Novacyl (Thailand) Ltd. 2/27/15

Department of Health and Human Services

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

Warning Letter

via **UPS**

WL: 320-15-07

February 27, 2015

Mrs. Choochit Poosanapanya
Managing Director
Novacyl (Thailand), Ltd.
321 Bangpoo Industrial Estate
Praeksa, Muang
Samutprakam, 10280
Thailand

Dear Mrs. Poosanapanya:

During our April 21, 2014 through April 25, 2014 inspection of your pharmaceutical manufacturing facility, Novacyl (Thailand), Ltd. located at 321 Bangpoo Industrial Estate, Praeksa, Muang, Samutprakam, Thailand, 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). 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 conducted a detailed review of your firm’s response dated May 9, 2014, and note that it lacks sufficient corrective actions. We also acknowledge receipt of your firm's additional correspondence dated July 1, 2014, November 24, 2014, and December 19, 2014.

Our investigator observed specific deviations during the inspection, including, but not limited to, the following:

1. Failure to ensure reprocessing procedures consistently yield API meeting its intended specifications.

Specifically,

a. You reprocessed **(b)(4)** as a raw material in the manufacture of your **(b)(4)** products following recurring process failures. Your firm rejected six lots of **(b)(4)** for failing to meet your established specifications for assay and **(b)(4)** content. Your drug master file (DMF) specifications required a greater than **(b)(4)** assay and less than **(b)(4)** content for the reprocessing of **(b)(4)**. For example, you reprocessed lot **(b)(4)** of **(b)(4)** that had an assay of **(b)(4)** and **(b)(4)** for **(b)(4)** content.

You **(b)(4)** the rejected **(b)(4)** by adding it in small quantities, along with passing **(b)(4)**, to the manufacturing batches of **(b)(4)** until you dispensed the entirety of the rejected material. You ultimately reprocessed the six rejected batches of **(b)(4)** into **(b)(4)** batches of **(b)(4)**.

In your response, you acknowledge that this reprocessing step "is not in compliance with the DMF." You also reference a validation study that indicates the use of out-of-specification (OOS) material with **(b)(4)** minimum assay and **(b)(4)** maximum content. However, this does not justify the use of significantly lower quality material, such as lot# **(b)(4)** with **(b)(4)** assay and **(b)(4)** content.

b. You reprocessed **(b)(4)**, lot# **(b)(4)**, after you rejected the lot due to an OOS result that failed to meet your limit for foreign particles. In your response, you indicate that your product contained "insoluble black specks (dirt), size 5-10 microns." You identified the source of the dirt as a poorly cleaned **(b)(4)**. Your firm reprocessed the lot by introducing material at an earlier point in the process and then filtering through a **(b)(4)** micron filter.

Your response did not explain why your quality unit failed to provide proper oversight of your firm's cleaning operations, contamination problems, and the adequacy of the reprocessing operations (i.e., to remove all the dirt particles between 5 and 10 microns from your OOS product). We are also concerned that you **(b)(4)** the product rejected for foreign matter.

In response to this letter, provide an in-depth review and evaluation of your reprocessing procedures, and an evaluation of all products made with reprocessed material within expiry. Provide a report of your investigation and state whether your firm has placed these reprocessed lots on the stability program. Also, describe any systemic improvements planned to enhance quality unit oversight and production supervision in your firm's manufacturing operation.

2. Failure to maintain complete data derived from all testing and to ensure compliance with established API specifications and expectations pertaining to data retention.

Your firm lacked sufficient information to evaluate the quality of your APIs due to the failure to maintain complete raw data from testing and method validation.

Specifically,

a. You did not retain complete raw data from testing performed to ensure the quality of your APIs. For example, your firm could not provide electronic raw data supporting your High Pressure Liquid Chromatography (HPLC) testing in your Validation Report BP-VR-0701/2010.

b. You failed to retain complete raw data documenting the weights and calculations used in method validation as specified in your standard operating procedure (SOP) "Recording of Raw Data."

c. Your analyst selectively invalidated data during related substance testing. For example, for **(b)(4)**, batch **(b)(4)** on May 15, 2013; you did not retain data from all six injections used

for the initial system suitability. Your analyst discarded one of the six injections performed with no justification.

Your response states that your firm will revise your SOPs to better control your raw data. While you "agree with the inspector that all data generated during validation… should be reported and kept appropriately," your commitment to only revise your procedures prospectively does not adequately address our concerns regarding the retention of data from your initial method validation or raw data from all product testing.

3. Failure to prevent unauthorized access or changes to data and to provide adequate controls to prevent omission of data.

The inadequate controls over access to your data raise questions about the authenticity and reliability of your data and the quality of the APIs you produce.

Specifically,

a. Your firm did not have proper controls in place to prevent the unauthorized manipulation of your laboratory's raw electronic data. Your HPLC computer software lacked active audit trail functions to record changes to analytical methods, including information on original methodology, the identity of the person making the change, and the date of the change. In addition, your laboratory systems did not have access controls to prevent deletion or alteration of raw data. During the inspection, your analysts demonstrated that they were given inappropriate user permissions to delete HPLC data files.

b. Moreover, the gas chromatograph (GC) computer software lacked password protection allowing uncontrolled full access to all employees.

Your response states that you commit to upgrading your HPLC systems to have audit trails and your GC system to have password protection by July 31, 2014. However, your response lacks sufficient detail of the systems and controls you will implement. Simply turning on audit trail functions is inadequate. In addition, you failed to review historical data to ensure the quality of your products distributed to the US market.

In response to this letter, provide specific details about the comprehensive controls in place to ensure the integrity of electronic raw data generated by all computerized systems during the manufacture and testing of your drugs. Your response should demonstrate an understanding of your processes and the appropriate controls needed for each stage of manufacturing and testing that generates electronic raw data. Your response should also describe the controls and procedures you will implement to retain and archive the raw data you generate.

An FDA inspection observed similar data integrity concerns at your Novacyl Wuxi Pharmaceutical Co. Ltd. site. See Warning Letter 320-15-04, issued on December 19, 2014 to Novacyl Wuxi Pharmaceutical Co. Ltd. Your firm's corporate management is responsible for ensuring the quality, safety, and integrity of products manufactured at all Novacyl sites. We recommend that Novacyl immediately undertake a comprehensive evaluation of global manufacturing operations of all your facilities to ensure compliance with CGMP expectations.

The above examples are serious CGMP deviations demonstrating that your global quality system does not adequately ensure the accuracy and integrity of the data generated at your facilities to support the safety, effectiveness, and quality of the drugs 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 requirements. However, it is your responsibility to ensure that any

third party audit includes appropriate evaluation of sophisticated electronic systems and the possibility for data integrity manipulation of such systems.

In response to this letter, provide the following to the Agency:

1. A comprehensive evaluation of the extent of the inaccuracy of the reported data. As part of your comprehensive evaluation, provide a detailed action plan to investigate the extent of the deficient documentation practices noted above;

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

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

a) As part of your corrective action and preventive action plan, describe the actions you have taken or 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 violative conditions discussed above.

b) In addition, as part of your corrective action and preventive action plan, describe the actions you have taken or 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.

Please note that a guidance document entitled “Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients” , prepared under the auspices of the International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use, describes 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/UCM073497.pdf**.

The deviations cited in this letter are not intended to be an all-inclusive list 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, as a result of receiving this warning letter or for other reasons, you are considering a decision that could reduce the number of 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 products.

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, your failure to correct these deviations may result in FDA refusing admission of articles manufactured at Novacyl (Thailand) Ltd., 321 Bangpoo Industrial Estate, Praeksa, Muang Samutprakam, Thailand 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 the APIs at issue, provide the date(s) and reason(s) you ceased production. Please identify your response with FEI # 3000287096.

Please send your reply to:

Joseph Duran
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U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Office of Compliance
Office of Manufacturing Quality
Division of Drug Quality II
White Oak, Building 51, RM 4237
10903 New Hampshire Ave
Silver Spring, MD 20993

Sincerely,
/S/
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Director
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