Department of Health and Human Services

Public Health Service
Food and Drug Administration
Dallas District Office
4040 North Central Expressway
Suite 300
Dallas, Texas 75204-3128

February 23, 2016

Ref: 2016-DAL-WL-12

WARNING LETTER

UPS OVERNIGHT MAIL

Hwansoo Lee
President and Owner
Chemolee Lab Corporation
3820 Conflans Road
Irving, Texas 75061

Dear Mr. Lee:

From January 12, 2015 through February 13, 2015, investigators from the U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Chemolee Lab Corporation, located at 3820 Conflans Road, Irving, Texas.

We identified significant violations of current good manufacturing practices (CGMP) for finished pharmaceuticals, Title 21, Code of Federal Regulations, Parts 210 and 211. These violations cause your drugs to be adulterated within the meaning of Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (the FD&C 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.

During the inspection, our investigators collected labeling for several products distributed by your firm. As formulated, labeled, and promoted, the following products are unapproved and/or misbranded drugs in violation of the FD&C Act: **(b)(4)** Restless Legs Cream, **(b)(4)** Restless Legs Cream, **(b)(4)** Shingles Anti-Itch Recovery Cream, **(b)(4)** Shingles Recovery Cream Anti-Itch Formula, **(b)(4)** Lung Cream Herbal Formula, **(b)(4)** Anti-Inflammatory & Pain Relief Cream, **(b)(4)** Diabetic Foot Cream Anti-Itch Formula, and **(b)(4)**.

We reviewed your March 6, 2015 response in detail. Your response lacks sufficient corrective actions. Our investigators observed specific violations during the inspection, including, but not limited to, the following:

CGMP Violations

1. Your firm failed to thoroughly investigate any unexplained discrepancy or failure of a batch or any of its components to meet any of its specifications, whether or not the batch has already been distributed, and failed to extend the investigation to other batches that may have been associated with the specific failure [21 CFR 211 .192].

We also observed this violation during our September 2011 inspection.

(b)(4) Acne Control Spot Treatment lots manufactured in August and September of 2013 were rejected because they failed established microbial specifications for total microbial count: "Fail if any CFU is greater than **(b)(4)**." Your quality control unit did not adequately investigate these specification failures.

For lot **(b)(4)**, three different objectionable microorganism tests failed. Specifically, you failed testing on media used for detecting Aspergillus niger, Candida albicans, and Pseudomonas aeruginosa. All three tests yielded levels that were too numerous to count (TNTC). You concluded that insufficient cleaning of the transfer pump was the root cause of these failures. On August 30, 2013, you implemented a new sanitization procedure in response to these microbial testing failures.

On September 12, 2013, the **(b)(4)** lot manufactured after implementation of this new sanitization procedure, lot **(b)(4)**, failed five different objectionable microorganism tests. Specifically, you failed testing on media used for detecting Aspergillus niger, Candida albicans, Staphylococcus aureus, Escherichia coli, and Pseudomonas aeruginosa. You concluded the source of this contamination "points to somewhere in the filling process."

Your response to the initial contamination event was ineffective as contamination continued to occur. You did not extend your investigations to other potentially affected lots such as those manufactured with common raw materials or equipment. Furthermore, your response to the second contamination event (lot **(b)(4)**) is also deficient in that you have not provided any data to justify your conclusion that contamination is occurring "somewhere in the filling process." You did not find the root cause of these contamination events, and thus you will not be able to prevent them from recurring.

In your response to the FDA 483, you stated that 1:10 other drug lots manufactured on the same equipment immediately before and after lots **(b)(4)** and **(b)(4)** were found to be out-of specification (OOS) for microbial testing. You also stated that you updated your **(b)(4)** procedure for non-conformances and your **(b)(4)** procedure for corrective and preventive actions to extend failure investigations to other associated batches. Your response is inadequate because you still failed to provide scientifically sound evidence to support your conclusions about contamination sources, affected lots, and corrective actions.

In your response to this letter, please conduct a detailed root cause investigation into the source(s) of these contaminations and provide an evaluation detailing other potentially affected

batches; an accelerated timeline for retroactive testing of retain samples of all distributed batches within expiry; and any further risk controls and process design improvements implemented as a result of your investigations and your determination of the root cause of contamination.

2. Your firm failed to clean, maintain, and, as appropriate for the nature of the drug, sanitize and/or sterilize equipment and utensils at appropriate intervals to prevent malfunctions or contamination that would alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements [21 CFR 211.67(a)].

a. Water System Failures:
Your firm failed to maintain your reverse osmosis (RO) water system for topical drug products. During the inspection, our investigators observed leakage in the RO water system. Your Director of Operations told our investigators that your RO water system had been leaking for more than six months since August 2014. No action was taken to repair the leaks during that entire time.

Our investigators also determined that your monitoring, inspecting, and repair of the RO water system was inadequate in ensuring that it was maintained in a validated state. Beyond the failure to maintain your RO system from January 8, 2014, through October 8, 2014, microbiological test results from water sampled at the RO **(b)(4)** were TNTC on **(b)(4)** occasions. Without justification, you discontinued sampling at the RO **(b)(4)** that yielded these results. We note that the finished product lots that you rejected in 2013 for microbial contamination included gross contamination with Pseudomonas aeruginosa, a microorganism commonly found in water.

In your response to the FDA 483, you stated that you replaced the gaskets of the RO membrane housings during the inspection, and leaks had stopped. You also updated procedure **(b)(4)** (Operation and Maintenance of the USP Water) to require **(b)(4)** leak checks for the RO system and the water loop.

However, your response is inadequate. You stated that high microbial counts from the RO **(b)(4)** are not a cause for concern because the water is further purified **(b)(4)**. However, you provide no scientific rationale to justify **(b)(4)** counts as high as TNTC in your system at the RO purification stage. The presence of waterborne microorganisms at levels TNTC in your finished product indicates that other components **(b)(4)** of your RO system are insufficient to prevent contamination of your finished products.

In your response to this letter, please provide trending results of **(b)(4)** microbial testing at all water purification system ports to demonstrate the effectiveness of your replaced gaskets, including counts and microbial identification; water system maintenance procedure(s) including the replacement frequency of filters and **(b)(4)**; sampling plans to monitor water quality; data to demonstrate to what degree the **(b)(4)** and **(b)(4)** filter installed immediately **(b)(4)** of the production points-of-use can control bioburden; a summary of your investigation to determine if gaskets were indeed the sole root cause of contamination; and an update on any further risk controls and improvements in system design that have been implemented as a result of your investigations.

b. Cleaning Procedures:

There is no assurance that your cleaning and sanitization methods are adequate or non-dedicated equipment used to manufacture topical drug products, including sunscreens and anti-fungal products. Cleaning and sanitizing procedures for kettles, vessels, and transfer pumps lack detailed instructions. This is particularly important for your product mix in that the insolubility of some excipients and active ingredients makes equipment difficult to clean, and could result in cross-contamination between your products.

No cleaning procedures were established for the **(b)(4)** production equipment used to fill topical drug products. For example, the **(b)(4)** was used to fill lot **(b)(4)** of **(b)(4)** Acne Control Spot Treatment. As mentioned in Charge 1, lot **(b)(4)** failed microbial testing.

In your response to the FDA 483, you provided an updated Master Cleaning Validation Plan. You will use a matrix approach to update your procedures. However, you provided insufficient detail for us to determine the adequacy of your new plan, or the effectiveness of your plans for products already manufactured on inadequately cleaned equipment.

In your response to this letter, please provide a detailed cleaning validation plan, including cleaning agent concentrations, hold times before cleaning, equipment disassembly instructions, cleaning frequencies, rinse times, and water temperatures; timeframes for completing your Master Cleaning Validation Plan; and a summary of your interim plan to ensure the quality of drugs that you continue to manufacture and distribute before you complete your corrective action and cleaning validation activities.

3. Your firm failed to establish procedures for production and process control designed to assure that the drug products have the strength, quality, and purity they purport or are represented to possess (21 CFR 211.100(a)).

Specifically, your firm has no evidence that your manufacturing processes have been validated for approximately **(b)(4)** different topical drug products, including **(b)(4)** Acne Control Spot Treatment, **(b)(4)** Skin Lightener (API 2% hydroquinone), and **(b)(4)** Anti-Fungal Treatment.

Your procedures for compounding, filling, and hold times for these products do not include defined process parameters such as mixing times, blending speeds, temperatures, and bulk hold times.

Establishing defined process parameters is particularly important in the manufacture of topical creams and ointments. Homogenous distribution of the active ingredients would be based largely upon adequate mixing of the ingredients throughout the batch. Your management was unable to provide any validation documentation to demonstrate that your manufacturing processes are adequately controlled to consistently ensure your drug products' potency and uniformity. You also lacked sufficient batch instructions to ensure reproducibility.

You stated in your response that you will develop a master process validation protocol by **(b)(4)** 2015, outline a plan to complete process validations for all topical drug products, and hire a validation engineer by the end of **(b)(4)** 2015. However, your response lacks sufficient details.

In your response to this letter, please provide an executive summary of the validation status of all of your products in distribution; an update on the master process validation protocol you committed to develop and your implementation strategy, including timeframes for completing process validations for all your products; a summary of your interim plan for any drugs distributed before validation activities are completed to ensure the quality of drugs that you continue to manufacture and distribute; an evaluation of the validation status of your water system; and the list of products that you ceased to distribute given that your processes have not been shown to be in a state of control and do not consistently prevent objectionable microbiological contamination.

4. Your laboratory controls do not include the establishment of scientifically sound and appropriate standards and test procedures designed to assure that components, in process materials, and drug products conform to appropriate standards of identity, strength, quality and purity [21 CFR 211.160(b)].

For microbiological testing media that you prepare **(b)(4)**, you use a mixture of **(b)(4)** water, and a **(b)(4)** product as sources of inoculum for **(b)(4)** controls. This method does not follow USP <61 > or USP <62>. In addition, your method cannot demonstrate the suitability of each lot of media. Therefore, you cannot ensure that any released drugs tested with your substandard media meet microbial specifications.

In your response to the FDA 483, you stated that you will use only a certified third party microbiological testing laboratory to perform **(b)(4)** control testing on **(b)(4)** until you update your laboratory methods. Your response is inadequate. First, you have not provided sufficient details about what specific activities your contract microbiology lab will perform (**(b)(4)** control only, **(b)(4)** control, other tests, or some combination). Second, you have not conducted a detailed review of all of you microbiology laboratory testing practices to determine whether the testing you perform is scientifically sound and designed to ensure that your products meet specification.

In your response to this letter, please provide an evaluation of the equipment, procedures, staff, and capabilities of your microbiology laboratory, and a determination of whether improvements are needed in the laboratory or a qualified third party should be utilized for other tests in addition to positive control preparation.

Unapproved New Drugs

Based on labeling claims for the topical drug products your firm manufactures and distributes, **(b)(4)** Restless Legs Cream, **(b)(4)** Restless Legs Cream, **(b)(4)** Shingles Anti-Itch Recovery Cream, **(b)(4)** Shingles Recovery Cream Anti-Itch Formula, **(b)(4)** Lung Cream Herbal Formula, **(b)(4)** Anti-Inflammatory & Pain Relief Cream, **(b)(4)** Diabetic Foot Cream Anti-Itch Formula, and **(b)(4)** are drugs as defined by 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.

Labeling statements documenting the intended uses of these products include, but are not limited to, the following:

(b)(4) Restless Legs Cream:
" ... help calm and soothe those painful and disruptive sensations caused by restless legs syndrome."

(b)(4) Restless Legs Cream:
" ... help calm and soothe those painful and disruptive sensations caused by restless legs syndrome."

(b)(4) Shingles Anti-Itch Recovery Cream:
" ... relieve the itching, inflammation, and discomfort associated with an outbreak of shingles."

(b)(4) Shingles Recovery Cream Anti-Itch Formula:
" ... relieve the itching, inflammation, and discomfort associated with an outbreak of shingles."

(b)(4) Lung Cream Herbal Formula:
" ... breathe easier ... works quickly to help minimize discomfort caused by wheezing and shortness of breath due to bronchitis, asthma, emphysema, and smoker's cough."

(b)(4) Anti-Inflammatory & Pain Relief Cream:
"Anti-Inflammatory & Pain Relief Cream"
"Help restore comfort to your sore, painful heels ... reduce inflammation and pain"

(b)(4) Diabetic Foot Cream Anti-Itch Formula:
"Anti-Itch Formula ... relieve and restore damaged feet by moisturizing and softening hardened callused skin to help eliminate painful cracks and fissures."

(b)(4)
"**(b)(4)** (sic) **(b)(4)** Treatment for all skin types ... Stop those zits ... "

(b)(4) Restless Legs Cream, **(b)(4)** Restless Legs Cream, **(b)(4)** Shingles Anti-Itch Recovery Cream, **(b)(4)** Shingles Recovery Cream Anti-Itch Formula, **(b)(4)** Lung Cream Herbal Formula, **(b)(4)** Anti Inflammatory & Pain Relief Cream, **(b)(4)** Diabetic Foot Cream Anti-Itch Formula, and **(b)(4)** are also "new drugs," as defined in Section 201(p) of the FD&C Act, 21 U.S.C. § 321{p), because they are not generally recognized as safe and effective for use under the conditions prescribed, recommended, or suggested in their labeling. Under Sections 301 (d) and 505{a) of the FD&C 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. You have no FDA-approved applications for these products. Therefore, marketing these products constitutes a violation of these provisions of the FD&C Act.

Misbranded Drugs

Because **(b)(4)** Restless Legs Cream, **(b)(4)** Restless Legs Cream, **(b)(4)** Shingles Anti-Itch Recovery Cream, **(b)(4)** Shingles Recovery Cream Anti-Itch Formula, **(b)(4)** Lung Cream Herbal Formula, **(b)(4)** Anti Inflammatory & Pain Relief Cream, and **(b)(4)** Diabetic Foot Cream Anti-Itch Formula are offered for conditions that are not amenable to self-diagnosis and treatment by individuals who are not medical practitioners, adequate directions cannot be written so that a layman can use the products safely for their intended uses. Thus, your products***1*** labeling fails to bear adequate directions for their intended uses, causing them to be misbranded under section 502(f)(1) of the FD&C Act, 21 U.S.C. § 352(f)(1).

The introduction or delivery for introduction of misbranded drugs into interstate commerce violates section 301(a) of the FD&C Act, 21 U.S.C. § 331(a).

Conclusion

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

Due to the CGMP violations at your firm, we recommend that you engage a third party consultant with appropriate CGMP expertise to assess your facility, procedures, processes, and systems to ensure that your drug products have appropriate identity, strength, quality, and purity.

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/or 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 that you have completed corrective actions.

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 and prevent the recurrence of violations detailed in this letter.

If you cannot complete corrective actions within 15 working days, state the reasons for the delay and the date by which you will have completed the corrections. If you no longer manufacture or distribute the drugs at issue, provide the date(s) and reason(s) you ceased production.

Your written response should be sent to Thao Ta, Compliance Officer, U.S. Food and Drug Administration, 4040 North Central Expressway, Suite 300, Dallas, Texas 75204. If you have questions regarding any issues in this letter, please contact Thao Ta at (214) 253-5217.

Sincerely,
/S/
Reynaldo R. Rodrigue, Jr.
Dallas District Director

cc:
Mr. Jerome Lee
Director of Operations
Chemolee Lab Corporation
3820 Conflans Road
Irving, Texas 75061

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1 "**(b)(4)**" is marketed as an OTC topical acne drug product. Drug products intended for acne indications are subject to the Final Monograph for Topical Acne Drug Products for Over-the Counter Human Use (21 CFR 333 Subpart D). However, **(b)(4)** is not marketed in conformance with this final monograph. The product label identifies camphor (3%) and sulfur (5%) as the two sole active ingredients. Although sulfur 5% is permitted under the final monograph, camphor, regardless of the percentage used, is not covered under 21 CFR 333 Subpart D. Camphor was classified as a non-monograph ingredient for use in the treatment of acne under 21 CFR 310.545(a)(1) because there are inadequate data to establish general recognition of the safety and effectiveness of this ingredient in the treatment of acne.