Inspections, Compliance, Enforcement, and Criminal Investigations

Laclede Inc 2/14/13

Department of Health and Human Services

Public Health Service
Food and Drug Administration
Los Angeles District
19701 Fairchild
Irvine, CA 92612-2506
Telephone: 949-608-2900
FAX: 949-608-4417

WARNING LETTER

VIA UNITED PARCEL SERVICE
SIGNATURE REQUIRED

February 14, 2013

WL# 23-1

Mr. Michael A. Pellico, President
Laclede, Inc.
2103 E. University Dr.
Rancho Dominguez, CA 90220

Dear Mr. Pellico:

During our June 19, 2012 through June 27, 2012, inspection of your facility at 2103 E. University Dr., Rancho Dominguez, California, an investigator from the Food and Drug Administration (FDA) identified significant violations of the 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(s) 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. In addition, this inspection also revealed that your firm is manufacturing and marketing an unapproved and misbranded over-the-counter (OTC) drug product, the drug component of the Luvena Prebiotic Vaginal Moisturizer & Lubricant (Luvena Prebiotic) combination product, in violation of sections 301(a) and (d), 505(a), 502(c), and 502(e)(1)(A)(ii) and (iii) of the Act [21 U.S.C. §§ 331(a) and (d), 355(a), 352(c), and 352(e)(1)(A)(ii) and (iii)]; and that your firm is manufacturing and marketing two unapproved topical fluoride prescription drug products, in violation of sections 301(d) and 505(a) of that Act [21 U.S.C. §§ 331(d) and 355(a)].

We have reviewed your firm's responses to the Los Angeles District office dated July 2, 2012 and July 16, 2012, and note that they lack sufficient corrective actions.

CGMP Violations

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

1. Your firm does not 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)

For example, your firm has not tested, and has not established requirements to test active ingredients, such as lactoferrin, lactoperoxidase, lysozyme, D-mannose, and glycogen contained in the Luvena Prebiotic product, prior to release.

In your response, you state that test methods do not exist for lactoferrin, lactoperoxidase, lysozyme, D-mannose, and glycogen in the finished dosage form in any compendia. In addition, you suggest that these components are not active ingredients, and you state that your firm will not start testing these active ingredients until after you meet with FDA and have established testing methods. Your response is insufficient. FDA identified these components as active ingredients of your Luvena Prebiotic product in its May 15, 2012 letter responding to your Request for Designation (RFD 120017). Your firm has failed to propose, in any detail, your intentions for past and future production lots, or a timeframe for implementing the required testing of active ingredients.

2. Your firm failed to establish and follow an adequate written testing program designed to assess the stability characteristics of drug products and to use results of such stability testing to determine appropriate storage conditions and expiration dates. 21 CFR § 211.166(a)

For example, your firm's stability test procedure for Luvena Prebiotic includes testing for color, odor/taste, appearance, pH, and microbial testing. However, your firm failed to establish stability-indicating test methods for lactoferrin, lactoperoxidase, lysozyme, D-mannose, and glycogen. As a result, your firm continues to market product with unknown potency or purity throughout the expiry period that you claim.

Your response to this CGMP violation is virtually identical to your response regarding your violation of 21 CFR § 211.165(a): you state that test methods do not exist for these components, you question whether they are active ingredients, and you state that your firm will not start testing these active ingredients until after you meet with FDA and have established testing methods. Your response is unacceptable. Under CGMP, you are required to have adequate stability testing data to support appropriate storage conditions and expiration dates.

3. Your firm failed to conduct at least one specific identity test on a component when relying on that component supplier's analysis, and failed to establish the reliability of the component supplier's analyses through appropriate validation of the supplier's test results at appropriate intervals. 21 CFR § 211.84(d)(2)

You have not adequately tested incoming components to determine if they are suitable for use in your drug products. CGMP generally requires full testing of each component for conformity with all appropriate written specifications for purity, strength, and quality, except that you may rely on a supplier's Certificate of Analysis provided that you conduct at least one specific identity test of the component and you have established the reliability of that supplier's analyses through an ongoing program to validate the supplier's test results at appropriate intervals.

In your response, you explain that your testing was incomplete where test methods were supplier-specific and no compendial test methods were available. However, these facts do not relieve your firm of its duty to establish that the ingredients in your products meet their required specifications. We acknowledge your commitment to identify the required tests and revise your standard operating procedure "to indicate this full testing requirement on all the materials annually." However, your response is inadequate because you do not explain how you will identify the required tests, nor do you provide a timeframe for developing and implementing test methods. Your response thus does not provide sufficient assurance that your drug product components meet all required specifications prior to their release for use.

Unapproved New Drug and Misbranding Violations:

In addition to violating CGMP, you violate the Act by manufacturing and marketing both OTC and prescription drug products without an approved application. We informed you on several occasions between September 2010 and May 17, 2012, that an approved new drug application (NDA) is required for you to legally market the OTC product, Luvena Prebiotic, in the United States. Notably, in our May 15, 2012, letter responding to your Request for Designation (RFD 120017), we notified you that Luvena Prebiotic, as formulated and labeled, is a combination product within the meaning of section 503(g) of the Act, consisting of a device (applicator) and drug (gel containing lactoferrin, lactoperoxidase, lysozyme, D-mannose, and glycogen) components, that the Center for Drug Evaluation and Research (CDER) is the lead Agency center for its premarket review and regulation, and that an NDA is necessary for you to legally market Luvena Prebiotic. In responding to your subsequent correspondence to the Agency, we have repeatedly reminded you of this designation.

During the inspection noted above, our investigator collected labeling for Luvena Prebiotic and noted that you continue to distribute that product without an approved NDA, in violation of the Act. A review of your labeling, which includes your website, www.luvenacare.com, demonstrates that as presently formulated, labeled, and promoted, the drug component of Luvena Prebiotic remains an unapproved and misbranded drug in violation of sections 301(a) and (d), 505(a), 502(c), and 502(e)(1)(A)(ii) and (iii) of the Act [21 U.S.C. §§ 331(a) and (d), 355(a), 352(c), and 352(e)(1)(A)(ii) and (iii)] as described below.

The following are examples of intended uses described in the labeling for this product:

From the package label ("20011511C")

- "Certified Natural & Restorative Prebiotic"
- "Provides Anti-Yeast Proteins + Natural Antibacterial Enzymes"
- "Causes of Vaginal Dryness / Changes: . . . Menopause . . . Antibiotics and Medications . . . Douching . . . Diabetes . . . Contraceptives . . . Autoimmune Disorders."

From your website, www.luvenacare.com

- "Why Women Need LUVENA® PreBiotic Moisturizer & Lubricant: Diabetes…Chemotherapy…Vaginosis…Yeast Infections…Compromised Immune System: Sjogrens. . .."

References found on your website to the following articles:

- "Methods and composition for the treatment of vaginal diseases employing peroxide-producing enzymes and peroxidases."
- "Preliminary evaluation of a vaginal cream containing lactoferrin in the treatment of vulvovaginal candidosis."
- "Sjogren's Syndrome"
- "Killing of Gram-negative Bacteria by Lactoferrin and Lysozyme"
- "Probiotics: Potential to Prevent HIV and Sexually Transmitted Infections in Women."

From your package insert

- "HOW LUVENA WORKS: LPG Bio-Enzyme System (Lactoperoxidase, Lysozyme, Lactoferrin) to correct the natural vaginal flora by inhibiting harmful bacteria.
- "Helps Prevent The Causes Of Vaginosis, Yeast Infection and Bad Odor."

Based on the above labeling claims, the gel component of Luvena Prebiotic is a "drug" as defined by section 201(g)(1) of the Act [21 U.S.C. § 321(g)(1)], because it is intended for use in the cure, mitigation, treatment, or prevention of disease, and/or because it is intended to affect the structure or any function of the body of man.

Lubricants and vaginal moisturizers are being evaluated under the OTC Drug Review. The Call for Data notice issued on December 31, 2003, for categories of ingredients including lubricants and vaginal moisturizers (68 FR 75586, 75588-89), is part of this evaluation. However, this notice does not include products that are intended as a probiotic and for uses such as vaginal yeast infections, Sjögrens Syndrome, prevention of HIV and sexually transmitted infections, nor does the notice cover vaginal dryness for specific reasons such as menopause, antibiotics and medications, douching, diabetes, contraceptives and/or autoimmune disorders. Furthermore, we are not aware of any evidence demonstrating that your product or a similarly formulated and labeled product is eligible for inclusion in the OTC Drug Review, nor are we aware of any information demonstrating your product is generally recognized as safe and effective as formulated and labeled. Therefore, your product is subject to the new drug provisions of section 505 of the Act, [21 U.S.C. § 355] and requires a new drug application (NDA) to be legally marketed in the United States. Under sections 301(d) and 505(a) of the Act [21 U.S.C. §§ 331(d) and 355(a)], a new drug may not be introduced or delivered for introduction into interstate commerce unless an FDA-approved application is in effect for it.

In addition, Luvena Prebiotic is misbranded under sections 502(c) of the Act, [21 U.S.C. § 352(c)] because the product does not contain required labeling in accordance with 21 CFR § 201.66. For instance, your product's labeling lacks a "Drug Facts" panel. Luvena Prebiotic is also misbranded under section 502(e)(1)(A)(ii) and (iii) of the Act, [21 U.S.C. 352(e)(1)(A)(ii) and (iii)] because its label fails to distinguish between its active and inactive ingredients. Specifically, lactoferrin, lactoperoxidase, lysozyme, D-mannose, and glycogen are promoted on your website, your outer package container, and your package insert in such a manner as to suggest that they are "active ingredients," as described i 21 CFR 201.66(b)(2). The introduction or delivery for introduction of a misbranded drug into interstate commerce is prohibited under section 301(a) of the Act [21 U.S.C. § 331(a)]. Therefore, the marketing of Luvena Prebiotic in the United States violates this provision of the Act.

Furthermore, you manufacture and distribute prescription drugs without an approved application at your facility at 2103 E. University Dr., Rancho Dominguez, CA 90220. These drugs are unapproved new drugs, and by introducing them into interstate commerce you are in violation of sections 301(d) and 505(a) of the Act [21 U.S.C. §§ 331(d) and 355(a)]. Based on the information your firm submitted to FDA's Drug Registration and Listing System and the information collected during the inspection, these unapproved prescription drugs include, but are not limited to, the following:

- One Minute Topical Fluoride Foam, Acidulated Phosphate Fluoride Solution containing 1.23% Fluoride Ion (pH 3.5), Bumble Bee Bubble Gum flavor, 5.8 oz (165 g)
- Oral-B Minute-Foam Topical Fluoride Foaming Solution, Acidulated Phosphate Fluoride Solution containing 1.23% Fluoride Ion, Strawberry flavor, 5.8 oz (165 g)

To ensure that all prescription and over-the-counter drugs marketed in the United States have been shown to be safe and effective, FDA published a Compliance Policy Guide (CPG) Section 440.100, Marketed Unapproved Drugs.**[1]** The CPG outlines the Agency's enforcement policies aimed at efficiently and rationally bringing all drugs requiring approved applications into the approval process without adversely affecting public health, imposing undue burdens on consumers, or unnecessarily disrupting the market. We highly encourage you to contact FDA's unapproved drugs coordinator, Dr. Sally Loewke, at 301-796-0710, for assistance in communicating with the FDA on the application process for your unapproved prescription drugs.

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 active pharmaceutical ingredients produced by your manufacturing facility, FDA requests that you contact CDER'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. In your response to this letter, indicate the name and address of any other manufacturer, distributor, or supplier of these products, and, if you are no longer marketing these products, indicate your progress in updating the Dru Listing files in accordance with 21 CFR 207.30(a)(2).

The violations 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 th 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 of distribute any of the drug products manufactured at this facility, and provide the date(s) and reason(s) you ceased production.

Your reply should be sent to the following address:

Mr. Blake Bevill
Director, Compliance Branch
U.S. Food and Drug Administration
19701 Fairchild
Irvine, CA 92612-2506

If you have questions regarding this letter, please contact Ms. Jessica Mu, Compliance Officer, at 949-608-4477, or via e-mail to Jessica.Mu@fda.hhs.gov.

Sincerely,
/S/
Alonza E. Cruse, Director
Los Angeles District

Cc:
Patrick Kennelly, Acting Branch Chief

California Department of Public Health
Food and Drug Branch
PO Box 997435
1500 Capitol Avenue, MS-7602
Sacramento, CA 95899-7413
Attn: FDA correspondence

[1] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070290.pdf[1]

Page Last Updated: 09/13/2013
Note: If you need help accessing information in different file formats, see Instructions for Downloading Viewers and Players.

Links on this page:

1. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070290.pdf