuracy and integrity of the data generated by your firm. A firm must maintain all raw data generated during each test, including graphs, charts, and spectra from laboratory instrumentation. These records should be properly identified to demonstrate that each released batch was tested and met release specifications. Appropriate record retention policies should also be in place. Our inspection reported that your firm has destroyed some old, but foundational records for your products. We recommend that your firm reconsider your record retention policy for application-related records. Should product quality or safety concerns arise in the future, the original records pertaining to batches listed in an application may be integral in providing reasonable assurances to the Agency regarding a product and integrity of data submitted to support it.

When destruction of documents is appropriate, you should follow a document destruction procedure that ensures documents are destroyed in a controlled manner. This would include, at a minimum, identification of the appropriate documents and retention timelines, documentation of what was destroyed, and the names and signatures of those who witnessed the destruction.

We recommend that you conduct a complete and extensive evaluation of your overall quality and manufacturing controls to ensure that all APIs manufactured at your facility meet the quality and purity characteristics they purport to possess. We highly recommend that you hire a third party auditor, with experience in detecting data integrity problems, who may assist you in evaluating your overall compliance with CGMP.

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.

Additionally, your firm is neither registered nor has it listed every API in commercial distribution in the United States with FDA, as required by 21 C.F.R. § 207.40 and section 510(i) of the Act [21 U.S.C. § 360(i)]. The FDA investigators discussed this issue with you during the inspection. Your response did not address this issue. Information on how to register and list is available at the following internet website: http://www.fda.gov/cder/drls/registration_listing.htm [1]. You must complete the required registration and listing and provide evidence that you have fulfilled these requirements in your response to this letter.

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 Ningbo Smart Pharmaceutical Co. Ltd. located at #1 Yicheng Road, Xiaogang, Beilun District, Ningbo, China-315803 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)].

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 and **(b)(4)** USP, and provide the date(s) and reason(s) you ceased production. Please identify your response with FEI # 3003585759.

If you have questions or concerns regarding this letter, contact Maan Abduldayem, 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) 796-3916
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Sincerely,
/Richard L. Friedman/
Richard L. Friedman
Director
Division of Manufacturing and Product Quality
Office of Compliance
Center for Drug Evaluation and Research

Links on this page:

1. http://www.fda.gov/cder/drls/registration_listing.htm