Yusef Manufacturing Laboratories, LLC 5/25/17

U.S. FOOD & DRUG ADMINISTRATION

Los Angeles District
19701 Fairchild Road
Los Angeles, CA 92612

Certified Mail
Return Receipt Requested

Warning Letter DEN-17-07-WL

May 25, 2017

Mr. Fielding R. Smith
President
Yusef Manufacturing Laboratories, LLC
Freeport West, F-4, #3
PO Box 160347
Clearfield, UT 84016-0347

Dear Mr. Smith:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Yusef Manufacturing Laboratories at Freeport West, F-4, #3, Clearfield, Utah, from May 23–26, 2016.

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 June 3, 2016, response in detail and acknowledge receipt of your subsequent correspondence.

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

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 (21 CFR 211.192).

Your quality unit released batch B-11701 of YMLabs Aloe Gel Sanitizer (62% ethyl alcohol), which failed the in-process specification for viscosity. According to the specification, the drug product is also required to be colorless, which you recorded on the certificate of analysis as passing specification. However, firm personnel acknowledged that the batch was, in fact, discolored. You did not investigate the failed test result for viscosity or colorlessness, and released the batch.

Your response is inadequate. You did not provide sufficient detail or evidence that you have investigated to determine the root cause, evaluated all potentially impacted batches, and implemented appropriate corrective actions to prevent recurrence of these defects.

In your response to this letter, summarize your investigation into the batch failure of YMLabs Aloe Gel Sanitizer B-11701. Include root cause(s), scope of the problem, corrective actions, and preventive actions.

2. Your firm failed to establish adequate written responsibilities and procedures applicable to the quality control unit and to follow such written procedures (21 CFR 211.22(d)).

Our investigator found that your quality unit had not checked your customer complaint hotline since February 17, 2015, a period of more than 15 months. Firm personnel stated the hotline had not been checked, and the voicemail box was most likely full. According to your standard operating procedure (SOP) *Written and Oral Complaints*, the quality unit is to check your complaint hotline every **(b)(4)** to **(b)(4)** days.

Your response is inadequate. You did not provide sufficient evidence that you have fully remediated your complaint system.

In your response to this letter, summarize your evaluation of each complaint from your hotline. Include details of each initiated complaint investigation. Also describe steps that your management will take to ensure that your staff follows written procedures, and that all of your written procedures are adequate.

During our September 2007 and February 2011 inspections, we also observed that your quality unit failed to ensure adequate evaluation of complaints.

3. 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 and freedom from objectionable microorganisms, prior to release (21 CFR 211.165(a), (b)).

You failed to test any of your finished drug products for chemical attributes, including identity and strength, prior to release. FDA collected and tested samples from different batches of your reserve samples of SPF 15 sunscreen lip balm products. FDA laboratory analysis found in all samples that the active ingredients octinoxate and oxybenzone were sub-potent. Both ingredients were found to have an average potency of 66%.

In addition, you failed to test each batch of your YMLabs Aloe Gel Sanitizer (62% ethyl alcohol) drug products for total count and objectionable microorganisms prior to release.

During our September 2007 and February 2011 inspections, we also observed your failure to test your drug products for identity and strength, prior to release. In addition, during our February 2011 inspection, we also observed your failure to test your drug products for objectionable microorganisms, prior to release.

Your response is inadequate. You did not provide sufficient detail or evidence of corrective actions.

In your response to this letter, include:

- a list of the current quality control criteria and test methods you currently use to test each drug product batch prior to release.
- a thorough assessment to determine insufficiencies in chemical, physical, and microbiological specifications and analytical methods established for each of your drug products. Include a full remediation plan with appropriate specifications and analytical methods to be used for testing each batch of drug product.
- an action plan and timelines for testing all in-date drug products for identity and strength of active ingredients, and all other appropriate chemical and microbiological quality attributes (e.g., total count, objectionable microorganisms). Regarding drug products found to be of substandard quality, including YMLabs Aloe Gel Sanitizers (62% ethyl alcohol) and SPF 15 sunscreen lip balm products, specify the actions that you will take, such as notifying customers and product recalls.

4. Your firm failed to test samples of each component for conformity with all appropriate written specifications for identity, purity, strength, and quality (21 CFR 211.84(d)(1), (2)).

You do not test incoming active pharmaceutical ingredients and other components used in manufacturing your SPF 15 sunscreen lip balm products for adherence to all appropriate quality attributes. Your procedures only required routine incoming component testing for color, odor, and appearance.

Your response is inadequate. You did not sufficiently address your program for testing incoming components.

In your response to this letter, provide a summary of test results obtained from full testing (e.g., strength, identity, purity) of all of your incoming components. Also provide your current incoming raw material batch release specifications for each component. Describe which tests are done for each batch and which are generally accepted based on a validated Certificate of Analysis (COA). Specify whether all incoming component batches are analyzed using at least one specific identity test. Also provide a procedure describing your supplier qualification program.

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

Poor Control of Manufacturing Processes
Your manufacturing processes lack an adequate state of control. Manufacturing processes must be designed and controlled to assure that in-process materials and finished products reliably and reproducibly meet predetermined parameters, manufacturing standards, and quality requirements.

FDA analyzed beginning, middle, and end samples of your SPF 15 sunscreen lip balm batch W12072. Our laboratory found that the batch was not of uniform character and quality. These analyses showed active ingredient results that widely varied in strength across the batch, with assay values ranging from 26% to 93% of label claim. It is essential that your firm's manufacturing processes, including mixing, provide for robust and homogenous distribution of active ingredients.

Inadequate Control of Water System
You also have not validated your "**(b)(4)**" water system. You must design your water system to reproducibly yield suitable water for use in production operations. Your firm had not demonstrated that you can effectively control, maintain, sanitize, and monitor the system so it consistently produces pharmaceutical grade water that, at a minimum, meets the USP monograph for purified water. The water from this unvalidated system is used as a component in your drugs.

You lacked testing of the water produced by this system. It is imperative that you routinely test water for chemical (e.g., total organic carbon, conductivity) and microbiological attributes.

In your response to this letter, provide an action plan:

- to ensure appropriate design, control, maintenance, and monitoring of your manufacturing processes and water system
- for validating your water system and your drug product manufacturing processes
- with detailed timelines for accomplishing each of these corrective actions

Repeat deficiencies at facility

In previous inspections, dated September 2007 and February 2011, FDA cited similar CGMP deficiencies. While you proposed specific remediations for the violations noted above, the planned remediations are essentially the same as your commitments following previous FDA inspections. These repeated failures demonstrate that your facility's oversight and control over the manufacture of drugs is inadequate.

Because of your failure to correct these repeat violations, we are concerned about your firm's fundamental understanding of regulatory requirements relating to drug manufacturing. You are responsible for the quality of the products you produce and must ensure safety, identity, strength, quality, and purity of your drug products in accord with section 501(a)(2)(B) of the FD&C Act.

Discrepancies in documents

Your response included SOP 05-105.00 *Master Formulation File Change Control*. According to this procedure, your Research & Development Department is responsible for approving changes to drug product formulations. You also provided SOP 00-100.5 *Quality Unit* which specifies your plant manager, president, and QA manager as members of the quality unit. It is important that your quality unit maintains appropriate independence, is adequately resourced, and is fully empowered to fulfill its accountabilities and responsibilities under CGMP.

Additional quality systems guidance

See FDA's guidance document, *Quality Systems Approach to Pharmaceutical CGMP Regulations*, for help implementing quality systems and risk management approaches that meet the requirements of CGMP regulations (21 CFR parts 210 and 211), at
https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070337.pdf
(https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070337.pd

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. Your use of a consultant

does not relieve your firm's obligation to comply with CGMP. Your firm's executive management remains responsible for fully resolving all deficiencies and ensuring ongoing CGMP compliance.

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. It is your responsibility to ensure that your firm complies with all requirements of federal law, including FDA regulations.

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 these violations are corrected, we may withhold approval of pending drug applications listing your facility. We may re-inspect to verify that you have completed your corrective actions. We may also refuse your requests for export certificates.

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 **Matthew.Dionne@fda.hhs.gov (mailto:Matthew.Dionne@fda.hhs.gov)** or mail your reply to:

CDR Steven E. Porter, Jr.
Director, Division of Pharmaceutical Quality Operations IV
United States Food and Drug Administration
19701 Fairchild Road
Irvine, California 92612

Please identify your response with FEI 3004845420.

If you have any questions regarding any issues in this letter, please contact Dr. Dionne via email or by phone at (303) 236-3064.

Sincerely,
/S/
CDR Steven E. Porter, Jr.
Director, Division of Pharmaceutical Quality Operations IV

More in 2017 (/ICECI/EnforcementActions/WarningLetters/2017/default.htm)