Aplicare, Inc. 12/15/16

U.S. FOOD & DRUG ADMINISTRATION

New England District Office
One Montvale Avenue
Stoneham, MA 02180

WARNING LETTER
CMS # 489281

UNITED PARCEL SERVICE
OVERNIGHT DELIVERY

December 15, 2016

Mr. Andrea F. Sama
Plant Manager
Aplicare, Inc.
550 Research Parkway
Meriden, CT 06450-7172

Dear Mr. Sama:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Aplicare, Inc., 550 Research Parkway, Meriden, Connecticut, from December 14, 2015 to January 15, 2016.

This warning letter summarizes significant violations of current good manufacturing practice (CGMP) for finished pharmaceuticals. See 21 CFR, parts 210 and 211.

Because your methods, facilities, or controls for manufacturing, processing, packing, or holding do not conform to CGMP, your drug products are adulterated within the meaning of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 351(a)(2)(B).

We reviewed your firm's February 8, 2016, response in detail, and acknowledge receipt of your subsequent correspondence.

Our investigators observed specific violations including, but not limited to, the following.

CGMP Violations

1. Your firm failed to follow appropriate written procedures that are designed to prevent microbiological contamination of drug products purporting to be sterile, and that include validation of all aseptic and sterilization processes (21 CFR 211.113(b)).

Your firm failed to implement adequate microbial controls for your povidone-iodine drug products, which purport to be sterile. These products are intended for significant indications, including the "disinfection of wounds or burns," as well as "preparation of skin and mucous membranes prior to surgery or injections."

Inadequate "sterilization" process

You failed to adequately validate your process and the claim that it achieves "sterilization." Your process relies **(b)(4)**. You used a biological indicator organism **(b)(4)** that your studies found is less resistant than organisms routinely found in your manufacturing environment, such as *Bacillus licheniformis*.

Further, since at least 2012, spore-forming microorganisms have been repeatedly isolated using your surrogate sterility test. You failed to adequately investigate and implement corrective actions to prevent recurrence of these contamination incidents. Examples of contamination found using your surrogate sterility test include:

- ¾ Fluid Ounce Povidone-Iodine Solution (Lot 2K040, November 14, 2012). *Paenibacillus polymyxa* and *Paenibacillus pasadenensis* were isolated.
- ¾ Fluid Ounce Povidone-Iodine Solution (Lot 2K052, November 14, 2012). *Paenibacillus barengoltzii* was isolated.
- One Povidone-Iodine Gel Swabstick (Lot 54751, October 09, 2013). *Brevundimonas vesicularis* was isolated.
- Large Winged Sponges with PVP-I Scrub (Lot 57448, June 11, 2014). Ba*cillus licheniformis* was isolated.
- Povidone-Iodine Ointment (Lot 59858, February 23, 2015). *Bacillus subtilis* was isolated.
- One Povidone-Iodine Gel (Lot 61995, November 12, 2015). *Nigrospora orzyae* was isolated.

In your response, you said that you would revalidate your "sterilization" process for povidone-iodine products. Specifically, you proposed to characterize the anti-microbial effects **(b)(4)**, assess biological indicator organism suitability, and requalify the process. You anticipated completion of this revalidation plan within 14 to 18 months.

Your response is inadequate because you have unsuccessfully attempted these actions as corrections in the past. While your firm provided references that indicate that your disinfection process is capable of substantial bioburden reduction, your references and other available literature also indicate that some microbes (e.g., certain species of spore-formers, Pseudomonas, or Burkholderia) can persist in povidone-iodine.

We also note that your firm failed to test numerous product lots for sterility using USP <71> or an equivalent method. You instead used a surrogate sterility test that lacks a representative sample of the batch and is insufficiently sensitive. We acknowledge that your firm commits to testing sterility of finished products using USP <71> in the future. It should be noted, however, that a passing sterility test alone is insufficient to support release of products unless the manufacturing operation is designed to robustly and reproducibly assure batch sterility.

You lack scientific justification that your process is capable of robustly rendering products sterile. In your response to this letter, describe improvements to your manufacturing operation that will establish a high level of sterility assurance. If you intend to implement a terminal sterilization process, provide us with a rigorous sterilization validation protocol and study results demonstrating that the new process can achieve a sterility assurance level of 10-6 or more, and using a biological indicator that represents the resistant spore-forming organisms found in your environment. If you

plan to continue to use the **(b)(4)** bioburden reduction step at the conclusion of processing, describe the facility and process improvements that will ensure that units subjected to that step are first produced under aseptic processing conditions.

In your response, also include the microbiological testing procedures that you will be using in your process validation studies.

2. Your firm failed to use appropriate air filtration systems for production areas (21 CFR 211.46(c)).

You do not manufacture your povidone-iodine drug products in production areas of appropriate air cleanliness. Your firm manufactures povidone-iodine drug products that purport to be sterile in unclassified areas. These are inadequate conditions to protect the drug and its packaging components during production.

Your firm's povidone-iodine products should be produced in cleanrooms that are designed and controlled to meet appropriate cleanliness standards and supplied with air from high-efficiency particulate air (HEPA) filters.

Your response acknowledges the need to establish cleanrooms. However, it lacks a detailed corrective action and preventive action (CAPA) that describes all actions to be taken relating to facilities, equipment, manufacturing methods, controls, and raw materials to assure sterility.

3. Your firm failed to have separate or defined areas or such other control systems necessary to prevent contamination or mix-ups (21 CFR 211.42(c)).

Your environmental monitoring of production areas where you manufacture povidone-iodine products is performed **(b)(4)**. This level of monitoring is insufficient to evaluate whether the manufacturing environment is in control. During your limited environmental monitoring, you have isolated *Bacillus* species in numerous instances and in various locations in your facility. For instance, approximately **(b)(4)** of **(b)(4)** samples collected in March 2015 were identified as *Bacillus* species, which are spore-forming bacteria.

In your response, you provided a revised environmental monitoring procedure. Your revised procedure is inadequate for the following reasons.

- You did not provide sufficient scientific rationale for establishing microbial alert/action limits. The limits appear to be based solely on historical average and standard deviation, without adequately considering other factors.
- The settle plate microbial action limits **(b)(4)** to be used in the newly established cleanrooms **(b)(4)** appear to permit unnecessarily high levels of air contamination.
- You did not provide an adequate program for identifying organisms in the environment. You currently selectively identify certain microbes (e.g., gram-positive spore-formers, filamentous fungi) and only when they reach microbial action limits.

Your firm should establish a comprehensive environmental monitoring program to assist in assuring control of the pre-sterilization bioburden of your products. The program should set appropriate alert and action limits in order to detect adverse environmental conditions and trigger prompt corrective actions that prevent contamination.

In response to this letter, please provide revised environmental monitoring procedures. These procedures should include appropriate:

- action and alert limits for each ISO classified area you intend to implement.
- instructions regarding investigations of out-of-limit (OOL) environmental monitoring results.

• plans for routinely identifying organisms. For example, microorganisms recovered from the filling and sealing room should be routinely identified.

In a previous inspection (October 16 through November 17, 2014) FDA cited similar environmental monitoring deficiencies and sterility positive findings.

4. Your firm failed to establish and follow an adequate written testing program designed to assess the stability characteristics of drug products (21 CFR 211.166(a)).

During your stability studies of povidone-iodine drug products, which purport to be sterile, you failed to test sterility. Therefore, there is no assurance that your povidone-iodine drug products can meet their specifications for sterility through their 36-month expiration period.

Products manufactured as sterile must maintain their container-closure integrity and sterility throughout the labeled expiration period.

For all povidone-iodine products labeled as sterile, provide us with data to demonstrate that each product is sterile at the end of the expiration period, that the integrity of the container-closure system is maintained throughout the shelf life, and that each product passes USP <51> “Antimicrobial Effectiveness Testing.”

Unapproved new drug charges for the following Aplicare products

- Aplicare 3/4 Fluid Ounce Povidone-Iodine Solution
- Aplicare One Povidone-Iodine Gel Swabsticks
- Aplicare One Povidone-Iodine Scrub Swabsticks
- Aplicare Three Povidone-Iodine Swabsticks

The product labels and websites (www.aplicare.com and https://www.cloroxprofessional.com/industry/health/overview/***1***) for Aplicare 3/4 Fluid Ounce Povidone-Iodine Solution, Aplicare One Povidone-Iodine Gel Swabsticks, Aplicare One Povidone-Iodine Scrub Swabsticks and Aplicare Three Povidone-Iodine Swabsticks (collectively, the Aplicare Povidone-Iodine products) include the following labeling claims that demonstrate the intended uses of the products. This list is not inclusive of all claims demonstrating the products’ intended use.

All four product labels include the following claims:

- “Use…antiseptic skin preparation”
- “ANTISEPTIC STERILE Solution”

Website claims at https://www.cloroxprofessional.com/industry/health/overview/ include:

Aplicare 3/4 Fluid Ounce Povidone-Iodine Solution
“Proven Efficacy…Broad-spectrum efficacy shown against skin pathogens, including gram-negative bacteria, gram-positive bacteria and yeasts”

Aplicare One Povidone-Iodine Gel Swabsticks
“Broad-spectrum against skin pathogens, including Gram-negative and Gram-positive bacteria, fungi, viruses, protozoa and yeasts”

Aplicare One Povidone-Iodine Scrub Swabsticks

“Proven Efficacy…Broad-spectrum efficacy shown against skin pathogens, including gram-negative bacteria, gram-positive bacteria and yeasts”
“Broad-spectrum against skin pathogens, including Gram-negative and Gram-positive bacteria, fungi, viruses, protozoa and yeasts”

Aplicare Three Povidone-Iodine Swabsticks
“Proven Efficacy…Broad-spectrum efficacy shown against skin pathogens, including gram-negative bacteria, gram-positive bacteria and yeasts”
“Broad-spectrum against skin pathogens, including Gram-negative and Gram-positive bacteria, fungi, viruses, protozoa and yeasts”

Based on their labeling, the Aplicare Povidone-Iodine products are “drugs” as defined under section 201(g)(1)(B) of the FD&C Act (21 U.S.C. 321(g)(1)(B)), because they are intended for the diagnosis, cure, mitigation, treatment, or prevention of disease, and/or under section 201(g)(1)(C) of the FD&C Act (21 U.S.C. 321(g)(1)(C)) because they are intended to affect the structure or any function of the body of man. Specifically, these products are intended as topical antiseptics and antifungals.

The antifungal claims, “Broad-spectrum against skin pathogens, including…fungi,” and “Broad-spectrum efficacy shown against skin pathogens, including…yeasts” subject the Aplicare Povidone-Iodine products to the requirements of the OTC Final Monograph for Topical Antifungal Drug Products (21 CFR 333.201). These products are neither formulated nor labeled in conformance with this final monograph. Specifically, these products do not contain the permitted antifungal active ingredients listed under 21 CFR 333.210. In addition, the products’ labeling does not include any of the required labeling for antifungal products under 21 CFR 333.250.

In addition, drug products intended for topical antiseptic general use to reduce bacteria and microorganisms on the skin such as the labeled purpose of the Aplicare Povidone-Iodine products are being evaluated under the ongoing rulemaking for OTC Topical Antimicrobial Drug Products within FDA’s OTC Drug Review. OTC Topical Antimicrobial Drug Products include OTC healthcare antiseptics and OTC consumer antiseptics such as these products. Tentative final monographs (TFM) for these products were first published in the Federal Register in 43 FR 1210 (January 6, 1978) and amended at 56 FR 33644 (July 22, 1991), 59 FR 31402 (June 17, 1994), 78 FR 76446 (December 17, 2013), and 80 FR 25166 (May, 1, 2015). These documents are available on FDA’s website: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Over-the-CounterOTCDrugs/StatusofOTCRulemakings/ucm070821.htm.

Pending a final monograph,***2*** FDA does not object to marketing OTC drugs that meet the formulation and labeling requirements described in the relevant TFM or that are otherwise eligible for inclusion in the OTC Drug Review (see 68 FR 75585 at 75590-91, Dec. 31, 2003). However, the Aplicare Povidone-Iodine products are not labeled in accordance with the Antimicrobial TFM. Specifically, the claims to the public referenced above regarding effectiveness against pathogens such protozoa and viruses go beyond merely describing the general intended use of a topical antiseptic as described in the relevant rulemaking. Moreover, such claims are not described in any OTC final monograph, tentative monograph, or any rulemaking being considered under the OTC Drug Review. Also, we are unaware of any evidence that a product formulated and labeled for such uses was marketed in the United States on or before the inception of the OTC Drug Review.

Therefore, the Aplicare Povidone-Iodine products are “new drugs” under section 201(p) of the FD&C Act (21 U.S.C. 321 (p)) because they are not generally recognized among scientific experts as safe and effective for the drug uses described in their labeling. “New drugs” may not be legally marketed in the United States without an approved application under section 505(a) of the FD&C Act (21 U.S.C. 355(a)). The Aplicare Povidone-Iodine products are not subjects of approved new drug applications; therefore, marketing these products in the United States is prohibited under section 301(d) of the FD&C Act (21 U.S.C. 331(d)), and violates section 505 the FD&C Act (21 U.S.C. 355).

Aplicare Benzalkonium Chloride Swabsticks

The label for Aplicare Benzalkonium Chloride Swabsticks includes a statement that the product is a “skin cleanser.” However, the website for Aplicare Benzalkonium Chloride Swabsticks includes a link to Safety Data Sheet for Aplicare Benzalkonium Chloride Swabsticks that states: “Recommended Use Topical skin antiseptic.” You also prominently declare the ingredient benzalkonium chloride on the immediate label and in the product name implying, in the context of your product’s labeling, that the ingredient has pharmacological activity. In fact, benzalkonium chloride is a well-known topical antimicrobial. Aplicare Benzalkonium Chloride Swabsticks is a drug as defined by section 201(g)(1)(B) of the FD&C Act (21 U.S.C. 321(g)(1)(B)) because it is intended to diagnose, cure, mitigate, treat, or prevent disease, and/or under section 201(g)(1)(C) of the FD&C Act (21 U.S.C. 321(g)(1)(C)) because they are intended to affect the structure or any function of the body of man.

Drug products intended for topical antiseptic general use are being evaluated under the ongoing rulemaking for OTC Topical Antimicrobial Drug Products within the OTC Drug Review. As mentioned above, pending a final monograph, the agency does not object to marketing OTC drugs that meet the formulation and labeling conditions described in the relevant TFM or that are otherwise eligible for inclusion in the OTC Drug Review. However, your product does not follow the formulation and labeling conditions described in the TFM. Products that are not marketed according to the conditions of the TFM and are not generally recognized as safe and effective by qualified experts would require an approved new drug application.

CGMP consultant recommended

We acknowledge that your firm has engaged a consultant to assist your firm in meeting CGMP requirements. Based upon the nature of the violations we identified at your firm, and your failure to correct repeat violations, we strongly recommend engaging a consultant qualified as set forth in 21 CFR 211.34 to assist your firm in meeting CGMP requirements. Your use of a consultant does not relieve your obligation to comply with CGMP. Your firm’s executive management remains responsible for fully resolving all violations and ensuring ongoing CGMP compliance.

Evaluating OOS results

Your program for handling OOS result is among the areas that should be reviewed by your consultant. For example, Aplicare General Procedure 7.9M, Packaging Machine Fill Pump Cleaning Validation, appears to permit averaging of discrete cleaning validation sample test results if the initial results are not within the specified criteria

Your laboratory should report each individual chemical test result, not averaged results, for your quality control unit to evaluate and consider. For guidance on evaluating out-of-specification test results, see FDA’s guidance document, Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production, at http://www.fda.gov/downloads/Drugs/.../Guidances/ucm070287.pdf.

In response to this letter, conduct a global assessment of your standard operating procedures to ensure that discrete sample results are considered separately. Provide us with a summary of the results of this assessment. In addition, provide the revised AGP 7.9M with evidence that you have trained your staff on the revised procedure.

Conclusion

Violations cited in this letter are not intended as an all-inclusive list. You are responsible for investigating these violations, for determining the causes, for preventing their recurrence, and for preventing other violations.

If you are considering an action that is likely to lead to a disruption in the supply of drugs produced at your facility, FDA requests that you contact CDER's Drug Shortages Staff immediately, at drugshortages@fda.hhs.gov, so that FDA can work with you on the most effective way to bring your operations into compliance with the law. Contacting the Drug Shortages Staff also allows you to meet any obligations you may have to report discontinuances or interruptions in your drug manufacture under 21 U.S.C. 356C(b) and allows FDA to consider, as soon as possible, what actions, if any, may be needed to avoid shortages and protect the health of patients who depend on your products.

Correct the violations cited in this letter promptly. Failure to promptly correct these violations may result in legal action without further notice including, without limitation, seizure and injunction. Unresolved violations in this warning letter may also prevent other Federal agencies from awarding contracts.

Until you completely correct all violations and we confirm your compliance with CGMP, FDA may withhold approval of any new applications or supplements listing your firm as a drug product manufacturer.

After you receive this letter, respond to this office in writing within 15 working days. Specify what you have done since our inspection to correct your violations and to prevent their recurrence. If you cannot complete corrective actions within 15 working days, state your reasons for delay and your schedule for completion.

Send your reply to:

Maya M. Davis, Compliance Officer
U.S. Food and Drug Administration
New England District Office
One Montvale Avenue
Stoneham, MA 02180

If you have any questions, contact Ms. Davis at (860) 240-4289 or Maya.Davis@fda.hhs.gov.

Please identify your response with CMS 489281.

Sincerely,
/S/
Joseph Matrisciano, Jr.
District Director
New England District Office

Cc:
Mr. Benno Dorer, CEO
The Clorox Company
1221 Broadway
Oakland, CA 94612

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1 Labels for these products include the website, www.aplicare.com, which redirects users to https://www.cloroxprofessional.com/industry/health/overview/.

2 Once a final monograph becomes effective, it may be necessary to reformulate and/or relabel such products to conform to its requirements, or, in the alternative, to seek FDA approval of a new drug application (NDA) under section 505 of the FD&C Act. (21 U.S.C. 355)