U.S. Department of Health & Human Services

FDA U.S. Food and Drug Administration

Inspections, Compliance, Enforcement, and Criminal Investigations

Klinge Chemicals Limited 12/21/10

Department of Health and Human Services

Public Health Service
Food and Drug Administration
Silver Spring MD 20993

Warning Letter

VIA UPS MAIL

WL: 320-11-007

December 21, 2010

Mr. Michael Klinge
Managing Director
Klinge Chemicals Limited
1 Bessemer Drive
Kelvin Industrial Estate East Kilbride
Glasgow, Scotland
United Kingdom

Dear Mr. Klinge:

During our June 1-3, 2010 inspection of your active pharmaceutical ingredient (API) manufacturing facility, Klinge Chemicals Limited located at 1 Bessemer Drive, Kelvin Industrial Estate East Kilbride, Glasgow, Scotland, United Kingdom, 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 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 June 11, 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 to ensure that **(b)(4)** water is of appropriate quality when used in the final purification step of an API, **(b)(4)** -USP, intended for use in a parenteral drug product.

For example, procedures for controlling and monitoring your **(b)(4)** water system have not been established and qualified. Appropriate control for microbial levels in your **(b)(4)** water has not been demonstrated.

Your response, dated June 11, 2010, is inadequate because it lacks written procedures for system maintenance and monitoring, as well as alert and action limits for microbial contamination. We expect manufacturers of non-sterile API, intended for use in parenteral drugs, to use water in the final isolation and purification steps that is monitored and controlled for total microbial counts, objectionable organisms, and endotoxins. We continue to have concerns about the impact of the water generated by your water system on the quality of the APIs manufactured at your facility.

We acknowledge that your firm is performing the second stage of qualification for this water system. However, this deficiency was brought to your attention during the last FDA inspection in 2003. Your failure to correct then leads us to question your commitment to manufacturing quality APIs. Please explain why your firm did not implement corrective action after the 2003 inspection and provide a comprehensive corrective action plan that will fully address this issue.

2. Failure to establish a stability program to monitor the APIs manufactured at your facility.

For example, your firm has not collected or tested a batch of **(b)(4)** API in the last three years. At least one batch per year of API should be tested as part of an ongoing stability program.

We acknowledge your response indicating that your outside contract for stability sample analysis was discontinued and that your firm intends to purchase equipment and conduct stability testing onsite. However, you have not adequately addressed the specific issues cited on the FDA-483. Your firm failed to have written procedures that govern the stability program to address your annual commitment and analyses to be performed.

We cannot consider your response adequate until you provide documentation that at least one batch per year of API manufactured at your facility is added to the stability monitoring program; that your stability program will monitor the characteristics of the APIs; and will be used to confirm that the expiry date and storage conditions on the label are appropriate.

3. Failure of your quality unit 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 finished product assay determination and volumetric solution standardization procedures and calculation formulas do not at least meet the current USP standards. There is no assurance that the final result for all finished products released by your firm are within specification. The FDA investigator noted that your firm had no access to the USP.

Your response is inadequate because it failed to evaluate whether or not the lots of **(b)(4)** (API) that have been released were within specification according to USP monograph. Your response indicated that your firm is evaluating the current procedures to ensure that they comply with the USP monographs.

Also, you have not addressed corrective actions you have taken, or will take, with respect to the performance of your quality control unit. Please provide adequate documentation to address this issue.

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 Klinge Chemicals Limited located at 1 Bessemer Drive, Kelvin Industrial Estate East Kilbride, Glasgow, Scotland, United Kingdom 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)**, and provide the dates and reasons you ceased production. Please identify your response with FEI # 1000429223.

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,

Grace McNally for
/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