Inspections, Compliance, Enforcement, and Criminal Investigations

DPT Lakewood, LLC 8/27/12

Department of Health and Human Services

Public Health Service
Food and Drug Administration
Central Region
Waterview Corporate Center
10 Waterview Blvd., 3rd Floor
Parsippany, NJ 07054

Telephone (973) 331-4910

August 27, 2012

VIA UPS Overnight

WARNING LETTER

Mr. Eugene Ciolfi
General Manager
OPT Lakewood, LLC
1200 Paco Way
Lakewood, New Jersey 08701-5938

File.No.: 12-NWJ-21

Dear Mr. Ciolfi:

During our February 15 to March 7, 2012 inspection of your pharmaceutical manufacturing facility located at 1200 Paco Way, Lakewood , NJ, an investigator from the Food and Drug Administration (FDA) identified significant violations of Current Good Manufacturing Practice (CGMP) regulations for Finished Pharmaceuticals, Title 21, Code of Federal Regulations, Parts 210 and 211. These violations cause your drug product, Santyl Ointment, 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)(8)], in that the methods used in, or the facilities or controls used for, the 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 March 22, 2012, and note that it lacks sufficient corrective actions.

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

1. Your firm has not thoroughly investigated the failure of a batch or any of its components to meet its specifications whether or not the batch has already been distributed [21 CFR 211.192].

For example,

a. Investigations into sterility failures of six lots of Santyl Ointment, 007885, 007856, 100329, 100336, 200005, and 200006, and one process validation lot, P905331H, at the 12-month stability station, were inadequate.

> i. Your investigation into the failures of lots 007885, 007856, and P905331H attributed the failures to your contract laboratory. However, the investigation conducted by the contract laboratory facility concluded that there was no laboratory error. Nevertheless, as part of your corrective actions, you ceased using the contract laboratory and started

conducting the sterility testing in house. Thereafter, lots of Santyl Ointment continued to fail sterility testing. The continued sterility failures of these products put in question your conclusion that the contract laboratory was at fault.

ii. Your investigation into the failures of lots 100329 and 100336 was inconclusive as to root cause. However, your investigation suggested two possible causes: 1) the potential lack of sterility of the **(b)(4)** used to liquefy the sample, and 2) the use of the cap puncture each Santyl Ointment tube to obtain product for testing. Your corrective actions included revising the sterility testing procedure to discontinue the practice of puncturing the tubes with the cap and providing additional aseptic technique training. However, the **(b)(4)** lot used for sterility testing of lots 100329 and 100336 did not fail sterility testing. In addition, Santyl Ointment lots continued to fail even after your firm implemented these corrective actions.

iii. Your investigation into the failure of lots 200005 and 200006 concluded that the two most probable causes for the sterility failures were the **(b)(4)** used to liquefy the sample prior to testing and microbial contamination from the water in the water bath used to warm the sample prior to the sterility testing. However, the **(b)(4)** lot used for sterility testing of lots 200005 and 20006 did not fail sterility testing. In addition, no testing of the water bath was performed to identify potential contamination.

b. The investigation into the failure of the media fill conducted in June 2011 was inadequate. A Bacillus species was identified in the samples incubated for the media fill. The failure was attributed to inadequate aseptic technique by an operator based on the video recording of the media fill operation. However, the Bacillus species identified is a ubiquitous environmental organism that could have been introduced into the aseptic area *via* multiple sources (e.g., design of the aseptic core, material flow, etc.). Nevertheless, you failed to consider other sources of contamination in your investigation. Subsequently, your quality unit released **(b)(4)** lots of Santyl Ointment manufactured between the last successful media fill in February 2011 and the failed media fill in June 2011 based on the review of the video recording of the manufacturing operations even though the review notes included deviations from procedures for many lots (e.g., **(b)(4)** were present in areas designated for **(b)(4)** as the maximum allowable limit). In contrast, the video review for lots 200005 and 200006, which were manufactured a month prior to the failed media fill of June 2011, did not note any deviations from procedures. However these lots failed sterility testing. Therefore, the review of video recordings of manufacturing operations is insufficient evidence on which to base a determination of the quality of the lots.

You stated in your response, that you will reevaluate the entire cleaning and disinfection program for the Santyl Ointment manufacturing areas and re-train operators. **(b)(4)** Re-training operators and conducting media fill runs have been your standard corrective actions following the sterility failures that were obtained from lots manufactured in December 2010 and May 2011. However, these actions have been insufficient to control the microbial contamination in your facility and to prevent recurrence. Following the May 2011 sterility failures and then the failed media fill conducted in June 2011, you committed to completing three successful media fills prior to resumption of manufacturing. However, these three simulations did not appear to provide adequate assurance that effective corrective actions were implemented, as evidenced by additional sterility failures in January 2012.

Your investigation should include well-supported, substantive conclusions as to the cause of the multiple sterility release testing and media fill failures, detailed corrective and preventive actions, and your assessment of the impact to the quality of distributed product.

2. Your firm has not established appropriate written procedures designed to prevent microbiological contamination of drug products purporting to be sterile [21 CFR 211.113(b)]. For example, your sterility testing revealed the presence of multiple organisms in your sterile drug products. Since approval in November 2010 your firm has manufactured **(b)(4)** lots of Santyl Ointment, and 6 of these lots have failed release testing for sterility. These sterility failures indicate that your firm does not have adequate aseptic procedures in place.

We acknowledge your commitment to implement several process improvements to strengthen your manufacturing controls in the aseptic area, including random environmental monitoring sampling of personnel, negative control for **(b)(4)** documenting sterility sample pull times, and use of sterile probes to puncture the tubes during sterility testing. However, we are not

confident that these changes will be sufficient to ensure that your aseptic manufacturing process will operate in a state of control. We recommend you conduct a comprehensive evaluation of your sterile drug operations, including but not limited to a thorough review of material flow, personnel practices, production supervision, operational procedures, quality assurance oversight, the training program, room design, equipment suitability, the environmental monitoring program, systems used to investigate contamination events (e.g., media fills, sterility test failures), and the clean area classification. In your response to this letter, please include a detailed description of the actions you will take to correct these issues and prevent recurrence. In addition, include your assessment of the impact of these violations on distributed drug products.

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 bulk drug substances produced by your manufacturing facility, FDA requests that you contact COER'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.

The violations cited in this letter are not intended to be an all-inclusive list of violations that may 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 new drug applications listing your facilities, until the above violations are corrected. FDA may re-inspect to verify corrective actions have been completed.

Within fifteen (15) working days of receipt of this letter, please notify this office in writing of the specific steps you have taken to correct violations. Include an explanation of each step 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 the drug products manufactured at these facilities, and provide the date(s) and reason(s) you ceased production.

Your response should be addressed to: U.S. Food and Drug Administration, 10 Waterview Boulevard, 3rd Floor, Parsippany, New Jersey, 07054, Attn: Joseph F. McGinnis, Director, Compliance Branch.

Sincerely,

/S/

Diana Amador-Taro
District Director
New Jersey District

cc: Paul Johnson
President & COO
DPT Laboratories, Ltd.
318 McCullough Avenue
San Antonio, Texas 78215

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