U.S. Department of Health & Human Services

U.S. Food & Drug Administration

Inspections, Compliance, Enforcement, and Criminal Investigations

Nobilus Ent 3/7/12

Department of Health and Human Services

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

Warning Letter

VIA UPS MAIL **WL: 320-12-10**

March 7, 2012

Tomasz Kozluk, Ph.D.
Owner
Nobilus Ent
Ul Metalowa 6a
Kutno, Poland

Dear Dr. Kozluk:

During our September 12 to 15, 2011, inspection of your active pharmaceutical ingredient (API) manufacturing facility, Nobilus Ent, located at UI Metalowa 6a, Kutno, Poland, 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.

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

1. Failure to use dedicated production areas, including facilities, air handling equipment, and process equipment, when performing operations with **(b)(4)**, a **(b)(4)** material.

Your firm uses **(b)(4)** as a raw material in your **(b)(4)** manufacturing process. From initial receipt of the **(b)(4)**, through storage, weighing, preparation of a **(b)(4)**, and processing to make **(b)(4)**, your firm's separation practices are insufficient to ensure that all other APIs manufactured in your facility are free from contamination of **(b)(4)**.

For example:

a. Your firm's reaction of the **(b)(4)** with **(b)(4)** is not designed to prevent cross-contamination. In addition to performing this **(b)(4)** operation in a non-dedicated facility, the operations occur in non-dedicated equipment in a non-dedicated room.

In your response, please address your plans to prevent potential cross-contamination of non-**(b)(4)** materials. This should include a commitment to fully segregate the **(b)(4)** manufacturing from non-**(b)(4)** operations.

b. Your firm cannot provide assurance that non-**(b)(4)** materials handled in the weighing area are not contaminated with **(b)(4)** because the weighing area is not dedicated.

In your response to this letter, please address how you plan to assure that the weighing area is fully dedicated to **(b)(4)** operations.

c. Your firm's raw material storage area for **(b)(4)** is not adequately separated from the rest of the facility. During the inspection, **(b)(4)** powder that appeared to be **(b)(4)** was scattered throughout the **(b)(4)** storage area, and multiple **(b)(4)** storage bins were observed to be damaged in the warehouse in which non-**(b)(4)** materials are stored. In addition, your controls in this area were inadequate to ensure personnel do not carry **(b)(4)** to other areas of the facility where other APIs are manufactured.

In your response to this letter, please describe the design and controls you will implement at your company to prevent potential for **(b)(4)** in the storage area from contaminating other APIs. You should address your comprehensive containment provisions, including physical facility segregation as well as controls to assure contamination will not be introduced by personnel or material transfers.

d. Your firm does not have adequate design necessary to ensure the air handling systems in the **(b)(4)** storage area of the warehouse, **(b)(4)** weighing room, **(b)(4)** Room **(b)(4)**, and the **(b)(4)** reaction room are completely separated from the air handling units servicing other parts of the facility.

We note that you have modified your HVAC system by adding **(b)(4)** with a **(b)(4)** surrounding Room **(b)(4)**. However, a **(b)(4)** is insufficient to prevent **(b)(4)** from entering other areas in the facility. In your response, please describe your plans to completely segregate the air handling systems that service all **(b)(4)** handling and processing areas from those servicing areas where other products are handled.

e. Your firm did not monitor the facility for **(b)(4)** cross-contamination. There was lack of surface monitoring in non-**(b)(4)** areas.

Your response should provide a plan to test for the presence of **(b)(4)** throughout your facility to address any risks from all manufacturing (including staging and storage) phases. Please note that the decision to limit your testing to compartments adjacent to Room **(b)(4)** is insufficient. In your response to this letter, include the rationale used to justify your sampling plan as part of your overall action plan to remediate deviations

found during the inspection. Include information regarding the selection of the sampling sites, the sampling frequency, and the analytical methodology.

f. Your firm does not routinely test all of your non-**(b)(4)** products (e.g., APIs) for the presence of **(b)(4)**.

Include in your response your plan for testing for **(b)(4)** contamination in all other APIs that may have been or may ultimately be shipped by you or others to the United States.

The current practices at your facility demonstrate an unacceptably high risk of **(b)(4)** cross-contamination of other APIs manufactured. You should conduct all **(b)(4)** operation activities in dedicated, segregated facilities with separate air handling systems and production equipment. Please also note that in order to demonstrate adequate conditions for the manufacture of an API, or that the API is not contaminated with **(b)(4)**, a test for the presence of **(b)(4)** only provides a small degree of assurance. Testing is only part of any risk assessment and can not substitute for properly designed and controlled facilities.

In your response to this letter, please describe your risk evaluation and comprehensive containment plan for your manufacturing practices using **(b)(4)**. You should demonstrate complete segregation of the **(b)(4)** areas from the non-**(b)(4)**-handling areas. Describe your program to prevent and detect any containment breaches, and the sampling plans and analytical methodology for environmental and product testing. You should include an evaluation of the risk of **(b)(4)** contamination in all drugs you have released from your facility. Also include your proposed action plan to address the hazards posed by your drugs with the potential for **(b)(4)** contamination.

Additionally, if you intend to discontinue **(b)(4)** operations at your facility, and dedicate it to non-**(b)(4)** manufacturing, you must provide assurance that future drugs manufactured at your facility will be free from **(b)(4)** contamination and will need to demonstrate that your facility has been decontaminated. Therefore, in your response to this letter, include your plans for decontamination, renovation, and requalification of your facility, including the decontamination agent, analytical methodology for environmental testing, and the studies used to support the effectiveness of the decontamination plan.

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. We recommend that you seek the advice of a third-party consultant for assistance with a complete evaluation to determine the significant actions that will be needed at your facility in order to meet the CGMP requirements for the manufacture of APIs.

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, until such time as your manufacturing practices are verified to comply with CGMP, including demonstrating that your facility has been comprehensively decontaminated, your firm will remain under FDA Import Alert, and FDA will continue to refuse admission of all articles manufactured at Nobilus Ent, UI Metalowa 6a, Kutno, Poland, into the United States. Because your firm is currently under Import Alert, the drugs you ship 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 # 3008517755.

If you have questions or concerns regarding this letter, contact Mary E. Farbman, Compliance Officer, at the below address and telephone number.

U.S. Food and Drug Administration
Center for Drug Evaluation and Research
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Division of International Drug Quality
White Oak, Building 51, Room 4214
10903 New Hampshire Ave
Silver Spring, MD 20993
Tel: (301) 796-4171
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Sincerely,
/S/
Steven Lynn
Director
Office of Manufacturing and Product Quality
Office of Compliance
Center for Drug Evaluation and Research

Links on this page:

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