Inspections, Compliance, Enforcement, and Criminal Investigations

Nostrum Laboratories Inc 4/27/09

Department of Health and Human Services

Public Health Service
Food and Drug
Administration
Kansas City District
Southwest Region
11630 West 80th Street
Lenexa, Kansas
66214-3340
Telephone: (913) 752-2100

April 27, 2009

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

WARNING LETTER
Ref: KAN 2009-04

Nirmal Mulye, PhD, President
Nostrum Pharmaceuticals, LLC
505 Thornall St., Suite 304
Edison, NJ 08837

Dear Dr. Mulye:

During the period of October 22 through November 14, 2008, Food and Drug Administration (FDA) investigators performed an inspection of your pharmaceutical manufacturing operation, Nostrum Laboratories, Inc., located at 1800 N. Topping Ave., Kansas City, MO Missouri. This inspection revealed serious deviations of the current Good Manufacturing Practice (CGMP) regulations, Title 21, Code of Federal Regulations, Parts 210 and 211 (21 CFR 210 and 211). These deviations cause your 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)). Section 501 (a)(2)(B) states that drugs are adulterated when they are not manufactured, processed, packed, or held according to good manufacturing practice. Failure to comply with CGMP constitutes a failure to assure that such drugs meet the requirements of the Act as to safety, and have the identity and strength, and meet the quality and purity characteristics, which they purport or are represented to possess.

FDA's list of inspectional observations, also known as FDA Form 483, was issued to and discussed with Manesh A. Dixit, President and CEO of Nostrum Laboratories, during a close-out meeting held on the final day of the inspection. A copy of the FDA Form 483 is enclosed for your information. Deviations observed during the establishment inspection include, but are not limited to, the following:

1. Drug products do not bear an expiration date determined by appropriate stability data to assure they meet applicable standards of identity, strength, quality, and purity at the time of use [21 CFR § 211.137(a)]. *Refer to FDA 483, Observation 2.* For example, the accelerated and long term stability data obtained for Sucralfate Tablets USP 1 g, as manufactured with the active pharmaceutical ingredient (API) from your new supplier are not sufficient to support the assigned five year expiration date. Your firm has not provided scientific justification for projecting a five year expiration date on the basis of **[(b)(2)]** the data gathered from the 90-day accelerated stability study you performed on one lot of finished product. This study shows the assay trending downward and approaching the lower limit of acceptability at the 90 day station. In addition, the failure of the API used to produce this lot to meet the specification for Sucrose Octasulfate assay at the 60-day station during its accelerated stability study calls into question the stability of any product made from it.

In your written response dated December 5, 2008 you provided stability data for finished product manufactured with API from your previous supplier. These data are not relevant to product manufactured with API from your current supplier. Furthermore, the information you provided on the root cause investigation performed in response to the failure of the API from the new supplier to meet specifications at the 60 day time station, when subjected to accelerated conditions, indicates that the investigation was not performed at the time of the failure or before the API was used to make lots of Sucralfate Tablet USP I gram finished product. No evidence of this investigation was presented during the October 22 to November 14, 2008 inspection of your firm, which took place seven months after the failure of the API to meet specifications.

2. Failure to thoroughly review any unexplained discrepancy whether or not the batch has already been distributed [21 CFR § 211.192]. *Refer to FDA 483, Observation 3*. For example, after a lot of Sucralfate USP API from your new source failed accelerated stability testing at the 60 day test interval, your firm did not investigate to determine the root cause of the failure. In addition, investigations of out-of-specification (OOS) test results from the 90 day and 30 day accelerated stability testing of Theophylline ER tablets, 400 mg and 600 mg, were inadequate in that they initially failed to identify the correct source of laboratory error and did not determine that the actual cause was incorrect mobile phase preparation until five months after the accelerated stability test was performed.

As stated above, your response does not include documentation that the investigation of the Sucralfate API stability failure, the determination of the root cause, or the assessment of the impact on the finished products made from it, were done in a timely manner. We acknowledge the corrective actions outlined in this response with respect to the investigation of the OOS results on the Theophylline ER product including the additional analyses and revised procedure. However, the response does not include this revised procedure or any documentation of additional testing with the correct mobile

phase.

3. Equipment and utensils are not cleaned at appropriate intervals to prevent contamination that would alter the safety, identity strength, quality, or purity of the drug product [21 CFR § 211.67(a)]. *Refer to FDA 483 Observations 4 and 5.* We observed multiple instances of rooms listed as cleaned in cleaning and maintenance logs that either showed visible residues in the room itself or contained dirty equipment.

You stated in your response of December 5 that most of the observed instances represented cleanings that were in-progress and not yet completed. We note that, for the **[(b)(4)]** tablet press in room **[(b)(4)]**,this would mean that the "campaign clean" initiated on September 16, 2008 still had not been completed by October 22, 2008. Your cleaning and use log for this room indicate that prior 'campaign cleans' had taken only 3 to 10 days.

4. There is a failure to establish and follow adequate written procedures for the cleaning and maintenance of equipment, including utensils, used in the manufacture, processing packing, or holding of a drug product [21 CFR §§ 211.67(b)(3) and (b)(5)]. *Refer to FDA 483, Observations 4 and 8*. For example, the cleaning verification study for the **[(b)(4)]** Sanitizer approved for the cleaning of production equipment does not demonstrate that the cleaning methods used will remove residues of this material. In addition, written procedures designed to prevent recontamination of clean equipment or areas prior to use, specifically your SOP **[(b)(4)]**, are not followed.

We acknowledge your response to these observations in your December 5 correspondence. However, as stated above, the cleaning verification data presented during the inspection did not address the question of residues of the **[(b)(4)]** product and no additional data was submitted with your response. Regarding the requirement in your SOP **[(b)(4)]** for proper employee gowning and footwear prior to entering "clean" areas from "dirty" ones, and, notwithstanding the assertion in your response that all employees have been trained on this SOP, our investigators observed numerous instances of employees failing to follow this SOP during the inspection.

5. Written production and process control procedures are not followed in the execution of production and process control functions [21 CFR § 211.100(b)]. *Refer to FDA 483, Observation 6*. For example, your firm failed to follow SOP **[(b)(4)]** in that all labeling and product documentation from previous production had not been removed from rooms **[(b)(4)]**, **[(b)(4)]**, and **[(b)(4)]** during product change cleanings, as required by this SOP. In addition, your firm failed to follow SOP **[(b)(4)]** in that there were no material folders created for six incoming lots of the Sucralfate API, as required by this SOP.

Your response states that **[(b)(4)]** of the **[(b)(4)]** production rooms have never been used for the manufacture of any commercial drug product. However, the **[(b)(4)]** rooms were used in the manufacture of **[(b)(4)]**, which is the subject of a pending application for approval with FDA. Please be advised that any biobatch or other lots of this product are subject to applicable CGMP controls. The assertion in your response that SOP **[(b)(4)]** does not apply to raw materials not intended for commercial drug

product production is contradicted by the language in your SOP.

6. The accuracy, sensitivity, specificity, and reproducibility of test methods employed by your firm have not been established [21 CFR § 2l1.165(e)]. *Refer to FDA 483, Observations 7 and 11.* For example, the related substances method used by your firm has not been adequately verified in that no testing has been performed to determine if the method can detect two of the known impurities of **[(b)(4)]** at the USP-specified limits. In addition, the limit of detection established for the related substances method for your firm's Sucralfate Tablets USP product does not demonstrate that the method can detect impurities at the level of not more than 0.1%. Furthermore, the actual procedure used by your firm to test Sucralfate Tablets USP 1 g for dissolution varied from the method validated by the developing contract laboratory. The method of calculation from the standard curve in the method validated by the developing contract laboratory was not the same in the procedure you use and your firm's policy on rounding of calculated test results, outlined in your SOP **[(b)(4)]**, had the practical effect of creating wider limits of acceptability for the bracketing standards than are specified in the validated method.

We acknowledge the corrective actions described in your December 5 correspondence with respect to the **[(b)(4)]** API, including the tightened impurity specifications and your statement that you have generated data to show the method can detect the specified impurities at these levels. However your response did not include any data in support of this assertion. With regard to the Sucralfate tablets related substance method, the limit of quantization (LOQ) and limit of detection (LOD) established by the new data submitted with your response are based on testing with the Sucralfate substance and not with the related substance impurities and, thus, this testing does not establish that the related substances themselves are detectable and quantifiable at these levels. Regarding the dissolution method for the Sucralfate Tablets USP 1 g, we acknowledge the corrective revisions to the written procedures outlined in your response and your statement that you have compared results obtained using both methods of calculation. However your response did not include any of the data from this comparison.

7. Failure to establish and follow adequate written procedures applicable to the quality control unit [21 CFR § 211.22(d)]. *Refer to FDA 483 Observations 6 and 14.* For example, your SOP [(b)(4)] "Material Review Board", does not reflect current company practice, was not being followed, and had not been reviewed by quality control unit personnel to assess the need for revision or replacement. In addition, the requirement, in both the original **[(b)(4)]** version of SOP **[(b)(4)]** "External Audit Procedure" and the **[(b)(4)]** revision, to rate the supplier as "acceptable," "marginally acceptable," or "unacceptable" has not been followed for any of the four audits completed.

We acknowledge your December 5, 2008 response to the FDA-483. Regarding your SOP **[(b)(4)]** we note your firm discontinued use of this SOP on **[(b)(4)]**, and we acknowledge your statement that other SOPs provide for investigations and follow-up. However, be aware that your firm's quality control unit has a responsibility to proactively assure that all written procedures applicable to the unit are current and are followed. Regarding SOP **[(b)(4)]**, you stated in your response to the FDA-483 that this SOP has only been in effect since **[(b)(4)].** However, the vendor rating

requirement also appeared in the **[(b)(4)]** version of the SOP.

8. Failure to maintain a written record and appropriate validation data of computer or other automated processes used to perform calculations in connection with laboratory analysis [21 CFR § 211.68(b)]. *Refer to FDA 483, Observation 12.* For example, the accuracy of calculations performed by the **[(b)(4)]** Spectrophotometer has not been verified.

We acknowledge the corrective actions described in your response, including your statement that you compared analytical results obtained by instrument's calculation program with those obtained through calculation from raw absorbance figures. However, you did not include any of this data in the response.

The violations cited in this letter are not intended to be an all-inclusive statement of violations that exist at your facility. You are responsible for investigating and determining the causes of the violations identified above and for preventing their recurrence or the occurrence of other violations. It is your responsibility to assure that your firm complies with all requirements of federal law and FDA regulations.

You should take prompt action to correct the violations cited in this letter. Failure to promptly correct these violations may result in legal action without further notice, including, without limitation, seizure, and injunction. Other federal agencies may take this warning letter into account when considering the award of contracts. Additionally, FDA may withhold approval of requests for export certificates, or approval of pending new drug applications listing your facility as a manufacturer until the above violations are corrected. A reinspection may be necessary.

Within 15 working days of receipt of this letter, please notify this office in writing of the specific steps that you have taken to correct violations. Include an explanation of each step being taken to prevent the recurrence of violations, as well as copies of related documentation. If you cannot complete corrective action within 15 working days, state the reason for the delay and the time within which you will complete the correction. If you no longer manufacture or market the above mentioned products, your response should so indicate, including the reasons that, and the date on which, you ceased production.

Your reply should be sent to Nadine Nanko Johnson, Compliance Officer, at the above letterhead address.

Sincerely,

/S/

John W. Thorsky
District Director
Kansas City District

Enclosure - FDA Form 483

cc:
Manesh A. Dixit, President & CEO

Nostrum Laboratories, Inc.
1800 N. Topping Ave.
Kansas City, MO 64120-1228