WARNING LETTER

BBC Group Limited

MARCS-CMS 614659 — AUGUST 04, 2021

Delivery Method:

VIA UPS

Product:

Drugs

Recipient:

Mr. Alan Wong

General Manager

BBC Group Limited

Yangxia Development Zone
Pumei Town Yunxiao County 363300
China

Issuing Office:

Center for Drug Evaluation and Research

United States

Warning Letter 320-21-53

August 4, 2021

Dear Mr. Wong,

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, BBC Group Limited, FEI 3010165327, at Yangxia Development Zone, Pumei Town, Yunxiao County, Zhangzhou, China, from March 22 to March 26, 2021.

This warning letter summarizes significant violations of Current Good Manufacturing Practice (CGMP) regulations for finished pharmaceuticals. See Title 21 Code of Federal Regulations (CFR), parts 210 and 211 (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).

In addition, your firm manufactures L.O.L. SURPRISE! (WATERMELON, STRAWBERRY, and CHERRY) SCENTED HAND SANITIZER products that 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(ee) of the FD&C Act, 21 U.S.C. 352(ee). Introduction or delivery for introduction of such 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.

We reviewed your April 13, 2021 response to our Form FDA 483 in detail. Your response is inadequate because it did not provide sufficient detail or evidence of corrective actions to bring your operations into compliance with CGMP.

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

CGMP Violations

1. Your firm failed to exercise appropriate controls over computer or related systems to assure that only authorized personnel institute changes in master production and control records, or other records (21 CFR 211.68(b)).

Your firm manufactures over-the-counter (OTC) drug products, including alcohol-based hand sanitizers[1]. During the inspection of your facility, our investigator attempted to review analytical data from your gas chromatograph (GC) supporting the release of drug products distributed to the United States. However, your firm stated that all testing data from 2018 to 2020 was lost approximately one month prior to the initiation of our inspection. The GC is used to analyze the identity and strength of active ingredients and impurities contained in your OTC drug products, as well as other critical parameters. According to firm management, the data is unrecoverable. While your firm retained a static copy of laboratory records for review (i.e., paper record), they were inadequate as they did not preserve the dynamic record format of the full chromatographs to support test results and they did not include system suitability documentation that are part of the complete, original record.

Additionally, our investigator observed that the computerized system and software associated with your GC lacked restricted access. For example, your laboratory employees who used the GC to perform analyses of drug products all logged in as “System Administrator,” which does not require a password, and had full system administration rights. In addition, audit trails on your GC were not enabled.

Furthermore, you did not retain all original, dynamic records, obtained during the course of testing on other laboratory equipment. Your viscometer and UV-Vis spectrophotometer had the capability to save data from product/material testing. Despite having this capability, your analysts failed to save the complete, dynamic testing data, and therefore the data was not available for review by the FDA investigator. The viscometer is used to measure the viscosity of finished drug products during release testing and the UV-Vis spectrophotometer is used to measure ethanol content during raw material testing.

Your firm also utilizes electronic spreadsheets to input data for your stability program. However, these spreadsheets are not controlled and there is no protection to prevent data manipulation, overwriting, or erasure.

In your response, you indicated that you purchased and/or installed additional equipment to address this violation, including, but not limited to, an uninterrupted power source, remote hard drive, electrical equipment, and new software. Your response also states that you have updated and developed associated procedures, created individual accounts for all personnel that utilize laboratory equipment, and conducted accompanying trainings. However, your response is inadequate because it lacked supporting documentation, including evidence to support that the computer security controls were effective at preventing data and document manipulation. Additionally, you did not perform a retrospective risk assessment into how system vulnerabilities may have impacted data integrity.

Your firm does not adequately ensure the accuracy and integrity of data to support the safety, effectiveness, and quality of the drugs you manufacture. See FDA's guidance document Data Integrity and Compliance With Drug CGMP for guidance on establishing and following CGMP compliant data integrity practices at https://www.fda.gov/media/97005/download (https://www.fda.gov/media/97005/download).

We strongly recommend that you retain a qualified consultant to assist in your remediation. In response to this letter, provide the following:

• A comprehensive investigation into the extent of the inaccuracies in data records and reporting including results of the data review for drugs distributed to the United States. Include a detailed description of the scope and root causes of your data integrity lapses.
• A current risk assessment of the potential effects of the observed failures on the quality of your drugs. Your assessment should include analyses of the risks to patients caused by the release of drugs affected by a lapse of data integrity and analyses of the risks posed by ongoing operations.
• A management strategy for your firm that includes the details of your global corrective action and preventive action plan. The detailed corrective action plan should describe how you intend to ensure the reliability and completeness of all data generated by your firm including microbiological and analytical data, manufacturing records, and all data submitted to FDA.
• A complete assessment of documentation systems used throughout your manufacturing and laboratory operations to determine where documentation practices are insufficient. Include a detailed Corrective Action and Preventive Action (CAPA) plan that comprehensively remediates your firm's documentation practices to ensure you retain attributable, legible, complete, original, accurate, contemporaneous records throughout your operation.
• A comprehensive, independent assessment and CAPA plan for computer system security and integrity. Include a report that identifies design and control vulnerabilities, and appropriate remediations for each of your laboratory computer systems. This should include, but not be limited to:
  o A list of all hardware that includes all equipment, both standalone and network, in your laboratory.
  o Identification of vulnerabilities in hardware and software, encompassing both networked and non-networked systems.
  o A list of all software configurations and versions, details of all user privileges, and oversight responsibilities for each of your laboratory systems. Regarding user privileges, specify user roles and associated user privileges (including the specific permissions allowed for anyone who has administrative rights) for all staff who have access to the laboratory computer systems, and their organizational affiliations and titles. Also describe how you will ensure laboratory staff are not given administrative rights, or other permissions that compromise data retention or reliability.
  o System security provisions, including, but not limited to, whether unique user names/passwords are always used, and their confidentiality safeguarded.
  o Detailed procedures for robust use and review of audit trail data, and current status of audit trail implementation for each of your systems.
  o Interim control measures and procedural changes for the control, review, and full retention of laboratory data.
  o A detailed summary of your procedural updates and associated training, including but not limited to system security control to prevent unauthorized access, appropriate user role assignments, secondary review of all analyses, and other system controls.
  o Provisions for oversight by QA managers, executives, and internal auditors with appropriate information technology (IT) expertise (e.g., to evaluate infrastructure, configuration, network requirements, data management practices, and segregation of duties including administrator rights).
  o A remediated program for ensuring strict ongoing control over electronic and paper-based data to ensure that all additions, deletions, or modifications of information in your records are authorized, and all data is retained. Include a full CAPA plan and any improvements made to date.
  o An independent, thorough retrospective assessment into the impact of laboratory system design, control,

and staff practices on your data accuracy, completeness, and retention since January 1, 2018.
• A comprehensive, independent assessment of your change management system. This assessment should include, but not be limited to, your procedure(s) to ensure changes are justified, reviewed, and approved by your quality unit. Your change management program should also include provisions for determining change effectiveness.

2. Your firm failed to establish laboratory controls that include scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that components, drug product containers, closures, in-process materials, labeling, and drug products conform to appropriate standards of identity, strength, quality, and purity (21 CFR 211.160(b)).

Your analytical test methods were not adequately validated, including those for the active ingredient ethanol, which is used to manufacture your alcohol-based hand sanitizers, and analysis for the impurity **(b)(4)**. Specifically, no system suitability requirements were present and reference standards were not identified. Data must be available to establish that the analytical procedures used in testing meet proper standards of accuracy, sensitivity, specificity, and reproducibility and are suitable for their intended purpose.

In your response, you indicated that you updated test methods, established method validation protocols, and completed test method evaluation. However, your response is inadequate for the following reasons.
• The response lacked information on the analyte reference standards used for the method validation.
• The response lacked method validation details on identity of the tested analytes, system suitability, method specificity data, preparations of the analyte stock solutions, and accuracy and precision data from spike and recovery experiments at different concentration levels.
• The response lacked an assessment of drug products manufactured utilizing the deficient methods.

In response to this letter, provide the following:
• A comprehensive, 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.
• An independent assessment of all test methods and data review procedures used by your firm to ensure they have appropriate instructions, method suitability criteria, and validation to determine whether they are fit for intended purposes.
• Your test results, using an adequately validated test method, of retains for all finished drug products, within expiry. You should test all appropriate quality attributes of each batch that you distributed into U.S. commerce to ensure that your drug products conform to appropriate standards of identity, strength, quality, and purity. If testing yields an OOS result, indicate the corrective actions you will take, including notifying customers and initiating recalls.

See FDA's guidance document *Analytical Procedures and Methods Validation for Drugs and Biologics* for general principles and approaches that FDA considers appropriate elements of method validation at: https://www.fda.gov/media/87801/download (https://www.fda.gov/media/87801/download).

3. 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)).

During our inspection, the investigator observed rust on **(b)(4)** and product contact surfaces of four of the **(b)(4)** used to manufacture drug products, including the manufacture of your OTC hand sanitizers. Upon request, you provided our investigator with manufacturing equipment maintenance logs for the aforementioned **(b)(4)**. These documents were only available in Chinese. After the conclusion of the inspection, the FDA had the document translated and found that the document provided was for equipment identified as "liquid washing

pan" with serial number WJB-001, which is located in Workshop **(b)(4)** on the **(b)(4)** floor, and not the **(b)(4)** with equipment ID's 12 through 15 located in Workshop **(b)(4)** on the **(b)(4)** floor that were observed with rust. FDA is concerned that you provided maintence records for different equipment than those requested during the inspection.

In your response, you indicated that you replaced all the **(b)(4)** in your **(b)(4)**. However, your response failed to address the rust documented in other parts of the **(b)(4)**. Additionally, your response is inadequate as you failed to revise your cleaning and maintenance procedures to prevent recurrence of this issue, you failed to perform a risk assessment of drug products manufactured in the four **(b)(4)** that contained rust, and you did not determine the root cause of why employees who perform **(b)(4)** inspections of manufacturing equipment did not observe the rust in the **(b)(4)**.

In response to this letter, provide the following:

• Your CAPA plan to implement routine, vigilant operations management oversight of facilities and equipment. This plan should ensure, among other things, prompt detection of equipment/facilities performance issues, effective execution of repairs, adherence to appropriate preventive maintenance schedules, timely technological upgrades to the equipment/facility infrastructure, and improved systems for ongoing management review.
• Your plan for continued manufacture of drug products in the aforementioned **(b)(4)** containing rust. Our inspection observed rust on and around the **(b)(4)** and other parts of the **(b)(4)**.
• A risk assessment for drug products manufactured in the four **(b)(4)** that contained rust to determine if a market action is warranted.

Unapproved New Drug and Misbranding Violations

L.O.L. SURPRISE! (WATERMELON, STRAWBERRY, and CHERRY) SCENTED HAND SANITIZER products 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 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 for use as a consumer topical antiseptic.

Examples of claims observed on the L.O.L. SURPRISE! (WATERMELON, STRAWBERRY, and CHERRY) SCENTED HAND SANITIZER product label and labeling that provide evidence of the intended uses (as defined in 21 CFR 201.128) of the products include, but may not be limited to, the following:

"HAND SANTIZER. . .**Drug Facts**. . .**Uses**. . . to decrease bacteria on the skin that could cause disease. . . **Direction** – rub a dime sized drop into hands."

This topical antiseptic 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 FD&C Act (which is not the case for this product, as further described below) or other exemptions not applicable here. No FDA-approved application pursuant to section 505 of the FD&C Act, 21 U.S.C. 355, is in effect for these drug products, nor are we aware of any adequate and well-controlled clinical studies in the published literature that support a determination that your L.O.L. SURPRISE! (WATERMELON, STRAWBERRY, and CHERRY) SCENTED HAND SANITIZER drug products are GRASE for use under the conditions suggested, recommended, or prescribed in its 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 have been the subject of rulemaking under FDA'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 "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)(Consumer Antiseptic Rubs Proposed Rule). Over the course of these rulemakings, three active ingredients (benzalkonium chloride, ethyl alcohol (ethanol), and isopropyl alcohol) were classified as Category III for use 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 in 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, L.O.L. SURPRISE! (WATERMELON, STRAWBERRY, and CHERRY) SCENTED HAND SANITIZER products do not conform to the 1994 TFM, as further amended by the 2016 Consumer Antiseptic Rubs 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 label, L.O.L. SURPRISE! (WATERMELON, STRAWBERRY, and CHERRY) SCENTED HAND SANITIZER products contain the active ingredient "chloroxylenol 0.015%." Chloroxylenol is not permitted as an active ingredient for use as a consumer antiseptic hand rub drug product under the 1994 TFM.[2] Such products do not conform with the TFM, nor are they consistent with the formulations described in FDA's temporary policies for hand sanitizers during the COVID-19 public health emergency.[3]

Additionally, these products are misbranded under section 502(ee) of the FD&C Act, 21 U.S.C. 352(ee) because L.O.L. SURPRISE! (WATERMELON, STRAWBERRY, CHERRY) SCENTED HAND SANITIZER products 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 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).

Disparities in Records Submitted to the Agency

FDA placed your firm on Import Alert 66-40 on September 30, 2020 as information you provided in your response to a FDA request for records pursuant to section 704(a)(4) of the FD&C Act, 21 U.S.C. 374(a)(4), did not appear to conform to CGMP. Specifically, your response to the FDA records request demonstrated a lack of analytical data supporting drug product release, as required under 21 CFR 211.165. Subsequent to your placement on Import Alert, you submitted additional data to the agency, now including test results of drug products you distributed to the United States. To evaluate the disparity in the records provided, and in part to evaluate if your firm should be removed from import alert, FDA conducted an inspection of your facility. However, upon physical inspection of your facility, the raw data related to your submitted test results were unavailable. The records you submitted electronically prior to the inspection were not consistent with what was observed during the FDA inspection of your facility. Your firm will remain on import alert until FDA is satisfied that the appearance of violations observed have been resolved.

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. 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 that exist at your facility/in connection with your products. You are responsible for investigating and determining the causes of any violations and for preventing their recurrence or the occurrence of other violations.

FDA placed your firm on Import Alert 66-40 on September 23, 2020.

Correct any violations promptly. FDA may withhold approval of new applications or supplements listing your firm as a drug manufacturer until any violations are completely addressed and we confirm your compliance with CGMP.We may re-inspect to verify that you have completed corrective actions to any violations.

Failure to address any violations may also result in the FDA continuing to refuse admission of articles manufactured at BBC Group Limited, FEI 3010165327, at Yangxia Development Zone; Pumei Town, Yunxiao County; Zhangzhou, China into the United States under section 801(a)(3) of the FD&C Act, 21 U.S.C. 381(a)(3). Articles under this authority that appear to be adulterated or misbranded may be detained or refused admission, 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 FD&C Act, 21 U.S.C. 351(a)(2)(B).

This letter notifies you of our findings and provides you an opportunity to address the above deficiencies. 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. In response to this letter, you may provide additional information for our consideration as we continue to assess your activities and practices. 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 CDER-OC-OMQ-Communications@fda.hhs.gov. Identify your response with FEI 3010165327 and ATTN: CDR Frank Verni.

Sincerely,
/S/

Francis Godwin
Director
Office of Manufacturing Quality
Office of Compliance
Center for Drug Evaluation and Research

CC:
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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 February 10, 2021. 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 rubs) 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. Are view of the purported formulations on the drug product's labeling indicates that this 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 denatured in accordance with Bureau of Alcohol, Tobacco and Firearms regulations. 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 L.O.L. SURPRISE! (WATERMELON, STRAWBERRY, and CHERRY) SCENTED HAND SANITIZER products are not consistent with the formulations described 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.

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