Firson Co., Ltd. 8/31/17

10903 New Hampshire Avenue
Silver Spring, MD 20993

Via UPS

Warning Letter 320-17-48

August 31, 2017

Mr. Kim Dong-Jin
President
Firson Co. Ltd.
47 Handeul 1-ro
Seobuk-gu, Cheonan-si
Chungcheongnam-do
Korea

Dear Mr. Kim:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Firson Co. Ltd. at 47 Handeul 1-ro, Seobuk-gu, Cheonan-si, Chungcheongnam-do, from November 3 to 11, 2016.

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).

We reviewed your November 28, 2016, response in detail and acknowledge receipt of your subsequent correspondence.

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

1. Your firm failed to establish and follow appropriate written procedures that are designed to prevent microbiological contamination of drug products purporting to be sterile, and that include validation of all aseptic and sterilization processes (21 CFR 211.113(b)).

You failed to demonstrate that your aseptic processes are capable of preventing microbial contamination of your **(b)(4)** drug products.

Inadequate Media Fills
Your media fill program was inadequate. Simulations were not performed at a sufficient frequency and were not representative of worst-case production conditions. Firm personnel reported that an extra cleaning was performed prior to a media fill. Alcohol was added to the growth media. Although your commercial process requires significant manual interventions and you fill more than **(b)(4)** units for approximately **(b)(4)**, your media fill only consisted of filling **(b)(4)** units over less than **(b)(4)**. The media fill program also was not designed and documented to fully simulate aseptic interventions (i.e., planned and unplanned) performed on the processing line and to simulate the maximum number of persons allowed in the room. Further, your minimal media fill records lacked other basic information, including the operators who participated in the media fills.

You have not demonstrated that your aseptic process prevents contamination of your **(b)(4)** drug products. Adequate media fill studies accurately simulate aseptic processing line practices and conditions, including any interventions that can be encountered during actual production. These studies are conducted at least semi-annually (for each shift) to evaluate whether each aseptic processing line remains in control and robustly yields sterile drugs that are fit for use by patients.

In your response, you provided *Media Fill Validation Protocol for Aseptic Process Simulation*, which your quality unit approved on January 16, 2017, with the results of new media fills. The response is inadequate as it lacks documentation (e.g., media fill batch record) of the interventions and examinations of filled units for contamination.

Inadequate Smoke Studies
Our inspection found that you lacked smoke studies to evaluate whether unidirectional airflow exists on your **(b)(4)** ointment aseptic processing line.

Your response states that you completed dynamic airflow studies, and you provided three brief smoke study videos. While you state that these studies were conducted under “dynamic” conditions, we note that they still lack an evaluation of operational conditions and aseptic interventions (e.g., reloading tubes and caps; filling the **(b)(4)**). In addition, the view of the aseptic processing zone was obstructed and the smoke manifold was not stationary for sufficient time.

Inadequate Sterilization

You lack a robust process to sterilize your drugs. Our investigator found that you use **(b)(4)** to **(b)(4)** your **(b)(4)** ointment drug products in a compounding tank to **(b)(4)** for **(b)(4)**. These conditions provide minimal lethality (**(b)(4)**). The batch records provided during the inspection lacked **(b)(4)**, to render your **(b)(4)** ointments sterile prior to distribution.

In your response to this letter:

- Provide a comprehensive review of your media fill program and corrective and preventive actions (CAPA) to ensure an appropriate simulation of the worst-case conditions of commercial manufacturing. Also detail how you examine units for presence of growth, and perform batch yield reconciliation.
- Describe whether your revised program requires **(b)(4)** to perform semi-annual media fills for each aseptic processing line.
- Provide a summary of all media fills performed since January 1, 2015, including processing line, date of media fill, number of units run, number examined, and number of potentially contaminated units found.
- Provide the complete sterility testing history for your **(b)(4)** products (include all sterility positives, irrespective of whether they were subsequently invalidated).
- Describe how you will adequately sterilize the drug formulation before aseptic filling. Provide your sterilization cycle parameters, validation protocols, validation reports, lethality of the process, and sterility assurance level.
- Describe whether your **(b)(4)** containers and closures are sterilized. Include sterilization methods, validation protocols, and validation reports for all **(b)(4)** containers and closures.
- Provide an action plan and timelines for implementing corrective actions, including notifying your customers and recalling any **(b)(4)** ointment drug products within expiry that were distributed to the U.S. and manufactured without adequate sterilization.
- Provide your environmental and personnel monitoring procedures. Justify monitoring locations, frequency, and action limits.
- Provide smoke studies under dynamic conditions that include a thorough and complete evaluation of aseptic interventions, and with unobstructed views. Also include your static smoke studies.

2. Your firm failed to thoroughly investigate any unexplained discrepancy or failure of a batch or any of its components to meet any of its specifications, whether or not the batch has already been distributed (21 CFR 211.192).

You failed to investigate customer complaints thoroughly. In 2016, you received 32 customer complaints concerning drugs intended for the U.S. market. These complaints included **(b)(4)** irritation, burning, pain, and discharge after using **(b)(4)** Ointment and **(b)(4)** Ointment.

Our investigator reviewed three investigation reports for **(b)(4)** Ointment. Each of your investigations consisted of testing “storage samples” andapplying drug product from at least three implicated complaint lots on your employees as “test subjects.”[1]

Your investigations lacked critical elements that help determine root causes. For example, the three investigations lacked an evaluation of the manufacturing process and associated records. You also did not routinely test complaint lots for all relevant quality attributes (e.g., sterility). Despite missing critical elements, your investigation

concluded that “there are no problems” with the implicated lots. Without thorough investigations, your quality unit lacks sufficient information to make reliable decisions on root causes and take effective action.

In your response, you stated that the quality department will make sure you perform sterility test validation, microbiological analysis (sterility testing) of the complaint sample, safety and efficacy testing, and review the manufacturing environment. You indicated that “through the process, we will figure out the cause.”

Your response is inadequate because it is unclear whether you will fully evaluate your manufacturing process (including raw materials) to ensure the above-mentioned complaints are properly investigated. You also did not demonstrate that your complaint investigation system is remediated.

In your response to this letter:

- Summarize the actions you have taken to comprehensively remediate your complaint investigation process. Include your revised investigation procedure(s) and the actions you are taking to ensure that your staff follows these procedures.
- Summarize your investigation findings using the revised procedures for each complaint related to drug quality received since January 2016. For each summary, include all test results, root causes, implicated batches distributed to the U.S. market, and CAPA.

3. 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)).

You failed to establish an identification test procedure with adequate specificity to appropriately test incoming lots of **(b)(4)** (an alternate name for **(b)(4)**). Your test procedure, based on the Korean Pharmacopoeia (KP), is inadequate to discriminate between the chemical structure of **(b)(4)** and similar compounds. The USP monograph for **(b)(4)** includes an appropriate test using infrared spectroscopy for identification.

In your response to this letter:

- Provide an accelerated timeline to complete retroactive identification testsusing an appropriate identification method for all potentially compromised batches. Respond promptly with all results. If your data indicates that defective products are in the U.S. marketplace, commit torecall the products.
- Determine if all methods used to test your raw and in-process materials and finished drug products use USP-NF, or if not, employ an equivalent or better method. Provide a CAPA to address any inadequate methods that are identified.

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. 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 violations and ensuring ongoing CGMP compliance.

Additional guidance on aseptic processing

See FDA's guidance document, *Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Practice*, to help you meet the CGMP requirements when manufacturing sterile drugs using aseptic processing, at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070342.pdf.

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 May 11, 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 Firson Co. Ltd., 47 Handeul 1-ro, Seobuk-gu, Cheonan-si, Chungcheongnam-do, 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:

LaKeesha Foster
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 3010219111.

Sincerely,
/S/
Thomas J. Cosgrove, J.D.
Director
Office of Manufacturing Quality
Office of Compliance
Center for Drug Evaluation and Research

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[1] This warning letter does not address the legality of this practice.