Fagron, Inc 8/29/18

Division of Pharmaceutical Quality Operations III
300 River Place, Suite 5900
Detroit. MI 48207
Telephone: (313) 393-8100
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August 29, 2018

WARNING LETTER

Case# 545906

UPS NEXT DAY
SIGNATURE REQUIRED

Rafael Padilla
CEO
Fagron BV
Lichtenauerlaan 182
3062 ME Rotterdam
The Netherlands

Dear Mr. Padilla:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Fagron, Inc. at 2400 Pilot Knob Road, Saint Paul, Minnesota, from November 14 to December 21, 2017.

This warning letter summarizes significant deviations from current good manufacturing practice (CGMP) for active pharmaceutical ingredients (API), and a significant violation of CGMP regulations for finished pharmaceuticals, 21 CFR parts 210 and 211.

Because your methods, facilities, or controls for manufacturing, processing, packing, or holding do not conform to CGMP, your drugs 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 January 12, 2018, response in detail.

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

API Deviations

1. Failure to transfer all quality or regulatory information received from the API manufacturer to customers.

Your quality unit omitted the names and addresses of the original manufacturers of your repackaged API on certificates of analysis (COA) you issued to your customers, and did not always include copies of original batch certificates. You generated your COA for repackaged API by replacing the original manufacturers' names and addresses with your own internal identification codes.

In your response, you asserted that your current practice is sufficient. Your response is inadequate in that you do not commit to ensure that COA contain information on the original manufacturer, including a copy of their COA for the given batch.

Customers and regulators rely on COA for information about the quality and source of drugs and their components. Omitting information from the COA compromises supply chain accountability and traceability, and may put consumers at risk.

We observed similar failures to convey necessary information on COA during our November 2013 and April 2015 inspections. In a meeting on June 10, 2014, we informed you that you must include the original manufacturers' names and addresses on the COA.

See ***Guidance for Industry: ICH Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients*** **(https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm073497.pdf)** for more information on how API, from original manufacturers as well as API repackagers and relabelers, should be labeled and clearly identify the original API manufacturer as the API moves through the supply chain. The guidance can be found at the following website: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073497.pdf

In response to this letter, provide the following:

- a remediated program for generating COA, including systems and procedures to assure that COA issued by your firm include necessary original manufacturer information;
- a retrospective review to determine how your failure to provide required information may have affected drug quality, and indicate any actions you have taken or will take, such as notifying customers, or invalidating previously issued COA for any drugs still within their labeled retest dates; and
- examples of recently-issued COA that include specific information regarding the original manufacturer, including a copy of their original batch certificate.

2. Failure to have a system or separate storage area to prevent the unintentional or unauthorized use of quarantined, rejected, returned, or recalled materials, until the decision as to their future use has been made.

Your firm lacked adequate procedures to maintain control over previously recalled estriol lots, and subsequently released the drug into distribution.

You initiated a recall of estriol lots on April 6, 2017, after the API manufacturer, **(b)(4)**. However, after you initiated the recall, between October 6 and October 23, 2017, your firm released and distributed six quarantined **(b)(4)**

estriol lots to multiple compounding pharmacies. On October 27, 2017, your firm initiated another recall of the previously recalled estriol lots.

In your response, you identified multiple root causes for the failure to maintain control of quarantined material, including unclear labeling, lack of detailed release instructions, and insufficient security of the hold bin for recalled material. You also indicated that you implemented new procedures to properly identify non-conforming material.

Your response is inadequate. You did not conduct an assessment to determine whether additional non-conforming drugs were improperly released due to this basic failure in your quality system. In addition, while you provided new procedures, you did not include documentation to demonstrate when they became effective.

In response to this letter, provide the following:

- a comprehensive assessment to determine whether additional drugs were improperly released. If so, identify any actions you have taken or will take, such as notifying customers or recalling products; and
- your firm's new procedures for preventing the release of non-conforming products, including the effective dates.

Finished Drug Violation

1. Failure to establish and follow an adequate written testing program designed to assess the stability characteristics of drug products that includes testing of the drug product in the same container-closure system as that in which the drug product is marketed, and to use results of such stability testing to determine appropriate storage conditions and expiration dates (21 CFR 211.166(a)(4)).

Your firm's drug product stability testing procedure did not define drug product storage requirements. Stability samples of your over-the-counter (OTC) Zinc Oxide Paste were held in your retain sample room and stored in their marketed containers, but were further enclosed in **(b)(4)** and **(b)(4)**. These additional storage layers could alter the validity of the data used to establish expiration dating.

In your response, you explained that your practice of using **(b)(4)** was to preserve sample labels from accidental damage. You further stated that you have demonstrated significantly more than six years of stability and consider it unnecessary to perform a retrospective analysis of previous results.

Your response is inadequate. You lacked a scientific rationale for not performing a retrospective analysis. You did not demonstrate that product stored within extra protective layers properly simulates the less-protected container closure system (CCS) you use for marketed drugs.

In response to this letter, provide the following:

- a corrective action plan to eliminate your current practice of enclosing stability samples in **(b)(4)** and **(b)(4)**, as well as any similar practices that could yield non-representative samples;
- procedure(s) to demonstrate adherence to requirements to store stability samples in the same CCS in which the drug product is marketed; and
- data to evaluate whether your currently marketed drug products are stable when stored in their current CCS without additional protections.

Concerns regarding glycerin

Your product list collected during the inspection, which is also available on your website, includes the drug glycerin. Diethylene Glycol (DEG) contamination has resulted in various lethal poisoning incidents in humans worldwide. See FDA's guidance document, *Testing of Glycerin for Diethylene Glycol,* to help you meet CGMP requirements when distributing glycerin for use in drug products, including testing for DEG and recommendations for supply chain integrity, at **https://www.fda.gov/downloads/Drugs/Guidances/ucm070347.pdf. (/ICECI/EnforcementActions/WarningLetters/default.htm)**

CGMP consultant recommended

Based upon the nature of the deviations and violation we identified at your firm, and because you failed to correct repeat deviations and violations, we strongly recommend engaging a consultant qualified to evaluate your operations 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.

Conclusion

The deviations and violation cited in this letter are not intended as an all-inclusive list. You are responsible for investigating these deviations and violation, for determining the causes, for preventing their recurrence, and for preventing other deviations and violations.

Correct the deviations and violation cited in this letter promptly. Failure to promptly correct these deviations and violation may result in legal action without further notice including, without limitation, seizure and injunction. Unresolved deviations and violation in this warning letter may also prevent other Federal agencies from awarding contracts.

Until these deviations and violation are corrected, we may withhold approval of pending drug applications listing your facility. We may re-inspect to verify that you have completed your corrective actions. We may also refuse your requests for export certificates.

After you receive this letter, respond to this office in writing within fifteen (15) working days. Specify what you have done since our inspection to correct your deviations and violation 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.

Please send your electronic reply to: ORAPHARM3_RESPONSES@fda.hhs.gov.

Attn: Eric M. Mueller
Compliance Officer
U. S. Food and Drug Administration
Division of Pharmaceutical Quality Operations III

Refer to the Unique Identification Number (Case# 545906) when replying. If you have questions regarding the contents of this letter, please contact Mr. Mueller by phone at (402) 331-1101.

Sincerely,
/S/
Art O. Czabaniuk
Program Division Director
Division of Pharmaceutical Quality Operations III

cc:
Teresa Fiedler
President
Fagron North America
Fagron Inc.
2400 Pilot Knob Road
St. Paul, MN 55120

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