Nox Bellcow Cosmetics Co. Ltd. 5/9/18

10903 New Hampshire Avenue
Silver Spring, MD 20993

Via UPS
Return Receipt Requested

Warning Letter 320-18-49

May 9, 2018

Mr. Shi Da Lin
President and General Manager
Nox Bellcow Cosmetics Co., Ltd.
No. 50 Dognfu North Road
Nautou Town, Zhongshan City
Guangdong Province
China

Dear Mr. Lin:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Nox Bellcow Cosmetics Co., Ltd. at No. 50 Dognfu North Road, Nautou Town, Zhongshan City, Guangdong Province, from September 18 to 22, 2017.

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 product is 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 October 22, 2017, response in detail. However, your response is inadequate because it did not provide sufficient commitments or evidence of corrective actions to bring your operations into CGMP compliance.

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

1. Your firm failed to establish an adequate quality control unit with the responsibility and authority to approve or reject all components, drug product containers, closures, in-process materials, packaging materials, labeling, and drug products (21 CFR 211.22(a)).

Your quality unit failed to exercise its responsibility to review and approve test results before batch release. Instead, your quality unit released your non-sterile over-the-counter (OTC) finished drug product, **(b)(4)**, before you received assay (% content) results for the active ingredient, **(b)(4)**, from your contract laboratory.

Further, your quality unit lacked adequate systems and documentation to oversee quality, including insufficient:

- change control;
- quality control testing practices;
- batch record review; and
- annual product reviews.

In response to this letter:

- Conduct a retrospective review of all assay results for active content used to manufacture drug product currently in the U.S. market to determine if the specification was met. If you identify out-of-specification (OOS) results, describe the actions you have taken or will take to ensure the quality of marketed products and protect patients, including notification of customers and recalls.
- Provide an independent, comprehensive assessment of the documentation systems used throughout your manufacturing and laboratory operations to determine where else you lack complete records. Include a detailed corrective action and preventive action (CAPA) plan with systemic remediations to assure your facility maintains complete records.
- Obtain an independent, comprehensive assessment of your quality unit. Provide a thorough CAPA that fully remediates your quality unit, including but not limited to procedures that detail appropriate responsibilities and authorities (e.g., final review of all production and control records before a final batch disposition decision) of your quality unit.

2. Your firm failed to conduct at least one test to verify the identity of each component of a drug product. Your firm also failed to validate and establish the reliability of your component supplier's test analysis at appropriate intervals (21 CFR 211.84(d)(1) and (2)).

You failed to perform appropriate identity tests on incoming active pharmaceutical ingredients (API). Instead, you accepted these materials based only on their appearance and odor. You also did not test API to determine their conformance to purity, strength, and other appropriate specifications. Your firm released API for use in drug product manufacturing based on certificates of analysis (CoA) from your supplier without establishing the reliability of the suppliers' analysis through appropriate validation.

In response to this letter:

- Provide your procedure for incoming component testing. Include a commitment to conduct at least one specific identity test for each incoming component (both active and inactive ingredients) lot.
- Describe in detail how you plan to test each incoming component lot for conformity with all appropriate written specifications for purity, strength and quality. If you accept your suppliers' CoA in lieu of testing each component lot for purity, strength, and quality, specify how you plan to establish the reliability of your suppliers' test results for these attributes through periodic validation.

3. You firm failed to establish and follow adequate written procedures for cleaning and maintenance of equipment (21 CFR 211.67(b)).

The cleaning validation for your non-dedicated **(b)(4)** tank, C2038, used to manufacture your drug product was inadequate. Your high-performance liquid chromatography (HPLC) chromatograms for residual disinfectant showed significant peaks for rinse samples with a retention time similar to that of your cleaning agent, **(b)(4)**. You failed to investigate these peaks.

During the inspection, you integrated these peaks, which yielded OOS results for residual disinfectant. Your cleaning validation failed multiple rinse samples tested for residual disinfectant.

In response to this letter, provide:

- An assessment of the impact of residual cleaning agents on the quality of your drug product.
- Your plan of action, with timelines, to develop and implement an appropriate cleaning validation program for your manufacturing equipment. Your program should include appropriate procedures to assure that your cleaning results comply with established acceptance criteria.
- A comprehensive, independent assessment of your overall system for investigations of deviations, atypical events, complaints, OOS results, and failures. Your CAPA should include but not be limited to improvements in investigation competencies, root cause analysis, documentation, written procedures, and quality unit oversight.

4. Your firm failed to ensure that laboratory records included complete data derived from all tests necessary to assure compliance with established specifications and standards (21 CFR 211.194(a)).

You failed to maintain data generated for numerous tests performed on your drug product. For example, during the inspection, you were not able to provide complete data for microbial, pH, weight, and dimension tests performed on your drug product.

In addition, you were not able to provide complete data to support testing of your API, in-process testing for **(b)(4)**, and microbial testing of **(b)(4)**.

You only reported final calculated results on your CoA and in analytical laboratory records for each of the tests performed.

In response to this letter, include the following:

- Describe how you will ensure that test methods and equipment are adequately validated, verified, or calibrated at appropriate intervals and fit for purpose.
- Provide a comprehensive, independent review of your laboratory practices, methods, equipment, and analyst competencies. Based on this review, provide a detailed CAPA plan to fully remediate your laboratory system. Your plan should also include your process for evaluating the effectiveness of the implemented CAPA.

5. Your firm failed to ensure that its drug product bore an expiration date that was supported by appropriate stability testing (21 CFR 211.137(a)).

During the inspection, you could not provide stability data to support the **(b)(4)** expiration date for your drug product. In addition, you indicated that you did not perform any ongoing monitoring of stability for your product.

In response to this letter, provide your plan, with timelines, to develop and implement a complete drug stability program. This plan should also include an assessment of the stability of drug product currently on the U.S. market.

Data Integrity Remediation

Your quality system does not adequately ensure the accuracy and integrity of data to support the safety, effectiveness, and quality of the drugs you manufacture. We strongly recommend that you retain a qualified consultant to assist in your remediation.

In response to this letter, provide the following.
A. A comprehensive investigation into the extent of the inaccuracies in data records and reporting. Your investigation should include:

- A detailed investigation protocol and methodology; a summary of all laboratories, manufacturing operations, and systems to be covered by the assessment; and a justification for any part of your operation that you propose to exclude.
- Interviews of current and former employees to identify the nature, scope, and root cause of data inaccuracies. We recommend that these interviews be conducted by a qualified third party.
- An assessment of the extent of data integrity deficiencies at your facility. Identify omissions, alterations, deletions, record destruction, non-contemporaneous record completion, and other deficiencies. Describe all parts of your facility's operations in which you discovered data integrity lapses.
- A comprehensive retrospective evaluation of the nature of the testing data integrity deficiencies. We recommend that a qualified third party with specific expertise in the area where potential breaches were identified should evaluate all data integrity lapses.

B. A current risk assessment of the potential effects of the observed failures on the quality of your drugs. Your assessment should include analysesof the risks to patients caused by the release of drugs affected by a lapse of data integrity, and risks posed by ongoing operations.

C. A management strategy for your firm that includes the details of your global corrective action and preventive action plan. Your strategy should include:

- A detailed corrective action plan that describes how you intend to ensure the reliability and completeness of all the data you generate, including analytical data, manufacturing records, and all data submitted to FDA.
- A comprehensive description of the root causes of your data integrity lapses, including evidence that the scope and depth of the current action plan is commensurate with the findings of the investigation and risk assessment. Indicate whether individuals responsible for data integrity lapses remain able to influence CGMP-related or drug application data at your firm.
- Interim measures describing the actions you have taken or will take to protect patients and to ensure the quality of your drugs, such as notifying your customers, recalling product, conducting additional testing, adding lots to your stability programs to assure stability, drug application actions, and enhanced complaint monitoring.
- Long-term measures describing any remediation efforts and enhancements to procedures, processes, methods, controls, systems, management oversight, and human resources (e.g., training, staffing improvements) designed to ensure the integrity of your company's data.
- A status report for any of the above activities already underway or completed.

Quality Unit Authority

Significant findings in this letter indicate that your quality unit is not able to fully exercise its authority and/or responsibilities. Your firm must provide the quality unit with the appropriate

authority and sufficient resources to carry out its responsibilities and consistently ensure drug quality.

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. The third-party consultant should comprehensively audit and assist with remediating your operations, including but not limited to investigations, raw materials, laboratory controls, data management systems, documentation, quality unit authorities and resources, and all other elements of your quality system.

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 for 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.

FDA placed your firm on Import Alert 66-40 on December 27, 2017.

Until you correct all violations completely and we confirm your compliance with CGMP, FDA may withhold approval of any new applications or supplements listing your firm as a drug manufacturer.

Failure to correct these violations may also result in FDA continuing to refuse admission of articles manufactured at Nox Bellcow Cosmetics Co., Ltd. at No. 50 Dognfu North Road, Nautou Town, Zhongshan City, Guangdong Province, into the United States under section 801(a)(3) of the FD&C Act, 21 U.S.C. 381(a)(3). Under the same authority, articles may be subject to refusal of 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).

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 CDER-OC-OMQ-Communications@fda.hhs.gov or mail your reply to:

Ms. Christina Alemu-Cruickshank
Compliance Officer
U.S. Food and Drug Administration
White Oak Building 51, Room 4212
10903 New Hampshire Avenue
Silver Spring, MD 20993
USA

Please identify your response with FEI 3006213806.

Sincerely,
/S/
Francis Godwin

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