WARNING LETTER

Polimeros y Servicios S.A.

MARCS-CMS 586323 — AUGUST 22, 2019

Delivery Method:

VIA UPS

Product:

Drugs

Recipient:

Dr. Enrique Feoli

Technical Director

Polimeros y Servicios S.A.

Parque Industrial Condal
Calle Pantano
Tibas, San Jose 11305
Costa Rica

Issuing Office:

Center for Drug Evaluation and Research

10903 New Hampshire Avenue
Silver Spring, MD 20993
United States

Warning Letter 320-19-39

August 22, 2019

Dear Dr. Feoli:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Polimeros y Servicios S.A. at Parque Industrial Condal, Calle Pantano, Tibas, San Jose, from February 4 to 8, 2019.

This warning letter summarizes significant violations of current good manufacturing practice (CGMP) regulations 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 March 1, 2019, response in detail.

During our inspection, our investigator observed specific violations including, but not limited to, the following.

1. Your firm failed to have, for each batch of drug product, appropriate laboratory determination of satisfactory conformance to final specifications for the drug product, including the identity and strength of each active ingredient, prior to release (21 CFR 211.165(a)).

Your firm manufactures and distributes topical analgesic, antifungal, acne, and skin protectant creams and **(b)(4)** for the U.S. market. Our inspection found that you did not test your over-the-counter (OTC) finished drug products to determine whether each batch meets identity and strength of active ingredient specifications before releasing those drug products to the U.S. market.

Complete testing of each batch before release is essential to determine if the drug products you manufacture meet appropriate specifications.
In your response, you stated that you will use a third-party testing laboratory to test for identity of the active ingredient in finished products using the analytical method established for accelerated stability testing. You also shared that you have initiated discussion with this third-party laboratory to perform purity testing of the final drug product.
Your response is inadequate because you did not include information about your third-party testing laboratory including procedures, methods, or a detailed description of the tests they will conduct (e.g., identity, strength and purity).
In response to this letter, provide:

- A list of all analytical test methods and specifications used to analyze each batch of your drug products before making the batch disposition decision. Include associated written procedures.
- A summary of test results obtained from retrospective testing of retain samples of all drug product batches currently in distribution in the United States. Include test results for identity and strength of active ingredients, and all other appropriate chemical and microbial quality attributes. If you released any batch that was out of specification, indicate the corrective actions you will take, such as customer notifications and product recalls.
- A comprehensive and independent review of your laboratory practices, procedures, methods, equipment, and analyst competencies. Based on this review, provide a detailed corrective action and preventive action (CAPA) plan to fully remediate your laboratory system. Your plan should also include the procedures you will use to evaluate the effectiveness of the implemented CAPA.
- Your procedure to ensure that any test methods performed by a contract testing laboratory on your behalf are properly validated before use.

2. Your firm failed to conduct at least one test to verify the identity of each component of a drug product. Your firm also failed to validate and establish the reliability of your component supplier's test analyses at appropriate intervals (21 CFR 211.84(d)(1) and (2)).

You failed to test incoming active pharmaceutical ingredients (API) and other raw materials used to manufacture drug products to determine their identity, purity, strength, and other appropriate quality attributes. Instead, your firm released API and other materials for use in manufacturing based solely on component suppliers' analyses reports without

establishing the reliability of your suppliers' analyses through appropriate validation. Your firm did not ensure that at least one specific identify test was conducted for each lot.

In your response, you stated your intent is to test the identity of raw materials using compendial monographs. You requested a six-month extension to establish identity testing either in-house or through a contract analytical testing laboratory. We acknowledge your attempt to set up a supplier qualification program.

Your response is inadequate because you did not commit to cease manufacturing of drugs until you have implemented required identity testing of raw materials prior to use in manufacturing, and you did not conduct a risk assessment for products already in distribution in the United States. You also did not provide an adequate procedure to establish the reliability of your suppliers' analyses.

In response to this letter, provide:

- The chemical and microbiological quality control specifications you will use to determine disposition of each incoming lot of components before use in manufacturing.
- A description of how you will test each component lot for conformity with all appropriate specifications for identity, strength, quality, and purity. If you intend to accept any testing results on your suppliers' certificates of analysis (COA) in lieu of testing each component lot for purity, strength, and quality, specify how you will first establish the reliability and consistency of your suppliers' test results for these attributes through initial validation (followed by periodic re-validation).
- A summary of test results obtained from full testing of all components to evaluate the reliability of the COA from each component manufacturer. Include your standard operating procedure that describes this COA validation program.
- A comprehensive, independent review of your material system to determine whether all containers, closures, and ingredients from each supplier are adequately qualified, assigned appropriate expiration or retest dates, and have incoming material controls adequate to prevent use of unsuitable containers, closures, and components.

3. Your firm failed to assure that the drug product bore an expiration date that was supported by appropriate stability testing (21 CFR 211.137(a)).

You firm has not established an adequate stability program. You lack data to demonstrate that the chemical, physical, and microbiological properties of your OTC drug products will remain acceptable throughout their labeled three-year expiry period.

In your response, you acknowledged that you had only conducted acclereated stability analysis on one of your drug product's process validation batches and stated that a third party will perform the accelerated stability testing of Klearactil Acne Treatment, but that testing for other drug products, which you have already distributed, will not be completed until 2020 due to financial constraints. You also note in your response that your Klearactil process validation samples placed on accelerated stability had technical issues regarding mixing methods and that you would need to prepare new material to support process validation requirements.

Your response is inadequate because you failed to provide stability protocols, including all relevant quality attributes and acceptance criteria, and you did not provide assurance that your test methods will indicate adequate stability. In addition, you did not indicate any actions taken to ensure that distributed drug products maintain their quality attributes through their labeled expiry. You also failed to provide a detailed process performance qualification protocol and a program for ensuring maintenance of a validated process throughout the product lifecycle.

In response to this letter, provide:

- A comprehensive, independent assessment and CAPA plan to ensure the adequacy of your stability program. Your CAPA plan should include, but not be limited to:

    - A remediated SOP describing your stability program

- Stability indicating methods
- Stability studies for each drug product in its container-closure system before distribution is permitted
- An ongoing program in which representative batches of each product are added each year to the program to determine if the shelf-life claim remains valid

- Specific attributes to be tested at each station

- A validation plan for ensuring a state of control throughout the product lifecycle. Include a timeline for performing appropriate process performance qualification (PPQ) for each of your drug products. Describe your program for monitoring batch-to-batch variation to ensure an ongoing state of control. See FDA's guidance document *Process Validation: General Principles and Practices* for general principles and approaches that FDA considers appropriate elements of process validation at https://www.fda.gov/media/71021/download (https://www.fda.gov/media/71021/download).

4. Your firm failed to establish and follow adequate written procedures for cleaning and maintenance of equipment (21 CFR 211.67(b)).

Your firm uses non-dedicated equipment to manufacture multiple topical OTC drug products without validated cleaning processes to prevent cross-contamination between products. In addition, your equipment cleaning protocol lacks sufficient detail to allow consistent, effective cleaning.
In your response, you provided an updated copy of your equipment cleaning procedure and you acknowledged that cleaning validation has not been completed.
Your response is inadequate because you failed to provide cleaning validation protocols for your shared manufacturing equipment and the timeframe to complete execution. The updated equipment cleaning procedure provided in your response is inadequate in its level of detail.
In response to this letter, provide:

- A comprehensive plan to evaluate cleaning procedures and practices and validation studies for each piece of manufacturing equipment used to manufacture more than one product.
- Scientific rationale for your cleaning validation strategy to ensure your cleaning procedures are effective.
- A copy of your cleaning validation protocols.
- A summary of updated SOPs that ensure an appropriate program is in place for verification and validation of cleaning procedures for new products, processes, and equipment.

Quality Systems Guidance

Your firm's quality systems are inadequate. See FDA's guidance document *Quality Systems Approach to Pharmaceutical CGMP Regulations* for help implementing quality systems and risk management approaches to meet the requirements of CGMP regulations 21 CFR, parts 210 and 211 at https://www.fda.gov/media/71023/download (https://www.fda.gov/media/71023/download).

CGMP Consultant Recommended

Based upon the nature of the violations we identified at your firm, we strongly recommend engaging a consultant qualified as set forth in 21 CFR 211.34 to assist your firm in meeting CGMP requirements if your firm intends to resume manufacturing drugs for the U.S. market. We also recommend that the qualified consultant perform a comprehensive audit of your entire operation for CGMP compliance and that the consultant evaluates the completion and efficacy of your corrective actions and preventive actions before you pursue resolution of your firm's compliance status with FDA.

Your use of a consultant does not relieve your firm's obligation to comply with CGMP. Your firm's executive management remains responsible for resolving all deficiencies and systemic flaws to ensure ongoing CGMP compliance.

Repeat Observations

FDA cited similar CGMP violations in an April 2017 inspection. You proposed specific remediation for these violations in your response. Repeated failures demonstrate that executive management oversight and control over the manufacture of drugs is inadequate.

Unapproved New Drug and Misbranding Charges

"BIOACTIL PAIN RELIEVING GEL"

"BIOACTIL PAIN RELIEVING GEL" 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 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 it is intended to affect the structure or any function of the body. Specifically, this product is intended for use as an external analgesic.

The printed label for "BIOACTIL PAIN RELIEVING GEL" includes the product website www.med-actil.com (http://www.med-actil.com) (http://www.fda.gov/about-fda/website-policies/website-disclaimer). Claims on the product label and labeling which establish the intended uses (as defined in 21 CFR 201.128) of the product include, but may not be limited to, the following:

Label Claims

"PAIN RELIEVING GEL . . . Arthritis • Sprains & Strains . . . Exercise Empowerment . . . Workout Recovery"

Website Claims

"Exercise enhancement . . . Post exercise recovery . . . Tendonitis . . . FIBROMYALGIA pain . . . healing properties . . . Bioactil creates a healthy cellular micro-environment to allow new healthy cell regeneration and cell reproduction . . . Uses Backaches, stiffness, swelling, strains, sprains . . ."

OTC drug products such as "BIOACTIL PAIN RELIEVING GEL" that are intended for external analgesic indications such as the relief of pain are being evaluated as part of the OTC Drug Review. They have been proposed to be classified as generally recognized as safe and effective and not misbranded under the Tentative Final Monograph (TFM) for External Analgesic Drug Products for OTC Human Use (48 Federal Register (FR) 5852, February 8, 1983) if they meet each condition in the TFM and each general condition in 21 CFR 330.1.

Pending the promulgation of a final rule, FDA generally does not intend to pursue regulatory action against products marketed in accordance with the conditions proposed in the TFM and each general condition in 21 CFR 330.1 unless a particular product poses a public health concern. Such marketing, however, is subject to the risk that a final rule may require reformulation and/or relabeling or FDA approval through the new drug procedures of the FD&C Act (section 505). However, "BIOACTIL PAIN RELIEVING GEL" does not meet these conditions for the reasons explained below.

The labeling for "BIOACTIL PAIN RELIEVING GEL" is not consistent with the conditions proposed for external analgesic drug products. See External Analgesic TFM 48 FR 5852, February 8, 1983. The product labeling includes indications such as "Exercise Empowerment . . . Workout Recovery" on the label and "Exercise enhancement . . . Post exercise recovery . . . Tendonitis . . . FIBROMYALGIA pain . . . healing properties . . ." on the website that are not proposed under this rulemaking, or any rulemaking being considered under the OTC Drug Review.

Furthermore, we are not aware of any adequate and well controlled clinical trials in the published literature that support a determination that "BIOACTIL PAIN RELIEVING GEL" is generally recognized as safe and effective for its labeled indications. Additionally, we are not aware of a similar OTC product as formulated and labeled that was available in the United States market on or before the inception of the OTC Drug Review.

"BIOACTIL PAIN RELIEVING GEL," as labeled, is therefore a new drug within the meaning of section 201(p) of the FD&C Act because it is not generally recognized among scientific experts as safe and effective for the drug uses described in its labeling. New drugs may not be introduced or delivered for introduction into interstate commerce unless an application approved by FDA under section 505 of the FD&C Act is in effect for the drug. "BIOACTIL PAIN RELIEVING GEL" is not the subject of an approved new drug application; therefore, marketing this product 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 of the FD&C Act.

"BIOACTIL PAIN RELIEVING GEL" is misbranded within the meaning of section 502(c) of the FD&C Act, 21 U.S.C. 352(c) because the label fails to bear a complete statement of identity as required under 21 CFR 201.61. In the case of a drug that has an established name, the statement of identity must contain the established name and the general pharmacological action(s) or principal intended action(s) of the drug in the principal display panel. The label for this product fails to include the established name of the drug, menthol, as part of the statement of identity on the product's principal display panel.

The introduction or delivery for introduction of a misbranded drug into interstate commerce is prohibited under section 301(a) of the FD&C Act, 21 U.S.C. 331(a). Therefore, the marketing of "BIOACTIL PAIN RELIEVING GEL" violates this provision of the FD&C Act.

"keractil plus ANTIFUNGAL GEL"

As defined by section 201(g)(1)(B) of the FD&C Act, 21 U.S.C. 321(g)(1)(B), "keractil plus ANTIFUNGAL GEL" is a drug because it is 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 it is intended to affect the structure or any function of the body. Specifically, this product is intended for use as a topical antifungal.

The printed label for "keractil plus ANTIFUNGAL GEL" includes the product website www.med-actil.com (http://www.med-actil.com) (http://www.fda.gov/about-fda/website-policies/website-disclaimer). Claims on the product label and labeling which establish the intended uses (as defined in 21 CFR 201.128) of the product include, but may not be limited to, the following: product include, but may not be limited to, the following:

Label Claims

"ANTIFUNGAL GEL . . . Cures fungus infections of the toes and fingers, including skin under and around nails, tinea pedis (athlete's foot), and tinea corporis (ringworm)"

Website Claims

"Antifungal . . . effective product for eliminating fungus . . . TESTIMONIALS . . . I have been fighting nail fungus for years; seems like I've tried everything. I've been using Keractil for a month and it has finally put a halt to the fungus . . . GOODBYE NAIL FUNGUS!"

OTC drug products intended for use as topical antifungals on the nails, such as "keractil plus ANTIFUNGAL GEL," are subject to the Final Rule for Topical Antifungal Drug Products under 21 CFR 310.545(a)(22)(iii). Under this final rule, any ingredient(s) labeled with claims or directions for use on the scalp or on the nails is regarded as a new drug within the meaning of section 201(p) of the FD&C Act for which an approved application is required for marketing.

As a new drug, “keractil plus ANTIFUNGAL GEL” may not be legally marketed in the United States absent approval of an application filed in accordance with section 505(a) of the FD&C Act, 21 U.S.C. 355(a). “keractil plus ANTIFUNGAL GEL” is not the subject of an FDA-approved application, and therefore, the current marketing of this product violates section 505(a) of the FD&C Act, 21 U.S.C. 355(a). Introduction or delivery for introduction of such product into interstate commerce is prohibited under section 301(d) of the FD&C Act, 21 U.S.C. 331(d).

Within the meaning of section 502(c) of the FD&C Act, 21 U.S.C. 352(c), “keractil plus ANTIFUNGAL GEL” is misbranded because its label fails to bear a complete statement of identity on the principal display panel as required under 21 CFR 333.250(a). For topical antifungal drug products such as “keractil plus ANTIFUNGAL GEL,” the statement of identity must contain the established name and identify the product as an antifungal. This product fails to include the established name, tolnaftate, as part of the statement of identity on the product’s principal display panel.

The introduction or delivery for introduction of a misbranded drug into interstate commerce is prohibited under section 301(a) of the FD&C Act, 21 U.S.C. 331(a). Therefore, the marketing of “keractil plus ANTIFUNGAL GEL” violates this provision of the FD&C Act.

“KLEARACTIL Acne Treatment”

“KLEARACTIL Acne Treatment” 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 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 it is intended to affect the structure or any function of the body. Specifically, this product is intended for use as a topical acne drug product.

The printed label for “KLEARACTIL Acne Treatment” includes the product website www.med-actil.com (http://www.med-actil.com) (http://www.fda.gov/about-fda/website-policies/website-disclaimer). Claims on the product label and labeling which establish the intended uses (as defined in 21 CFR 201.128) of the product include, but may not be limited to, the following:

Label Claims

“Acne Treatment . . . Clears acne pimples, acne blemishes, blackheads and whiteheads . . .”

OTC drug products intended for use as topical acne products, such as “KLEARACTIL Acne Treatment,” must comply with all of the requirements of section 502 of the FD&C Act and all pertinent regulations found in Title 21 of the Code of Federal Regulations (21 CFR). However, “KLEARACTIL Acne Treatment” does not meet these requirements for the reasons described below.

“KLEARACTIL Acne Treatment” is misbranded within the meaning of section 502(c) of the FD&C Act, 21 U.S.C. 352(c), because its label fails to bear a complete statement of identity on the principal display panel, as required under 21 CFR 333.350(a). For topical acne drug products, such as “KLEARACTIL Acne Treatment,” the statement of identity must contain the established name, followed by either the description “acne medication” or “acne treatment” and then the dosage form. Specifically, the label fails to include the established name, salicylic acid, as part of the statement of identity on the product’s principal display panel.

The introduction or delivery for introduction of a misbranded drug into interstate commerce is prohibited under section 301(a) of the FD&C Act, 21 U.S.C. 331(a). Therefore, the marketing of “KLEARACTIL Acne Treatment” violates this provision of the FD&C Act.

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.

FDA placed your firm on Import Alert 66-40 on July 11, 2019.

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

Failure to correct these violations may also result in FDA continuing to refuse admission of articles manufactured at Polimeros y Servicios S.A. located at Parque Industrial Condal, Calle Pantano, Tibas, San Jose, Costa Rica into the United States under section 801(a)(3) of the FD&C Act, 21 U.S.C. 381(a)(3). Under the same authority, articles may be subject to refusal of admission, in that the methods and controls used in their manufacture do not appear to conform to CGMP within the meaning of section 501(a)(2)(B) of the FD&C Act, 21 U.S.C. 351(a)(2)(B).

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 electronic reply to CDER-OC-OMQ-Communications@fda.hhs.gov (mailto:CDER-OC-OMQ-Communications@fda.hhs.gov) or mail your reply to:

Carlos M. González

Compliance Officer

U.S. Food and Drug Administration

White Oak Building 51, Room 4359

10903 New Hampshire Avenue

Silver Spring, MD 20993

USA

Please identify your response with FEI 3011778211.

Sincerely,

/S/

Francis Godwin

Director

Office of Manufacturing Quality

Office of Compliance

Center for Drug Evaluation and Research

More Warning Letters (/inspections-compliance-enforcement-and-criminal-investigations/compliance-actions-and-activities/warning-letters)