U.S. Food and Drug Administration
Protecting and Promoting *Your* Health

Novacyl Wuxi Pharmaceutical Co., Ltd. 12/19/14

Department of Health and Human Services

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

Warning Letter

WL: 320-15-04

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

December 19, 2014

Yonhui (William) Liu, General Manager
Novacyl Wuxi Pharmaceutical Co. Ltd.
8 Guang Shi Xi Road
Wuxi, Jiangsu, 214185, China

Dear Mr. Liu:

During our October 14, 2013 through October, 18, 2013 inspection of your pharmaceutical manufacturing facility, Novacyl Wuxi Pharmaceutical Co. Ltd. located at 8 Guang Shi Xi Road Wuxi, Jiangsu, 214185, China, an investigator from the U.S. Food and Drug Administration (FDA) identified significant deviations from current good manufacturing practice (CGMP) for the manufacture of active pharmaceutical ingredients (APIs) and significant violations of the CGMP regulations for finished pharmaceuticals, Title 21, Code of Federal Regulations, Parts 210 and 211. These deviations and violations cause your APIs and drug products 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.

Our inspection noted that your firm produces **(b)(4)** synthesized **(b)(4)** API and **(b)(4)** (a **(b)(4)** of **(b)(4)** and excipients). The **(b)(4)** is by definition an in-process material for a finished drug product under Title 21, Code of Federal Regulations, section 210.3(b)(9),

and therefore subject to the CGMP regulations at 21 CFR 211.We have conducted a detailed review of your firm's response dated November 06, 2013, and note that it lacks sufficient corrective actions.

Our investigator observed specific deficiencies during the inspection of the API manufacturing facility, including, but not limited to, the following:

API: CGMP DEVIATION

1. Failure to manage laboratory systems with sufficient controls to ensure conformance to established specifications and prevent omission of data.

Our inspection revealed serious deficiencies related to your documentation practices, including missing raw data. It is a basic responsibility of your quality unit to ensure that your firm retains the supporting raw data that demonstrates your APIs meet specifications that they are purported to possess.

For example, during the inspection, our investigator found a chromatogram related to **(b) (4)**, API in the trash, dated October 15, 2013, which reported an additional chromatographic peak when compared to the standard. During the inspection, your firm stated that the analyst discarded the chromatogram because it was present in the blank injection. However, the analyst was unable to retrieve the blank chromatogram from the system because it was overwritten by a subsequent injection.

In addition, the inspection documented that your firm made changes to integration parameters for the impurities test without appropriate documentation or justification. Your firm relied upon hand written notes on a chromatogram discovered in a drawer at the laboratory as the documentation for this change. Furthermore, your firm implemented this change without an audit trail that would have captured the date of the change and who made the change.

Other significant deficiencies noted in your laboratory system include:

a) Failure to have a written procedure for manual integration despite its prevalence.
b) Failure to use separate passwords for each analyst's access to the laboratory systems.
c) Use of uncontrolled worksheets for raw analytical data in your laboratory.
d) Presence of many uncontrolled chromatograms, spreadsheets and notes of unknown origin found in a drawer.

The lack of controls on method performance and inadequate controls on the integrity of the data collected raise questions as to the authenticity and reliability of your data and the quality of the APIs you produce.

Your firm's response, dated November 06, 2013, stated that your firm will create a validation program for all uncontrolled computer systems, create a new standard operating procedure (SOP), and retrain all analysts performing analytical tests. However, observations found during the most recent inspection regarding the inadequacy of your HPLC system raises questions regarding your ability to implement sustainable corrective and preventive actions, as previous commitments made to the agency were not fulfilled. Please provide specific milestones and your detailed plan on how you intend to implement the appropriate corrective actions. We will also encourage you to submit monthly reports to the agency of your progress.

As part of your response, provide a complete validation plan for your laboratory computerized systems. This plan should include an audit trail component and other appropriate controls to prevent deletion and overwriting of data. In addition, include a retrospective review of the analytical data and batch records for all of the APIs distributed that remain within expiration, along with an evaluation of data that may have been generated to support a drug application, including any Drug Master File. This investigation should include a review of all APIs manufactured at your site. Furthermore, provide details of the systemic corrective actions taken to prevent recurrence of these deficiencies.

Please note that a guidance document entitled "Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients" (ICH CGMP guidance), prepared under the auspices of the International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use, describes current good manufacturing practice (CGMP) for the manufacture of APIs. The guidance is intended to help ensure that all APIs meet the standards for quality and purity they purport or are represented to possess. FDA considers the expectations outlined in ICH Q7, as well as alternatives intended to accomplish the same goals and provide an equivalent level of quality assurance, in determining whether a firm's APIs have been manufactured, processed, packed, and held according to current good manufacturing practice under section 501(a)(2)(B) [21 USC 351(a)(2)(B)] of the Act. To obtain the ICH CGMP guidance document for your reference, please refer to the following page of FDA's website: **http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073497**

FINISHED PRODUCT: CGMP VIOLATIONS

2. Your firm did not properly document or investigate out-of-specifications (OOS) and other discrepancies (21 CFR 211.192).

For example, the inspection documented that OOS Investigation #1203, related to the presence of metal particles in **(b)(4)**, failed to determine the root cause of the contamination or explain why the **(b)(4)** step was unable to prevent the contamination.

3. Your firm failed to establish laboratory controls that include scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that components, drug product containers, closures, in-process materials, labeling, and drug products conform to appropriate standards of identity, strength, quality, and purity (21 CFR 211.160(b)); and,

4. Your firm did not record all CGMP activities at the time these were performed. The lack of contemporaneous documentation of CGMP activities increases the likelihood of recording erroneous data (21 CFR 211.188).

For example, your firm failed to ensure testing documentation was complete and accurate. For example, on October 15, 2013, our inspection revealed analysts working with unlabeled tubes reportedly of **(b)(4)** to perform the **(b)(4)** UV-Vis test. When entering the data onto the UV Spectrophotometer, the analyst entered "unknown" in the sample identification column for each sample where the lot number and sample number should have been recorded. In addition, examination of the **(b)(4)** UV-Vis test from September 02, 2013, revealed that the analyst had entered "unknown" in the sample identification column for each sample. Later, we noted that the analytical worksheet from September 02, 2013, had appropriate sample identifiers; however, the raw data on the worksheet cannot be properly linked to the sample preparations. In your response, you indicate that the analyst remembered the order in which the samples were prepared and placed into the test tube rack. We are concerned that you rely on the memory of your employees, rather than on

actual supporting documentation. A basic principle of CGMP is to record activities at the time of performance to ensure that complicated activities and critical steps are performed according to written procedures. Identifying samples under test is essential to the integrity of the analysis.

In addition, our inspection documented multiple instances where the analysts did not record raw material lot numbers during sample preparation, making it impossible to link the raw materials used to the appropriate test worksheet. This raises concerns about the authenticity of the data that your laboratory testing generates.

Your firm's response states that you will revise relevant test records and SOPs, and conduct training on these revisions. Your described corrective actions are insufficient to ensure that you can determine the extent of your CGMP deficiencies and their effect on product quality. They are also insufficient to prevent recurrence of the deficient practices.

The deviations and violations cited in this letter are not intended to be an all-inclusive list of deviations and violations 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.

SUMMARY

The above examples are serious CGMP deficiencies and violations demonstrating that your quality system does not adequately ensure the accuracy and integrity of the data generated and available at your facility to support the safety, effectiveness, and quality of the APIs and drug products you manufacture. We strongly recommend that you hire a qualified third party auditor/consultant with experience in detecting data integrity problems to assist you with coming into compliance with CGMP regulations and statutory authorities. In your response to this letter, provide the following to the Agency:

1. A comprehensive evaluation of the extent of the deletion and destruction of records. As part of your comprehensive evaluation, provide a detailed action plan to investigate the extent of the deficient documentation practices;

2. A risk assessment regarding the potential effect on the quality of APIs and drug products. As part of your risk assessment, determine the effects of your deficient documentation practices on the quality of the API and drug product released for distribution; and

3. A management strategy for your firm that includes details of your global corrective action and preventive action plan.

    a) As part of your corrective action and preventive action plan, describe the *corrective* actions you will take, such as contacting your customers, recalling product, conducting additional testing and/or adding lots to your stability programs to assure stability, monitoring of complaints, or other steps to assure the quality of the product manufactured under the deficient and violative conditions discussed above.
    b) In addition, as part of your corrective action and preventive action plan, describe the *preventive* actions you will take, such as revising procedures, implementing new controls, training or re-training personnel, or other steps to prevent the recurrence of CGMP violations, including breaches of data integrity.

If, as a result of receiving this warning letter or for other reasons, you are considering a decision that could reduce the 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 so that we can work with you on the most effective way to bring your operations into compliance with the law. Contacting the Drug Shortages Program also allows you to meet any obligations you may have to report discontinuances in the manufacture of your drug under 21 U.S.C. 356C(a)(1), and allows FDA to consider, as soon as possible, what actions, if any, may be needed to avoid shortages and protect the health of patients who depend on your APIs and drug products.

Until all corrections have been completed and FDA has confirmed corrections of the deviations and violations and your firm's compliance with CGMP, FDA may withhold approval of any new applications or supplements listing your firm as a drug product or an API manufacturer. In addition, your failure to correct these deficiencies may result in FDA refusing admission of articles manufactured at Novacyl Wuxi Pharmaceutical Co., Wuxi, China into the United States under Section 801(a)(3) of the Act, 21 U.S.C. 381(a)(3). The articles may 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).

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 and prevent the recurrence of deviations, and provide copies of supporting documentation. If you cannot complete corrective actions within fifteen working days, state the reason for the delay and the date by which you will have completed the corrections. Additionally, if you no longer manufacture or distribute **(b)(4)** or **(b)(4)**, provide the date(s) and reason(s) you ceased production. Please identify your response with FEI # 3004117396.

Please send your reply toDavid S. Jones, Compliance Officer, White Oak Building 51, Room 4220, 10903 New Hampshire Ave, Silver Spring, MD 20993-0002.

Sincerely,
/S/
Thomas Cosgrove
Acting Director,
Office of Manufacturing and Product Quality
Office of Compliance
Center for Drug Evaluation and Research