Nan San (HK) Pharmaceutical Factory Ltd. 2/23/18

U.S. FOOD & DRUG ADMINISTRATION

10903 New Hampshire Avenue
Silver Spring, MD 20993

Via UPS

Warning Letter 320-18-36

February 23, 2018

Ms. Cheuk Yin Cheung
Owner
Nan San (HK) Pharmaceutical Factory Limited
Hoi Bun Industrial Building
6 Wing Yip Street, Unit C1, 10/F
Kwun Tong Kowloon, 5678
Hong Kong

Dear Ms. Cheung:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Nan San (HK) Pharmaceutical Factory Limited at Hoi Bun Industrial Building, 6 Wing Yip Street, Unit C1, 10/F, Kwun Tong Kowloon, Hong Kong, from September 25 to 29, 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 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 also manufactures misbranded drug products. Specifically, as formulated and labeled, Musflex and Easy-Flex are misbranded under sections 502(e)(1)(A)(ii), (iii) and (f)(2) of the FD&C Act, 21 U.S.C. 352(e)(1)(A)(ii), (iii) and (f)(2).

CGMP Violations

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

1. Your firm failed to perform, 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, prior to release, and for each batch of drug product required to be free of objectionable microorganisms, appropriate laboratory testing, as necessary (21 CFR 211.165(a) and (b)).

Your firm failed to test all batches of over-the-counter (OTC) topical liquid analgesics for conformance to their specifications before releasing each batch. For example, you did not perform microbial limit tests for each batch of your Easy-Flex analgesic lotion released between 2013 and 2016. Instead, you performed microbial limit testing on one batch in 2013, and reported the same results to release subsequently-manufactured batches to the United States.

You also used a contract laboratory to conduct finished product testing. Although your finished drug products contain **(b)(4)** active ingredients, your contract laboratory only tested for the strength and identity of one of those ingredients in the finished product testing on which you relied to release your drug products.

2. Your firm failed to establish 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)).

You have not validated the processes used to manufacture your OTC drug products. You did not perform process qualification studies, and you also lacked an ongoing program for monitoring process control to ensure stable manufacturing operations and consistent drug quality. See FDA's guidance document, *Process Validation: General Principles and Practices*, for approaches that FDA considers appropriate elements of process validation, at **https://www.fda.gov/downloads/drugs/guidances/ucm070336.pdf (https://www.fda.gov/downloads/drugs/guidances/ucm070336.pdf)**.

3. Your firm failed to conduct at least one test to verify the identity of each component of a drug product (21 CFR 211.84(d)(1)).

Your firm failed to test incoming active pharmaceutical ingredients and other components for identity, purity, strength, and quality prior to use in your drug manufacturing process.

4. Your firm failed to establish and follow an adequate written testing program designed to assess the stability characteristics of drug products and to use results of such stability testing to determine appropriate storage conditions and expiration dates (21 CFR 211.166(a)).

Your firm labeled your drug products with a **(b)(4)**-year expiration date without adequately assessing the stability characteristics of these drug products. Your firm does not have adequate stability data to support the assigned expiration date.

We acknowledge your response to the Form FDA 483 regarding the CGMP observations that you submitted to the FDA on November 14, 2017. Your response to the CGMP observations, including the violations discussed above, was inadequate because it did not provide sufficient evidence of corrective actions to bring your operations into compliance with CGMP.

CGMP Consultant Recommended

Based upon the nature of the CGMP 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.

***Misbranding Violations**: Musflex and Easy-Flex*

Examples of claims observed on your product labels for Musflex and Easy-Flex that establish the intended uses of the products include, but may not be limited to, the following:

> "Uses: For the temporary relief of minor aches and pains of muscles and joints associated with simple backache, arthritis, strains, bruises, and sprains."

Based on the above claims, Musflex and Easy-Flex 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 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, this product is intended as an external analgesic.

Drug products such as Musflex and Easy-Flex that are intended as external analgesics, such as the temporary relief of minor aches and pains, are being evaluated as part of the OTC Drug Review. They have been proposed to be classified as generally recognized as safe and effective and not misbranded under the *Tentative Final Monograph (TFM) for External Analgesic Drug Products for Over-the-Counter (OTC) Human Use* (48 FR 5852, February 8, 1983) if they meet each condition in the TFM and each general condition in 21 CFR 330.1.

Pending a final rule, FDA does not intend to pursue regulatory action against products marketed in conformance with the conditions proposed in the TFM and each general condition in 21 CFR 330.1. Such marketing, however, is subject to the risk that a final rule may require reformulation and/or relabeling or FDA approval through the "new drug" procedures of the FD&C Act (section 505). The labeling for such drugs, like all OTC drugs, must comply with all the requirements of section 502 of the FD&C Act and all pertinent regulations found in Title 21 of the Code of Federal Regulations (21 CFR).

Musflex and Easy-Flex are misbranded under section 502(e)(1)(A)(ii) and (iii) of the FD&C Act, 21 U.S.C. 352(e)(1)(A)(ii) and (iii), because their labels fail to declare active ingredients, the proportion of each active ingredient, and inactive ingredients. It was observed during the inspection that **(b)(4)**, menthol, and **(b)(4)** are used in the manufacturing of Musflex and Easy-Flex.

Furthermore, your firm acknowledged that these **(b)(4)** ingredients are used as active ingredients in both products, but all **(b)(4)** ingredients are not declared as active ingredients on the product labels. Specifically, the Musflex product label fails to declare **(b)(4)** as an active ingredient and the Easy-Flex product label fails to declare **(b)(4)** as active ingredients. It was also observed during the inspection that your firm used a **(b)(4)** of inactive ingredients in the manufacturing of Musflex and Easy-Flex. Your firm was unable to provide a complete list of all the ingredients that made up the **(b)(4)** of inactive ingredients, and you acknowledged that not all inactive ingredients are declared on the product labels.

Musflex and Easy-Flex are also misbranded under Section 502(f)(2) the FD&C Act, 21 U.S.C. 352(f)(2) because the products' labeling fails to bear all of the required warnings. For example, both products fail to disclose the required warning, "Do not use otherwise than as directed." See 21 CFR 201.314(g)(1).

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). Therefore, the marketing of Musflex and Easy-Flex violate this provision of the FD&C Act.

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 January 8, 2018.

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 Nan San (HK) Pharmaceutical Factory Limited, Hoi Bun Industrial Building, 6 Wing Yip Street, Unit C1, 10/F, Kwun Tong Kowloon, Hong Kong 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 (mailto:CDER-OC-OMQ-Communications@fda.hhs.gov)** or mail your reply to:

CDR Frank Verni, R.Ph.
Compliance Officer
U.S. Food and Drug Administration
White Oak Building 51, Room 4359
10903 New Hampshire Avenue
Silver Spring, MD 20993
USA

Please identify your response with FEI: 3003723042.

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

cc:
Mr. Chi Pun Cheung

Director
Nan San (HK) Pharmaceutical Factory Limited
Hoi Bun Industrial Building
6 Wing Yip Street, Unit C1, 10/F
Kwun Tong Kowloon, 5678
Hong Kong

More in Warning Letters (/ICECI/EnforcementActions/WarningLetters/default.htm)