WARNING LETTER

4E Global, S.A.P.I. de C.V.

MARCS-CMS 608940 — OCTOBER 23, 2020

Delivery Method:

VIA UPS

Product:

Drugs

Recipient:

Jorge González Olvera

General Director

4E Global, S.A.P.I. de C.V.

Av. Uno Notre No. 15 Bodega 1F
Parque Industrial Cartagena 54918 Tultitlan,
Mexico

Issuing Office:

Center for Drug Evaluation and Research | CDER

United States

Warning Letter 320-21-04

October 23, 2020

Dear Mr. González Olvera:

Your firm is registered as a human drug manufacturer. The U.S. Food and Drug Administration (FDA) conducted testing of consumer antiseptic hand rub drug products (also referred to as consumer hand sanitizers), labeled as blumen Advanced Instant Hand Sanitizer Clear Ethyl Alcohol 70% and blumen Clear Advanced Hand Sanitizer Extra Soft. These drug products were declared as being manufactured at your facility, 4E Global S.A.P.I de C.V. FEI 3010078513, at Av. Uno Notre No. 15 Bodega 1F Parque Industrial Cartagena Tultitlan 54918 Mexico and, following an attempt to import these drug products into the United States, blumen Advanced Instant Hand Sanitizer Clear Ethyl Alcohol 70% and blumen Clear Advanced Hand Sanitizer Extra Soft were detained and refused admission at the border.

The results of FDA laboratory testing demonstrated that batches of blumen Advanced Instant Hand Sanitizer Clear Ethyl Alcohol 70% and blumen Clear Advanced Hand Sanitizer Extra Soft hand sanitizer drug products are adulterated within the meaning of section 501(d)(2) of the Federal Food, Drug, and Cosmetic Act (FD&C Act or Act), 21 U.S.C. 351(d)(2), in that a substance was substituted wholly or in part therefor. In addition, these products are adulterated within the meaning of section 501(a)(2)(B) (21 U.S.C. 351(a)(2)(B)), in that the substitution demonstrates that the quality assurance within your facility is not functioning in accordance with Current Good Manufacturing Practice (CGMP) requirements.

In addition, these drug products are unapproved new drugs introduced or delivered for introduction into interstate commerce in violation of section 505(a) of the FD&C Act, 21 U.S.C. 355(a), and are misbranded under sections 502(j), (a), (e), (f)(2), and (ee) of the FD&C Act, 21 U.S.C. 352(j), (a), (e), (f)(2), and (ee). Introduction or delivery for introduction of these products into interstate commerce is prohibited under sections 301(d) and (a) of the FD&C Act, 21 U.S.C. 331(d) and (a). These violations are described in more detail below.

Adulteration Violations

The drug product blumen Advanced Instant Hand Sanitizer Clear Ethyl Alcohol 70% is labeled to contain 70% volume/volume (v/v) of the active ingredient alcohol (ethanol). However, FDA laboratory testing found that this product contained an average of 0.2% ethanol and 74% of methanol v/v. Another sample of the same product contained an average of 14% ethanol and 65% of methanol v/v. Additionally, blumen Clear Advanced Hand Sanitizer Extra Soft is labeled to contain 70% v/v of the active ingredient alcohol (ethanol). However, FDA laboratory testing found that your blumen Clear Advanced Hand Sanitizer Extra Soft contained an average of 6.6% ethanol and 69% methanol v/v. Three additional samples of blumen Clear Advanced Hand Sanitizer Extra Soft was tested and the first sample contained an average of <5% ethanol and 74% methanol v/v. The second sample contained an average of 8.9% ethanol and 65% methanol v/v. The third sample contained an average of 0% ethanol and 70% methanol v/v. These drug products are adulterated under section 501(d)(2) of the Act in that the active ingredient of ethanol was substituted wholly or in part with methanol, a dangerous chemical when in contact with human skin or ingested.

Methanol is not an acceptable ingredient for hand sanitizers and should not be used due to its toxic effects. Skin exposure to methanol can cause dermatitis, as well as transdermal absorption with systemic toxicity. Substantial methanol exposure can result in nausea, vomiting, headache, blurred vision, permanent blindness, seizures, coma, permanent damage to the nervous system, or death. Although all persons using these products on their hands are at risk, young children who accidentally ingest these products and adolescents and adults who drink these products as an alcohol (ethanol) substitute are most at risk for methanol poisoning.

On July 6, 2020, FDA held a teleconference with you and your registered U.S. agent, Registrar Corp. We recommended you consider removing your hand sanitizer drug products currently in distribution to the U.S. market. FDA notified the public of the methanol contamination of your drugs at the following website: https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-hand-sanitizers-consumers-should-not-use (https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-hand-sanitizers-consumers-should-not-use)

On July 11, you agreed to recall certain lots of hand sanitizers that were distributed in the U.S. at the following website: https://www.fda.gov/safety/recalls-market-withdrawals-safety-alerts/4e-brands-north-america-issues-nationwide-voluntary-recall-hand-sanitizer-due-potential-presence (https://www.fda.gov/safety/recalls-market-withdrawals-safety-alerts/4e-brands-north-america-issues-nationwide-voluntary-recall-hand-sanitizer-due-potential-presence)

FDA held a subsequent teleconference with you on July 20, 2020 to discuss the serious health implications regarding methanol contamination. After the call, you agreed to expand the scope of the recall to include all hand sanitizer products within expiry that were distributed in the U.S. market due to potential presence of Undeclared Methanol (Wood Alcohol). On July 24, 2020, you expanded the scope of the recall to all hand sanitizer brands as shown at the following website:

https://www.fda.gov/safety/recalls-market-withdrawals-safety-alerts/4e-brands-north-america-issues-expanded-nationwide-voluntary-recall-hand-sanitizer-due-potential (https://www.fda.gov/safety/recalls-market-withdrawals-safety-alerts/4e-brands-north-america-issues-expanded-nationwide-voluntary-recall-hand-sanitizer-due-potential)

In response to this letter provide:

• A detailed investigation into how hand sanitizer drug products labeled as manufactured at your facility, and labeled as containing ethanol, were substituted in part or in whole with methanol.
• A list of all raw materials used to manufacture all of your hand sanitizer drug products, including the suppliers' names, addresses, and contact information.
• A list of all batches of any hand sanitizer drug products shipped to the United States by your firm, and a full reconciliation of all material you distributed.
• Copies of the complete batch records for all batches distributed to the U.S.
• We note that on August 7, 2020, your outside counsel indicated that you are engaging an independent CGMP consultant to assist you. Please describe the scope of the operations the consultant will be reviewing.
• During a teleconference with the FDA on July 20, 2020, you stated that you were using specific gravity for your identity test method for incoming raw material analysis of ethanol. Note that specific gravity is an inadequate test to differentiate between ethanol and methanol. Provide your revised test methods for testing raw materials and your hand sanitizer drug products.
• During a teleconference with the FDA on July 20, 2020, you admitted that you did not test all of your drug products prior to release for strength and identity of the active ingredient. Discuss the corrective action to remediate this issue in your response.

The substitution and methanol contamination found in hand sanitizer drug products declared as manufactured in your facility demonstrates that the quality assurance within your facility is not functioning in accordance with CGMP requirements under section 501(a)(2)(B) of the FD&C Act.[1]

Unapproved New Drug and Misbranding Violations

Your blumen Advanced Instant Hand Sanitizer Clear Ethyl Alcohol 70% and blumen Clear Advanced Hand Sanitizer Extra Soft are "drugs" under section 201(g)(1)(B) of the FD&C Act, 21 U.S.C. 321(g)(1)(B), because they are intended for use in 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. Specifically, these products are intended as consumer antiseptic rubs.

Examples of claims observed on the blumen Advanced Instant Hand Sanitizer Clear Ethyl Alcohol 70% and blumen Clear Advanced Hand Sanitizer Extra Soft labeling that provide evidence of the intended use (as defined in 21 CFR 201.128) of the product include, but may not be limited to, the following:

"HAND SANITIZER . . . Drug Facts . . . Uses Hand sanitizer to help decrease bacteria on the skin"

These hand sanitizer products are "new drugs" within the meaning of section 201(p) of the FD&C Act, 21 U.S.C. 321(p), because they are not generally recognized as safe and effective (GRASE) for use under the conditions prescribed, recommended, or suggested in their labeling. New drugs may not be introduced or delivered for introduction into interstate commerce without prior approval from FDA, as described in section 505(a) of the FD&C Act, 21 U.S.C. 355(a), unless they are lawfully marketed under Section 505G of the Act (which is not the case for these products, as further described below). No FDA-approved application pursuant to section 505 of the FD&C Act, 21 U.S.C. 355, is in effect for either of these hand sanitizer products, nor are we aware of any adequate and well-controlled clinical studies in the published literature that support a determination that your blumen Advanced Instant Hand Sanitizer Clear Ethyl Alcohol 70% and blumen Clear Advanced Hand Sanitizer Extra Soft drug products are GRASE for use under the conditions suggested, recommended, or prescribed in their labeling. Accordingly, these products are unapproved new drugs marketed in violation of sections 505(a) and 301(d) of the FD&C Act, 21 U.S.C 355(a) and 331(d).

We note that over-the-counter (OTC) topical antiseptic products had been the subject of rulemaking under the Agency's OTC Drug Review. In particular, such products were addressed in a tentative final monograph (TFM) entitled "Topical Antimicrobial Drug Products for Over-the-Counter Human Use; Tentative Final Monograph for Health-Care Antiseptic Drug Products," Proposed Rule, 59 FR 31402 (June 17, 1994) (1994 TFM), as further amended by the "Safety and Effectiveness of Consumer Antiseptics; Topical Antimicrobial Drug Products for Over-the-Counter Human Use; Proposed Amendment of the Tentative Final Monograph; Reopening of Administrative Record," Proposed Rule, 81 FR 42912 (June 30, 2016). Over the course of these rulemakings, benzalkonium chloride, ethyl alcohol, and isopropyl alcohol were classified in Category III for use as an active ingredient in consumer antiseptic rub products, meaning that additional safety and effectiveness data are needed to support a determination that a drug product containing one of these active ingredients would be GRASE for use as a consumer antiseptic rub.

Section 505G of the FD&C Act addresses nonprescription drugs marketed without an approved application. Under 505G(a)(3) of the FD&C Act, drugs that were classified as Category III for safety or effectiveness in a TFM that is the most recently applicable proposal or determination for such drug issued under 21 CFR Part 330 – and that were not classified as Category II for safety or

effectiveness – are not required to have an approved application under section 505 in order to be marketed, as long as they are in conformity with the relevant conditions of use outlined in the applicable TFM, including the active ingredient, and comply with all other applicable requirements.

However, blumen Advanced Instant Hand Sanitizer Clear Ethyl Alcohol 70% and blumen Clear Advanced Hand Sanitizer Extra Soft do not conform to the 1994 TFM, as further amended by the 2016 Consumer Antiseptic Rub proposed rule nor any other TFM, proposed rule, or final rule, and do not meet the conditions under section 505G(a)(3) of the FD&C Act for marketing without an approved application under section 505.

According to the product labels, blumen Advanced Instant Hand Sanitizer Clear Ethyl Alcohol 70% and blumen Clear Advanced Hand Sanitizer Extra Soft purportedly contain the active ingredient ethyl alcohol (ethanol) 70% v/v. However, as previously discussed, FDA laboratory analyses revealed that samples of blumen Advanced Instant Hand Sanitizer Clear Ethyl Alcohol 70% and blumen Clear Advanced Hand Sanitizer Extra Soft detained at the border contain a concentration of ethanol that is far less than the 70% declared on the labels and far less than the amount of ethanol described in the 1994 TFM.[2] Thus, these products do not conform with the TFM and other applicable requirements, nor are they consistent with the formulations described in FDA's temporary policies for hand sanitizers during the COVID-19 public health emergency.

FDA laboratory analyses also revealed that samples of blumen Advanced Instant Hand Sanitizer Clear Ethyl Alcohol 70% and blumen Clear Advanced Hand Sanitizer Extra Soft contain significant concentrations of the undeclared ingredient methyl alcohol (methanol). Use of methanol as an active ingredient is not in conformance with the 1994 TFM, nor is it included in the formulations described in FDA's *Temporary Policy for Preparation of Certain Alcohol-Based Hand Sanitizer Products During the Public Health Emergency (COVID-19)* Guidance for Industry.[3] Furthermore, methanol is not acceptable as an inactive ingredient in hand sanitizers. As previously discussed, methanol has significant and sometimes fatal toxic effects and, therefore, does not meet the requirements under 21 CFR 330.1(e) that its inactive ingredients be safe and suitable.[4]

Additionally, these methanol-containing drug products, blumen Advanced Instant Hand Sanitizer Clear Ethyl Alcohol 70% and blumen Clear Advanced Hand Sanitizer Extra Soft, are misbranded under sections 502(j), (a), (e), (f)(2), and (ee) of the FD&C Act, 21 U.S.C. 352(j), (a), (e), (f)(2), and (ee). They are misbranded under section 502(j) of the FD&C Act, 21 U.S.C. 352(j), because they are dangerous to health when used according to their labeling as hand sanitizers. As previously stated, skin exposure to methanol could lead to systemic absorption, and substantial methanol exposure can potentially result in, among other things, blindness, permanent nervous system damage, and even death. These hand sanitizers are misbranded under section 502(a) of the FD&C Act, 21 U.S.C 352(a), because their labeling is false and misleading. As noted above, blumen Advanced Instant Hand

Sanitizer Clear Ethyl Alcohol 70% and blumen Clear Advanced Hand Sanitizer Extra Soft Clear are labeled to contain ethyl alcohol 70% v/v. However, FDA laboratory analyses revealed that samples of these products detained at the border contain less ethyl alcohol than indicated on the labeling and instead contain significant concentrations of methyl alcohol (methanol), an ingredient that is not declared on the product labels.

Section 201(n) of the FD&C Act, 21 U.S.C. 321(n), provides that "in determining whether the labeling or advertising is misleading there shall be taken into account . . . not only representations made or suggested . . . but also the extent to which the labeling or advertising fails to reveal facts material in the light of such representations or material with respect to consequences which may result. . .." Thus, the misleading label representations of the concentration of the active ingredient ethyl alcohol (ethanol) and the failure of both the product labels to disclose the presence of the methyl alcohol in the products causes these products to be misbranded under section 502(a) of the FD&C Act, 21 U.S.C. 352(a). Lastly, the failure of these products to list methyl alcohol (methanol) as an ingredient on their labels causes them to be misbranded under section 502(e)(1)(A) of the FD&C Act, 21 U.S.C. 352(e)(1)(A).

Your blumen Advanced Instant Hand Sanitizer Clear Ethyl Alcohol 70% and blumen Clear Advanced Hand Sanitizer Extra Soft are also misbranded under section 502(f)(2) of the FD&C Act, 21 U.S.C. 352(f)(2), because the product labels do not include all of the applicable warnings as required under 21 CFR 330.1(g). Specifically, the labels do not include the warning statement required for drugs used topically that reads "If swallowed, get medical help or contact a Poison Control Center right away."

Lastly, these products are misbranded under section 502(ee) of the FD&C Act, 21 U.S.C. 352(ee), because blumen Advanced Instant Hand Sanitizer Clear Ethyl Alcohol 70% and blumen Clear Advanced Hand Sanitizer Extra Soft are nonprescription drugs subject to section 505G of the FD&C Act, 21 U.S.C. 355h, but do not comply with the requirements for marketing under that section and are not the subject of an application approved under section 505 of the FD&C Act, 21 U.S.C. 355.

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).

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 evaluate your operations and 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.

Conclusion

The violations cited in this letter are not intended to be an all-inclusive list of violations associated with your drug products. You are responsible for investigating and determining the causes of these violations and for preventing their recurrence or the occurrence of other violations.

Note that FDA placed all drugs and drug products manufactured by your firm on Import Alert 66-78 on July 16, 2020, as the methods used in and controls used for the manufacture, processing, packing, or holding of these products do not appear to conform to current good manufacturing practice within the meaning of section 501(a)(2)(B) of the FD&C Act. Your drugs and drug products may be subject to detention without physical examination.

All drugs and drug products manufactured by your firm may remain listed on this import alert until there is evidence establishing that the conditions that gave rise to the appearance of the violation have been resolved, and the Agency has confidence that future entries will be in compliance with the Act. This may include an inspection prior to the agency considering the appearance of adulteration to be addressed.

If you decide you want to manufacture drugs for the United States in the future, request a Regulatory Meeting to discuss corrective actions.

After you receive this letter, respond to this office in writing within 15 working days. Specify what you have done 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. If you believe that your products are not in violation of the FD&C Act, include your reasoning and any supporting information for our consideration.

Send your electronic reply to CDER-OC-OMQ-Communications@fda.hhs.gov

Identify your response with FEI 3016678056 and ATTN: Daniel W. Brisker.

Sincerely,
/S/
Francis Godwin
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1 Due to an increased demand for alcohol-based hand sanitizers during the COVID-19 pandemic, FDA published the Guidance for Industry: *Temporary Policy for Preparation of Certain Alcohol- Based Hand Sanitizer Products During the Public Health Emergency (COVID-19)* on March 19, 2020, and subsequently updated the guidance several times, most recently on August 7, 2020. This guidance communicates the Agency's temporary policy that we do not intend to take action against firms for CGMP violations under section 501(a)(2)(B) of the FD&C Act if such firms prepare alcohol-based hand sanitizers for consumer use (or for use as health care personnel hand rub) during the public health emergency, provided certain circumstances described in the guidance are present. These circumstances include preparation of hand sanitizer products using only the ingredients and formulas set forth in the guidance. In addition to the violative sample results detailed above that demonstrate the presence of methanol in your hand sanitizer products, a review of your drug product labeling further indicates that these products are not prepared consistent with FDA's temporary policy set forth in the guidance. Therefore, these products do not fall within the Agency's temporary policy not to take action against firms manufacturing hand sanitizer products for violations of section 501(a)(2)(B) of the FD&C Act.

2 The 1994 TFM, which does not distinguish between antiseptic hand washes and rubs, proposed for antiseptic handwashes and healthcare personnel handwashes an alcohol concentration of 60 to 95% by volume in an aqueous solution: 59 FR at 31442. Later amendments to the 1994 TFM distinguished between antiseptic hand washes and rubs, and between consumer and healthcare personnel antiseptics, but did not change the alcohol concentration originally proposed in 1994.

3 See, e.g., *Temporary Policy for Preparation of Certain Alcohol-Based Hand Sanitizer Products During the Public Health Emergency (COVID-19)*. Because blumen Advanced Instant Hand Sanitizer Clear Ethyl Alcohol 70% and blumen Clear Advanced Hand Sanitizer Extra Soft are not consistent with the formulations in these guidances, they do not fall within any temporary Agency policy not to take action against firms manufacturing hand sanitizer products for violations of section 505 of the FD&C Act.

4 An inactive ingredient used in over-the-counter (OTC) monograph drugs must meet the requirements of 21 CFR 330.1(e), which requires, among other things, that inactive ingredients must be safe in the amount administered.

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