WARNING LETTER

Grupo Insoma, S.A.P.I de CV

MARCS-CMS 608768 — OCTOBER 23, 2020

Delivery Method:

VIA UPS

Product:

Drugs

Recipient:

Mr. Aldo Montera

Manager

Grupo Insoma, S.A.P.I de CV

Antoine Lavoisier #31
54730 Cuanutitlan,
Mexico

Issuing Office:

Center for Drug Evaluation and Research | CDER

United States

Warning Letter 320-21-03

October 23, 2020

Dear Mr. Montera:

Your firm was recently registered as a human drug manufacturer. The U.S. Food and Drug Administration (FDA) conducted testing of a consumer antiseptic hand rub (also referred to as consumer hand sanitizers), labeled as Hand Sanitizer Gel Unscented 70% Alcohol 1000Lts (also referred to as "Hand Sanitizer Gel"). This drug product was listed as manufactured at your facility, Grupo Insoma, S.A.P.I. de C.V. Antoine Lavoisier #31 Cuanutitlan Mexico (FEI 3016750033). Following an attempt to import this drug product into the United States, Hand Sanitizer Gel Unscented 70% Alcohol 1000Lts was detained and refused admission at the border.

The results of the FDA laboratory testing of batches of this product detained at the border demonstrate that Hand Sanitizer Gel Unscented 70% Alcohol 1000Lts, listed as manufactured at your facility, is adulterated within the meaning of section 501(d)(2) of the Federal Food, Drug, and Cosmetic Act (FD&C Act or the "Act"), 21 U.S.C. 351(d)(2), in that a substance was substituted wholly or in part therefor. In addition, this product is adulterated within the meaning of section 501(a)(2)(B) of the FD&C Act, 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, Hand Sanitizer Gel Unscented 70% Alcohol 1000Lts drug product is an unapproved new drug 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 is misbranded under sections 502(j), (a), (e), (f)(2), (x), and (ee) of the FD&C Act, 21 U.S.C. 352(j), (a), (e), (f)(2), (x), and (ee). Introduction or delivery for introduction of this product into interstate commerce is prohibited under sections 301(d) and (a) of the FD&C Act, 21 U.S.C. 331(d) and (a).

Adulteration Violations

Hand Sanitizer Gel Unscented 70% Alcohol 1000Lts, listed as manufactured at your facility, is labeled to contain 70% volume/volume (v/v), of the active ingredient ethyl alcohol (ethanol). However, FDA laboratory testing of batches of this product detained at the border found that the hand sanitizer contained 0% ethanol and greater than 60% methanol v/v. Therefore, this

hand sanitizer drug product is adulterated under section 501(d)(2) of the Act in that the active ingredient, 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 June 29, 2020 FDA held a teleconference with you and CIRG Waste & Recycling Solutions U.S. LLC, your registered U.S. agent and consignee. We recommended you consider removing your firm's hand sanitizer drug products currently in distribution in 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#products (https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-hand-sanitizers-consumers-should-not-use#products)

On August 5, 2020 FDA held a subsequent teleconference with your registered U.S. agent, CIRG Waste & Recycling Solutions U.S. LLC. During this call your U.S. agent agreed to recall all hand sanitizer drug products currently in distribution to the U.S. market. However, your US agent later sent an email on August 6, 2020, stating that he reached out to you and that he needed to get your firm to recall.

FDA is concerned that to date, neither you nor your US Agent have initiated a recall as agreed to on August 5th.

In response to this letter provide:
• A detailed investigation into how the drugs described above, which were listed as manufactured at your facility and which were 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, and a full reconciliation of all material you distributed.
• Copies of the complete batch records for all batches distributed to the U.S.
• During the teleconference on August 5, 2020, your US Agent stated that you tested the material. In an email to FDA on July 3, 2020, you stated that you test all material you receive and measure the quantity and quality of your final product. Considering

FDA test results directly contradict your assertions and demonstrate gross substitution, FDA questions the validity of test results generated by your facility or by others on your behalf. Provide a complete, comprehensive, and independent assessment of your laboratory practices, procedures, methods, equipment, documentation, and analyst competencies. Based on this review, provide a detailed plan to remediate and evaluate the effectiveness of your laboratory system.

The substitution and contamination with methanol in drug products listed as manufactured at your facility demonstrates that the quality assurance within your facility is not functioning in accord with CGMP requirements under section 501(a)(2)(B) of the Act.[1]

Unapproved New Drug and Misbranding Violations

Hand Sanitizer Gel is a "drug" as defined by section 201(g)(1)(B) of the FD&C Act, 21 U.S.C. 321(g)(1)(B), because it is 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 it is intended to affect the structure or any function of the body. Specifically, this product is intended as a consumer antiseptic rub.

Examples of claims observed on the product label 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 Gel . . . Antimicrobial . . . Uses . . . To help reduce bacteria on the skin"

"Directions . . . Place product on hand . . . rub until dry"

This hand sanitizer product is a "new drug" within the meaning of section 201(p) of the FD&C Act, 21 U.S.C. 321(p), because it is not generally recognized as safe and effective (GRASE) for use under the conditions prescribed, recommended, or suggested in its 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 this product, 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 this hand sanitizer product, nor are we aware of any adequate and well-controlled clinical studies in the published literature that support a determination that your Hand Sanitizer Gel drug product is GRASE for use under the conditions suggested, recommended, or prescribed in its labeling. Accordingly, this product is an unapproved new drug 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 active ingredients 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, Hand Sanitizer Gel does 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 does 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 label, Hand Sanitizer Gel purportedly contains the active ingredient ethyl alcohol (ethanol) 70%. However, as previously discussed, FDA laboratory analysis of batches of this product revealed that samples of Hand Sanitizer Gel contain 0% ethanol, a concentration that is far less then the 70% stated on its product label and far less than the amount of ethanol described in the 1994 TFM.[2] Such a product does not conform to the TFM and the other applicable requirements, nor is it consistent with the formulations described in FDA's temporary policies for hand sanitizers during the COVID-19 public health emergency.[3]

FDA laboratory analyses of batches of this product also revealed that samples of Hand Sanitizer Gel 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*.

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 an OTC drug product's inactive ingredients be safe and suitable.[4]

Finally, this methanol-containing drug product, Hand Sanitizer Gel, is misbranded under sections 502(j), (a), (e), (f)(2), (x), and (ee) of the FD&C Act, 21 U.S.C. 352(j), (a), (e), (f)(2), (x), and (ee). It is misbranded under section 502(j) of the FD&C Act, 21 U.S.C. 352(j), because it is dangerous to health when used according to its labeling as a hand sanitizer. 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. This hand sanitizer is misbranded under section 502(a) of the FD&C Act, 21 U.S.C 352(a), because its labeling is false and misleading. As noted above, Hand Sanitizer Gel is labeled to contain ethyl alcohol 70%. However, FDA laboratory analysis revealed that a sample of this product contains less ethyl alcohol (ethanol) than indicated on the labeling and instead contains a significant concentration of methyl alcohol (methanol), an ingredient that is not declared on the product label. 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 representation of the concentration of the active ingredient ethyl alcohol (ethanol) and the failure to disclose the presence of the ingredient methyl alcohol (methanol) in this product causes this product to be misbranded under section 502(a) of the FD&C Act, 21 U.S.C. 352(a). The failure of this product to list methyl alcohol (methanol) as an ingredient on its label causes it to be misbranded under section 502(e)(1)(A) of the FD&C Act, 21 U.S.C. 352(e)(1)(A).

In addition, Hand Sanitizer Gel is also misbranded under section 502(f)(2) of the FD&C Act, 21 U.S.C. 352(f)(2), because the product label does not include all of the applicable warnings as required under 21 CFR 330.1(g). Specifically, the label does 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."

Furthermore, Hand Sanitizer Gel is misbranded under section 502(x) of the FD&C Act, 21 U.S.C. 352(x), because the product label fails to disclose a domestic address or domestic telephone number through which the responsible person may receive a report of a serious adverse event with such drug.

Lastly, this product is misbranded under section 502(ee) of the FD&C Act, 21 U.S.C. 352(ee) because Hand Sanitizer Gel is a nonprescription drug subject to section 505G of the FD&C Act, 21 U.S.C. 355h, but does not comply with the requirements for marketing under that section and is 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 10, 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 3016750033 and ATTN: Daniel W. Brisker.

Sincerely,
/S/
Francis Godwin
Director
Office of Manufacturing Quality
Office of Compliance
Center for Drug Evaluation and Research

CC:
Registered US Agent / Consignee
Dean Putegnat
CIRG Waste & Recycling Solutions US, LLC
5250 Coffee Port Road
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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 hand sanitizer products listed as manufactured at your facility, a review of the your drug product labeling further indicates that the product is not prepared consistent with FDA's temporary policy set forth in the guidance. Therefore, this product does 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 Hand Sanitizer Gel is not consistent with the formulations in these guidances, it does 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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