Inspections, Compliance, Enforcement, and Criminal Investigations

Jabones Pardo S.A. 8/22/13

Department of Health and Human Services

Public Health Service
Food and Drug Administration
Silver Spring, MD 20993

Warning Letter

WL: 320-13-25

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

August 22, 2013

Mr. Miguel Pardo Rodriguez, General Manager
Jabones Pardo S.A.
Sierra Nevada, 1
Fuenlabrada 28946, Madrid, Spain

Dear Mr. Rodriguez:

During our March 11 – 14, 2013 inspection of your pharmaceutical manufacturing facility, Jabones Pardo S.A. located at Sierra Nevada, 1, Fuenlabrada, Madrid, Spain, an investigator from the U.S. 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 products 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.

Our inspection also revealed that your firm failed to fulfill its registration obligations under Section 510(i)(1) of the Act and its listing obligations under Sections 510(i)(2) and 510(j), which is prohibited under Section 301(p). 21 U.S.C. 360(i)(1) and (2), 360(j), and 331(p).

We acknowledge receipt of your firm's correspondence dated April 22, 2013.

Our investigator(s) observed specific violations during the inspection, including, but not limited to, the following:

CGMP Violations

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 failed to test its products for the identity and strength of each active ingredient prior to release. The investigator obtained certificates of analyses (COAs) for your drug products showing your firm did not perform identity and strength testing for the release of these over-the-counter

(OTC) drug products: **(b)(4)**, *Le'dermis Skin Solutions Anti-Acne Medicated Cream, and* **(b)(4)** distributed to the US market. For those drug products, your firm failed to test for the active ingredients **(b)(4)**%, **(b)(4)**%, Salicylic Acid 1%, and Octinoxale 1%.

Additionally, you failed to perform antimicrobial effectiveness testing on your drug products, in accord with United States Pharmacopeia <51>.

In response to this letter, state whether your firm has established test methods for identity and strength of the specific active pharmaceutical ingredients (APIs), including documentation showing that your firm has validated those methods and performed antimicrobial effectiveness testing. In addition to the above, indicate dates of training for each of these new practices and procedures. Provide completion dates for all corrections.

2. Your firm failed to test samples of each component for conformity with all appropriate written specifications for purity, strength, and quality. Also, your firm failed to establish the reliability of the component supplier's analyses through appropriate validation of the supplier's test results at appropriate intervals. As well, your firm failed to conduct at least one specific identity test on a component when relying on that component supplier's analysis (21 CFR 211.84(d)(2)).

For example, your firm does not perform at a minimum one specific identity test on each incoming lot of components, including, but not limited to, **(b)(4)**, **(b)(4)**, and salicylic acid APIs. You also rely on the suppliers' certificates of analyses although you have not established the reliability of their analyses through appropriate validation of their test results.

In your response to this letter, describe procedures for conducting at least one specific identity test for each incoming lot of components before releasing it for use in your finished drug products. Include a description of your sampling procedure for raw materials and the number of samples tested for each incoming lot. Provide documentation that demonstrates your firm has performed method validation for each test method. Provide test results for your reserve samples, within retention period, of each lot of API that you used in the manufacture of finished drug products distributed to the U.S. market. Additionally, include your API supplier qualification procedures and results.

3. 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)).

Your firm failed to establish and follow an appropriate testing program to assess stability characteristics of your drug products, **(b)(4)**, *Le'dermis Skin Solutions Anti-Acne Medicated Cream, and* **(b)(4).** For example, your stability procedure fails to specify the sample size for stability and the long-term stability storage conditions. In addition, your firm failed to perform assay testing during the stability study. Your quality unit did not adequately ensure that the drug products released to the market were supported by appropriate stability data.

In response to this letter, provide evidence that you have evaluated the stability program for its adequacy. Generate proper expiration dates for your drug products using a scientifically sound stability program. Provide completion dates for all corrections.

4. Your firm's quality control unit failed to review and approve all drug product production and control records to determine compliance with all established, approved written procedures before a batch is released or distributed (21 CFR 211.192).

For example, your firm's quality unit failed to adequately review and approve your firm's production and control records. There is no assurance that the quality unit fully reviewed and approved all batch-related documentation prior to release of finished product to the U.S. market. Specifically, your firm distributed the following lots to the U.S. market without adequate review: **(b)(4)** lot **(b)(4)**, **(b)(4)** lot **(b)(4)**, **(b)(4)** lot **(b)(4)** and **(b)(4)** *and Le'dermis Skin Solutions Anti-Acne Medicated Cream lot 130058.*

In response to this letter, provide your corrective actions to improve your quality unit's release and approval processes. Additionally, provide evidence of a retrospective documentation review of all drug

products distributed to the U.S. within the last three years to determine those products' compliance with all established written procedures, identify any information gaps in the records, and ensure any deviations and atypical events are investigated. Provide completion dates for all corrections.

5. Your firm failed to routinely calibrate, inspect, or check according to a written program designed to assure proper performance and to maintain adequate written records of calibration checks and inspections of automatic, mechanical, electronic equipment, or other types of equipment, including computers, used in the manufacture, processing, packing, and holding of a drug product (21 CFR 211.68 (a)).

Specifically, your firm failed to establish a validation program for the computer software Microsoft Dynamics used for production, inventory, lot number generation, and laboratory test methods used for raw material, bulk, and finished product test release. Your firm also uses the Microsoft Dynamics program to assist your quality unit for product, document and component control.

In response to this letter, provide your validation plan/protocol for the Microsoft Dynamics system. Include timelines and a schedule of all corrections.

Unapproved and Misbranded Over-the-Counter (OTC) Charges

Le'dermis Skin Solutions Anti-Acne Medicated Cream

The labeling for *Le'dermis Skin Solutions Anti-Acne Medicated Cream* identifies salicylic acid 1% and octinoxate 1% as active ingredients. The statements of identity for this product include anti-acne and sunscreen indications. Based on the package label, *Le'dermis Skin Solutions Anti-Acne Medicated Cream* 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 diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or function of the body of man.

As an OTC drug intended for anti-acne purposes, *Le'dermis Skin Solutions Anti-Acne Medicated Cream* is subject to the requirements of the OTC Final Monograph for Topical Acne Drug Products (21 C.F.R. Part 333, Subpart D), which sets forth conditions for general recognition of safety and effectiveness.

Although, salicylic acid 1% is an active ingredient that is covered under the acne final monograph (21 C.F.R. 333.310), *Le'dermis Skin Solutions Anti-Acne Medicated Cream* also contains octinoxate 1% as a sunscreen active ingredient. This combination of active ingredients is not permitted under the Topical Acne final monograph nor in general is a combination acne and sunscreen product covered under this final monograph or any ongoing OTC sunscreen monograph rulemaking. Therefore, *Le'dermis Skin Solutions Anti-Acne Medicated Cream* is a new drug as defined by Section 201(p) of the Act [21 U.S.C. § 321(p)] because we are not aware of sufficient evidence to show that it is generally recognized as safe and effective.

Moreover, as presently formulated, labeled, and promoted, *Le'dermis Skin Solutions Anti-Acne Medicated Cream* is an unapproved new drug in violation of Section 505(a) of the Act, respectively [21 U.S.C. § 355(a)]. Under Section 301(d) of the Act [21 U.S.C. § 331(d)], a new drug may not be introduced or delivered for introduction into interstate commerce unless an FDA-approved application is in effect for it. *Le'dermis Skin Solutions Anti-Acne Medicated Cream* does not have an approved application, and its introduction into interstate commerce violates these provisions of the Act.

In addition to new drug charges, *Le'dermis Skin Solutions Anti-Acne Medicated Cream* is misbranded under 502(c) of the Act [21 U.S.C. § 352(c] because there is no expiration date, as required by 21 C.F.R. §§ 201.17 and 211.137, and the product is not exempt from the expiration date requirement in part because we observed there was no stability data demonstrating at least three years of stability.

Caro Light Skin Lightening Lotion* and *Topiclear Skin Lightening Lotion

We also note your products, *Caro Light Skin Lightening Lotion* and *Topiclear Skin Lightening Lotion* are drugs as defined by 201(g)(1) of the Act [21 U.S.C. § 321(g)(1)] because they are intended to treat disease and to affect the structure or function of the body of man, specifically to lighten the skin. These

products are misbranded under 502(c) of the Act [21 U.S.C. § 352(c] because they lack expiration dates, as required by 21 CFR §§ 201.17 and 211.137, and the product is not exempt from the expiration date requirement in part because we observed there was no stability data demonstrating at least three years of stability. We also note that within the Drug Facts Panel, the purpose of the ingredient Octyl Methoxycinnamate 0.5% is written as "Sun Screen." The purpose should be listed as "Sunscreen."

In addition to the above specific citations, our review noted some general concerns. The significance of current findings indicates that your quality unit is not able to fully exercise its responsibilities. It is essential that you provide the quality unit with the appropriate authority and staff to carry out its responsibilities. We recommend that you hire a qualified consultant to provide your firm's staff with CGMP guidance and training on CGMP.

We are also concerned about your firm's fundamental understanding of the overall regulatory expectations for a firm that enters into agreements with contract testing laboratories, including the critical quality unit responsibilities required by 21 CFR 211. Although you have agreements with other firms that may delineate specific responsibilities to each party (e.g., quality control testing), you are ultimately responsible for the quality of your products. The Food and Drug Administration is aware that many manufacturers of pharmaceutical products utilize extramural independent contract facilities (e.g., contract testing laboratories) and regards extramural facilities as an extension of the manufacturer's own facility. Regardless of who performs your operations, or the agreements in place, you are required to ensure your products were made in accordance with section 501(a)(2)(B) of the Act so as to provide for their identity, strength, quality, purity, and safety, and are suitable for marketing.

The following guidances should be helpful to your firm in establishing corrections to the above citations and concerns:

Guidance for Industry: Quality Systems Approach to Pharmaceutical CGMP Regulations
http://www.fda.gov/downloads/Drugs/.../Guidances/UCM070337.pdf[1]

ICH Q10 Guidance for Industry: Pharmaceutical Quality System
http://www.fda.gov/downloads/Drugs/Guidances/ucm073517.pdf[2]

ICH Q1A (R2): Stability Testing of New Drug Substances and Products
http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm128204.pdf[3]

Guidance for Industry: Process Validation: General Principles and Practices
http://www.fda.gov/downloads/Drugs/.../Guidances/UCM070336.pdf[4]

The violations cited in this letter are not intended to be an all-inclusive list of violations that 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.

Until all corrections have been completed and FDA has confirmed corrections of the violations and your firm's compliance with CGMP, FDA may withhold approval of any new applications or supplements listing your firm as a drug product manufacturer. In addition, your failure to correct these violations may result in FDA continuing to refuse admission of articles manufactured at Jabones Pardo S.A. in Fuenlabrada, Spain into the United States under Section 801(a)(3) of the Act, 21 U.S.C. 381(a)(3). The articles may be subject to refusal of admission pursuant to Section 801(a)(3) of the Act, 21 U.S.C. 381(a)(3), 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 Act, 21 U.S.C. 351(a)(2)(B).

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 and prevent the recurrence of violations, and provide copies of supporting documentation. If you cannot complete corrective actions within fifteen working days, state the reason for the delay and the date by which you will have completed the corrections. Additionally, if you no longer manufacture or distribute the drug products at issue, provide the date(s) and reason(s) you ceased production. Please identify your response with FEI # 3003569504.

Please send your reply to: David S. Jones, Compliance Officer, at the address listed below:

U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Office of Manufacturing and Product Quality
Division of International Drug Quality
White Oak, Building 51
10903 New Hampshire Ave
Silver Spring, MD 20993
Tel: (301) 796-3759
Fax: (301) 847-8742

Sincerely,
/S/
Michael D. Smedley
Acting Director
Office of Manufacturing and Product Quality
Office of Compliance
Center for Drug Evaluation and Research

Links on this page:

1. http://www.fda.gov/downloads/Drugs/.../Guidances/UCM070337.pdf
2. http://www.fda.gov/downloads/Drugs/Guidances/ucm073517.pdf
3. http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm128204.pdf
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