



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

511792

Food and Drug Administration
466 Fernandez Juncos Avenue
San Juan, Puerto Rico, 00901
Compliance Branch
Telephone: 787-474-9500
FAX: 787-729-6658

April 24, 2009

WARNING LETTER
SJN-2009-07

Certified Mail
Return Receipt Requested

Mr. Ag Lafley, CEO
Procter and Gamble
PO Box 599
Cincinnati, OH 45202

Dear Mr. Lafley:

This letter is in reference to inspections of your OTC human drug products and cosmetics manufacturing facility Olay LLC., located at Carretera # 735 Km 2.3, Bo. Rio Llano, Cayey, Puerto Rico 00736, conducted between August 25 to October 1, 2008 and November 5 to November 12, 2008, by an investigator from the Food and Drug Administration (FDA). The inspection revealed that your firm's manufacture, processing, packing, or holding of human OTC drug products deviate from the Current Good Manufacturing Practice (CGMP) Regulations as stated within 21 CFR Part 211, rendering the drugs adulterated within the meaning of 501 (a)(2)(B) (21 USC § 351(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (the Act). The manufacture and processing of your OTC drug products do not conform with CGMPs to assure that the drug products meet the requirements of the Act as to safety, and have the identity and strength and meet the quality and purity characteristics that it purports or is represented to possess. The inspection also revealed that your OTC drug products have been prepared, packed and held under insanitary conditions whereby they may have been contaminated with filth or rendered injurious to health, and are, therefore, adulterated within the meaning of 501(a)(2)(A) of the Act (21 USC § 351(a) (2)(A).

Additionally, several of your cosmetic products have been prepared, packed, or held under insanitary conditions whereby they may have become contaminated with filth, or whereby they may have been rendered injurious to health, and are, therefore, adulterated within the meaning of 601(c) of the Act (21 U.S.C. § 361(c).

At the conclusion of the inspections a List of Inspectional Observations (Form FDA-483) was issued to Mr. Ezio Garciamendez-Budar, Plant Manager at the facility. Mr. Garciamendez-Budar responded to the FDA-483s by letters dated October 31, 2008 and December 12, 2008. We addressed these responses below, in relation to each of the noted violations where appropriate.

Investigation (b) (4) was closed on (b) (4); however, those potentially affected lots were released from (b) (4) to (b) (4)

- As a corrective action, the hopper was placed out-of-use and a caustic wash/extended cleaning was performed on the equipment. However, the sampling plan after the caustic wash was limited to the two routine points of your monitoring program (b) (4) and (b) (4). There is no assurance that the corrective action was effective in cleaning all the parts that showed microbial growth during the special sampling. Also, there is no assurance that the routine cleaning as prescribed by SOP (b) (4) is effective.
- Your firm's investigation concluded that poor practices of cleaning and sanitization led to the presence of (b) (4). According to the investigation, the technicians were not disassembling the filler. However, the investigation failed to address why the cleaning verification step was ineffective in identifying this deficiency and whether or not the current monitoring program is adequate to detect contamination.

We reviewed your October 31, 2008 response letter which addressed this observation. You indicated that the corresponding finished product microbial content testing confirmed no recovery of the micro-organisms initially detected on the filling equipment monitoring samples. You concluded that "this is indicative of a low level transient contamination that was killed off by the product preservatives system." We find this conclusion highly objectionable because the purpose of adding preservatives to drug and cosmetic products is not to kill microorganisms present in your finished products due to poor manufacturing practices, but rather to prevent the growth of microorganisms in products manufactured in compliance with good manufacturing practices. Please indicate in the response to this letter how you will demonstrate that your current cleaning practices are effective to produce products free from objectionable microorganisms.

- b. Inspectional evidence shows that from (b) (4) to (b) (4), your firm received (b) (4) health effect-related complaints for the Vick Sinex product that could indicate a failure of the product to meet its specifications. None of these were referred for a manufacturing investigation.

2. Failure to follow written procedures for cleaning and maintenance of equipment, including utensils, used in the manufacture, processing, packing, or holding of a drug product, as required by 21 CFR § 211.67(b). For example, your investigation of the contamination with (b) (4) of a product that was manufactured on filling line (b) (4) revealed that employees failed to follow your SOP (b) (4) by failing to completely disassemble the hopper and rinse all parts as required.

3. Failure to establish control procedures which monitor the output and validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product as required by 21 CFR § 211.110 (a). Specifically,

- a. Sinex Long Acting Nasal Spray had appearance failures in stability samples in (b) (4) (b) (4) and (b) (4) and (b) (4), (b) (4) and (b) (4). The precipitate detected was identified as a (b) (4)

of one of the preservatives. Appearance failures occurred previously from (b) (4) to (b) (4). At that time, you identified the precipitate as (b) (4). Your firm concluded that the exposure to the amount of (b) (4) in this (b) (4) was acceptable as compared with exposure to (b) (4). In February 2001, changes to the manufacturing process were implemented to eliminate the precipitate formation. However, these changes were not effective to prevent the precipitate formation as evidenced by the latest stability failures.

Technical justification (b) (4), approved in (b) (4), proposed a reduction of the upper limit of the preservative in the formulation to eliminate the precipitate. You determined that the change in the formula did not require a new validation because the issue is only seen over time. In addition, as of (b) (4), no information about stability studies with the new formulation had been provided. You have not demonstrated that this proposed action will prevent the recurrence of the stability failures. Based on your firm's past history with this product, it not clear that your firm has a thorough understanding of the physical stability of the product throughout its shelf life.

Moreover, technical justification (b) (4) states that a potential effect of this failure could be seen in complaints reporting (b) (4). A review of complaints received from (b) (4) to (b) (4) found approximately (b) (4) complaints reporting similar issues. However, your firm identified these complaints as (b) (4) meaning that no investigation was required.

We reviewed your October 31, 2008 response letter which addressed this observation and found it inadequate. You indicated that a formulation change is being pursued for your Sinex Long Acting Nasal Spray, but you do not mention whether you are planning to validate the new manufacturing process, and we note, as discussed above, that you have made other changes to the formulation of this product without validating their effectiveness. You have observed the formation of this precipitate since (b) (4). You have stability data at ambient conditions showing the formation of this precipitate since the (b) (4). In (b) (4) you made changes to the manufacturing process without conducting a revalidation of the process. Specifically, you (b) (4) to (b) (4) and to ensure that particles that produced the turbidity were removed. You also modified the (b) (4) addition step and established a new visual method. These changes were not effective in eliminating the (b) (4) precipitate as evidenced by the stability appearance failures observed in stability samples analyzed in (b) (4) (b) (4) and (b) (4) (for example, lot (b) (4)). We find it highly objectionable that corrective actions identified in the technical justification (b) (4) report, which documents the investigation of stability failures from (b) (4), have not been validated or implemented as of (b) (4), and that you continued manufacturing and distributing this product. When our investigator asked your Quality Manager the reason for the delay she explained that this was a lower priority based on the firm's assessment of the safety/health risk and your firm was focused on other priorities.

In addition, the justification provided in your response for failing to conduct an investigation of about (b) (4) complaints reporting (b) (4) and (b) (4) is inadequate. You indicated that these complaints were not investigated because they did not meet your

criteria in terms of complaints reported per month (b) (4) required for initiating a manufacturing investigation. The number of complaints received should not be the only factor considered to initiate a manufacturing investigation, especially when manufacturing issues could be related to the complaints received.

Please provide in your response to this letter the following information:

- Additional justification in support of the current (b) (4) expiration date for your product Sinex Long Acting Nasal Spray. The most recent stability data show appearance failures in (b) (4).
- Your proposed timeframe for the implementation of corrective and preventive actions and your plans to revalidate the manufacturing process of this product.
- An evaluation in support of your conclusion regarding the safety of the presence of undetermined amounts of the (b) (4) in your drug product. Please indicate why you used cosmetics literature in your assessment to determine that the presence and level of this salt in your drug product does not represent a risk to the safety and efficacy of this product.
- A complete evaluation of all the consumer complaints associated with your product Sinex Long Acting Nasal Spray. Please include a copy of your revised corporate complaint SOP for our evaluation.

b. In addition, the inspection conducted during the period of November 5 through November 12, 2008, disclosed that you distributed a reformulated version of your product Vicks Early Defense Hand Sanitizer (VED) prior to approving and completing your validation exercise. Validation Report (b) (4) was approved on (b) (4); however, the (b) (4) validation batches that were filled into (b) (4) were released from (b) (4) to (b) (4), prior to the approval of the validation. Specifically, batch (b) (4) was distributed to the consumers in (b) (4). We acknowledge receipt of a letter dated November 6, 2008, in which you communicated to this Agency that as November 4, 2008, Procter and Gamble has ceased all production and promotion of the VED product. Nevertheless, we would like to remind you that it is unacceptable for a manufacturer of drug products to distribute products prior to completing its validation.

We evaluated your December 12, 2008 response letter addressing this observation. In this response, you indicated that your process validation SOP would be revised by the end of (b) (4). Please include a copy of this revised SOP with the response to this letter for our evaluation.

4. Failure to establish adequate written procedures for the handling of all written and oral complaints regarding drug products, including provisions for review by the quality control unit of any drug complaint involving the failure of a drug product to meet any of its specifications and for such drug products, a determination as to the need for an investigation in accordance with § 211.192, as required by 21 CFR § 211.198(a).

Specifically, SOP (b) (4), version (b) (4), "Quejas del Consumidor" (Consumer Complaints) states that complaints related to health effects (Action 3) are not investigated unless there is a trend. A review of complaints related to your OTC drug product Vicks Sinex found that complaints related to (b) (4), (b) (4), and (b) (4) were not referred for a manufacturing investigation although lot numbers were available. As noted above in item (b) (4) of this letter, from (b) (4) to (b) (4), there were (b) (4) complaints related to health effects and none of them were adequately investigated because none were referred for a manufacturing investigation.

We reviewed your October 31, 2008 response letter which addressed this observation. You indicated that the complaint SOP will be revised by (b) (4), to ensure clarity in the decision making process for initiating manufacturing investigations on Action (b) (4) complaints. Please include in your response to this letter a copy of this revised SOP for our evaluation.

In addition, our investigators found that your OTC drug products have been prepared, packed and held under insanitary conditions whereby they may have been contaminated with filth or rendered injurious to health, and are, therefore, adulterated within the meaning of 501(a)(2)(A) of the Act. As noted in item (b) (4), above, at least (b) (4) each of (b) (4) of your firm's OTC drug products were manufactured on filling line (b) (4), which included product contact surfaces that were later found to be contaminated with multiple species of (b) (4). This indicates that the sanitization practices employed by your firm were insufficient to prevent contamination with these organisms. Although you had evidence of possible contamination in your manufacturing equipment prior to the manufacture of these products, you proceeded to use this filling line to manufacture drug products and did not quarantine the products or provide a rationale for allowing the products to remain in distribution when this contamination was later confirmed.

Cosmetics:

Our inspection also revealed that several of the hair care and skin care cosmetics manufactured in your facility, including your Olay Total Effects Revitalizing Daily Foam, Olay Regenerist Micro Sculpting Cream, Olay Moisture Foaming Face Wash, and Olay Moisture Rich Cream Cleanser, are adulterated within the meaning of Section 601(c) of the Act because they have been prepared, packed, or held under insanitary conditions whereby they may have become contaminated with filth, or whereby they may have been rendered injurious to health.

Specifically, the inspection revealed that your current procedures and controls are not adequate to prevent your cosmetic products from being contaminated with gram negative organisms. As discussed above, your firm initiated Investigation (b) (4) because a (b) (4) was detected in your Olay Total Effects Revitalizing Daily Foam product. As a result of the investigation, your firm found that several parts of your filling line (b) (4) which was used to fill approximately (b) (4) of OTC drug products and cosmetics in (b) (4), were contaminated with (b) (4). Your firm determined that the source of this contamination was your technicians' failure to disassemble the filler. However, your firm did not address why the cleaning verification step did not identify your technicians' failure to disassemble the filler and whether your current monitoring program is adequate to detect contamination.

We reviewed your October 31, 2008 response letter and determined that it does not adequately address this violation. You state in this response that your cleaning and sanitization SOP will be revised to include the steps required for disassembly of parts prior to cleaning and sanitization and to include verification of this procedure by a second technician, a step already listed in your current SOP. You also state that a systemic evaluation of manual cleaning procedures will be performed to ensure proper disassembly and verification. However, this response does not address how you will ensure that the verification step is being performed.

Your firm initiated an investigation in (b) (4) to determine the cause of a (b) (4), being detected in your Olay Moisture Rich Cream Cleanser during the filling process on filler line (b) (4). Your investigation found that the cause of this contamination was related to employees' failure to perform extended sanitization of filler line (b) (4) when the equipment was idle, and you failed to provide assurance that you had adopted procedures that are effective to prevent such contamination from recurring.

We reviewed your October 31, 2008 response letter and determined that it does not adequately address this violation. Your response indicates that the forms used to document extended sanitizations do not provide a space to (b) (4) and that you have revised these forms to include a space in which to document these sanitizations. However, your response does not address how you will ensure that your technicians are performing extended sanitizations or other steps that are adequate to prevent your equipment from being contaminated.

Your firm issued several Quality Notices in 2008 because you found growth of the (b) (4) in several (b) (4), and (b) (4). These tanks are used to hold cosmetic products prior to filling. Even though you had evidence of (b) (4) in your manufacturing equipment, you released the products based on acceptable bulk and finished product testing. Our investigator determined that, despite evidence that your portable tanks had been contaminated with these organisms, you continued your practice of monitoring these tanks on a monthly basis and did not modify your cleaning and sanitization procedures to prevent such contamination from recurring.

We reviewed your October 31, 2008 response letter which addressed this observation and determined that it does not adequately address this violation. Your response indicates that the contamination was at a (b) (4). Although the level of contamination may have been low, the presence of any (b) (4) may render products held in your tanks injurious to health because, if tanks are contaminated with these organisms, these organisms can be incorporated into finished products, and any amount of (b) (4) in a finished product has the potential to cause illness.

You also indicate in your response that your finished-product microbial content testing did not detect the organisms initially detected in the monitoring samples because they were (b) (4) by preservatives in the product. However, this statement does not address your failure to adopt procedures sufficient to prevent contamination of your cosmetic products by (b) (4). Even though your firm's testing did not (b) (4) in the finished

products that had been held in your portable tanks, these test results do not guarantee that these products are not contaminated; rather, they indicate that, on average, there is less than 1 bacterium per analytical portion of the product. Preservatives in these products may fail to eliminate gram-negative organisms and, therefore, your finished cosmetic products may be rendered injurious to health by such organisms even if finished-product testing does not indicate their presence.

You also indicate that the contamination was caused by use of (b) (4) and that you eliminated the use of these (b) (4) for delivering the (b) (4) for your portable tanks on (b) (4). However, it is not clear if the (b) (4) are used for purposes other than the (b) (4) and whether these (b) (4) may, therefore, cause contamination outside of this process. Accordingly, your response does not explain why eliminating the use of the (b) (4) to deliver the cold-water rinse is adequate to prevent your portable tanks from contamination during other procedures.

Please include in your response to this letter specific steps that you are planning to take to ensure that your current sanitization process is adequate to prevent the growth of organisms that may be injurious to health.

The violations cited in this letter are not intended to be an all-inclusive list of the deficiencies 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 or the occurrence of other violations. It is your responsibility to assure that your operations at this facility and all other facilities under your control comply 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.

Mr. Ag Lafley, CEO
Procter & Gamble/OLAY LLC
WL-2009-07
Page 9

Your reply should be sent to the Food & Drug Administration, San Juan District Office, 466 Fernandez Juncos Ave., San Juan, PR 00901-3223, to the attention of Margarita Santiago, Compliance Officer.

Sincerely,

A handwritten signature in black ink, appearing to read "Maridalia Torres". The signature is fluid and cursive, with a long horizontal stroke extending to the right.

Maridalia Torres
District Director
San Juan District

Enclosures: FDA 483

cc: Mr. Ezio Garciamendez
Plant Manager
Olay LLC
PO Box 7000
Cayey, PR 00736