U.S. Department of Health & Human Services

U.S. Food & Drug Administration

Inspections, Compliance, Enforcement, and Criminal Investigations

NuSil Technology LLC 3/22/12

Department of Health and Human Services

Public Health Service
Food and Drug Administration
San Francisco District
Pacific Region
1431 Harbor Bay Parkway
Alameda, CA 94502-7070
Telephone: 510-337-6700
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WARNING LETTER

Via UPS
Delivery Signature Requested

March 22, 2012

Mr. Scott Mraz, President
NuSil Technology LLC
1050 Cindy Lane
Bakersfield, CA 93013

Ref: FEI3005140091

Dear Mr. Mraz:

During our April 18 thru May 4, 2011 inspection of your active pharmaceutical ingredient (API) manufacturing facility, NuSil Technology LLC, located at 2343 Pegasus Drive, Bakersfield, CA, investigators from the Food and Drug Administration (FDA) identified significant violations of Current Good Manufacturing Practice (CGMP) for the manufacture of APIs. These violations cause your active pharmaceutical ingredients 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 May 18, 2011 and note that it lacks sufficient corrective actions.

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

CGMP Violations

1. Your firm failed to have an adequate out-of-specification (OOS) procedure to conduct thorough and scientifically sound investigations including corrective actions.

For example, the OOS report number **(b)(4)** for lot **(b)(4)** of Simethicone Emulsion USP (30%), MED-341, dated September 17, 2010, states that your firm performed two retests as part of the investigation of a microbial test result of> 11,000 CFU/g. You released the lot based on the results of retesting, which were within the specification of **(b)(4)**. You did not justify the invalidation of the original results, nor identify the root cause of the failure. You relied solely on the acceptable retest results to release the lot. Your OOS Report procedure (SOP#**(b)(4)**), is deficient because it does not require an analysis of the data, assessment as to whether a significant problem exists, identification of root causes, or allocation of the tasks for corrective actions.

In your response, you stated that you have modified your SOP# **(b)(4)** to include testing of lots before and after a failing result in your procedure. However, your response is inadequate because you failed to provide evidence that your firm will scientifically justify and document retesting of a lot that fails to meet a microbiological specification, and conduct an appropriate investigation.

2. Your firm failed to establish procedures to adequately clean and store equipment and utensils to prevent contamination or carry-over of material that would alter the API beyond the established specifications.

For example, our inspection established that you do not routinely perform equipment cleaning after each manufacturing run. Your cleaning procedure requires you to clean the equipment when it has been more than **(b)(4)** since you manufactured the last batch in the same equipment, yet your cleaning validation does not contain data to support a **(b)(4)** "dirty hold time." Your firm determined that failure to clean a transfer hose before use was the probable cause of the microbial contamination of the Simethicone Emulsion USP (30%).

In your response, you stated that you performed a study to evaluate the cleaning step for the transfer hose and that you will sanitize the cleaned hoses with a dry heat treatment prior to use for future batches. Your response is inadequate because it does not provide data to support that your cleaning procedure for the transfer hose cleans and sanitizes the hose adequately. Please provide a validation report that includes microbial test data that evaluates whether your cleaning and sanitization procedures for your transfer hoses and other equipment is adequate.

3. Your firm failed to adequately validate and monitor the treatment process for your purified water system.

For example, your firm uses purified water as a key ingredient in the manufacture of Simethicone Emulsion USP (30%), MED-341. Between September 2009 and January 2011, you have conducted microbiological tests and found recurrent *Burkholderia cepacia* contamination.
Your firm failed to assure that your water system is suitably designed and operated to produce appropriate water quality. Regarding the latter, your firm has not established and validated appropriate cleaning and sanitizing schedules for your purified water system.

You have hired a water process subject matter expert and taken other steps to strengthen monitoring of the purified water system. Your response is not acceptable because you have not demonstrated that your purified water system is capable of operating in a continuing state of control. Please provide a validation plan for your purified water system and describe any interim actions that your firm will take to ensure that purified water used in manufacture of your drug products meets its action limits.

4. Your firm has failed to identify and define critical process parameters and the ranges expected that could affect critical quality attributes.

For example, your firm states that the Simethicone Emulsion USP (30%), MED-341, manufacturing process is designed to prevent objectionable microbiological contamination with the use of pH and temperature controlling steps. However, your validation protocol and report did not identify pH

and temperature as critical parameters. Using this manufacturing process, between September 2010 and November 2010, you produced and distributed several Simethicone lots later found to be contaminated with microbiological organisms, particularly *Burkholderia cepacia*.

We acknowledge your voluntary recall of Simethicone Emulsion USP 30% lots potentially contaminated with *Burkholderia cepacia*. In your response, you stated you relied on pH and temperature controlling steps to prevent objectionable microbiological contamination of your active pharmaceutical ingredients. Your response failed to provide information and data to support other specific manufacturing (including but not limited to quality of the input ingredients and storage time limitations) operation provisions that are needed to provide assurance that objectionable microbial contamination is prevented by your process design. Furthermore, your manufacturing process has multiple steps after your pH and heating step that would provide vectors for microbial contamination. For more information on *Burkholderia cepacia* contamination and control please refer to the article *Burkholderia cepacia: This Decision Is Overdue, (PDA J Pharm Sci and Tech* 2011, 65 535-543) which can be viewed at the following link, http://joumal.pda.org/content/65/5/535.full.pdf+html. Please provide a report in which you fully identify your manufacturing failure modes and critical control points to prevent objectionable microbiological contamination' and provide documentation to justify significant manufacturing ranges established.

The deviations 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 and the occurrence of other violations. It is your responsibility to assure compliance 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 drug applications listing your facility, until the above violations are corrected. FDA may re-inspect to verify corrective actions have been completed.

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 violations. Include an explanation of each step being taken to prevent the recurrence of violations 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 products, and provide the date(s) and reason(s) you ceased production.

Please send your reply to the attention:

Darlene Almogela
Director, Compliance Branch
U.S. Food and Drug Administration
San Francisco District
1431 Harbor Bay Parkway
Alameda, CA 94502

If you have any questions regarding any issue in this letter, please contact Brandon Bridgman, Compliance Officer at (510) 337-6794, or by fax at (510)337-6703.

Sincerely,

/s/

Barbara J. Cassens
District Director

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