WARNING LETTER

B & B Pharmaceuticals, Inc.

MARCS-CMS 570613 — 04/06/2019

Delivery Method:

SIGNATURE CONFIRMED DELIVERY

Product:

Drugs

Recipient:

Mr. Matthew T. Johnson

B & B Pharmaceuticals, Inc.

8591 Prairie Trail Drive, Suite C-600
Englewood, CO 80112
United States

Issuing Office:

Division of Pharmaceutical Quality Operations IV

19701 Fairchild
Irvine, CA 92612-2506
United States

WARNING LETTER

VIA SIGNATURE CONFIRMED DELIVERY

June 4, 2019

Mr. Matthew T. Johnson

President

B&B Pharmaceuticals, Inc.

8591 Prairie Trail Drive, Suite C-600

Englewood, CO 80112

Dear Mr. Johnson:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, B&B Pharmaceuticals, Inc. (FEI 3000719772) at 8591 Prairie Trail Drive, Suite C-600, Englewood, Colorado, from October 17 to 30, 2018.

This warning letter summarizes significant deviations from current good manufacturing practice (CGMP) for active pharmaceutical ingredients (API).

Because your methods, facilities, or controls for manufacturing, processing, packing, or holding do not conform to CGMP, your API 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 commercially distributes NANDROLONE DECANOATE POWDER (NDC 63275-9989) and TESTOSTERONE PROPIONATE POWDER (NDC 63275-9878). A review of FDA's drug listing database confirms that these drugs are currently not listed with FDA as required by section 510 of the FD&C Act (21 U.S.C. 360(j)), which is prohibited under section 301(p) of the FD&C Act (21 U.S.C. 331(p)). Failure to properly list a drug with the FDA will also render it misbranded under section 502(o) of the FD&C Act (21 U.S.C. 352(o)).

We reviewed your November 2, 2018, response in detail and acknowledge receipt of your subsequent correspondence.

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

CGMP Charges

1. **Failure of your quality unit to exercise its responsibility to ensure the API manufactured at your facility are in compliance with CGMP.**

Your facility repacks API. Your quality unit (QU) failed to perform several critical functions to ensure that the API you supply met CGMP requirements.
For example, your QU failed to thoroughly investigate complaints regarding subpotent API (e.g., progesterone and meperidine) and failure to meet particle size specifications. Your investigations did not determine the cause of these quality issues. You also failed to routinely notify the original API manufacturer about complaints.

Your QU also failed to adequately review batch records for completeness and accuracy. For example, you did not reliably detect discrepancies in bottle counts or deviations in manufacturing processes. In some cases, batch records lacked QU signatures. In addition, your QU was not independent of your production operations. We noted that some QU personnel were also performing production functions for the same batch.

In your response, you stated that you will review all complaints since January 2017, revise the complaint procedure, and harmonize your complaint management system with your parent organization, Fagron. Also, you will conduct a retrospective review of 2017 and 2018 batch records, revise relevant procedures, and conduct training.

Your response is inadequate because you did not provide justification for limiting your retrospective review of batch record and complaint review to **(b)(4)**. The timeframe of your retrospective assessment should be based on the longest API retest dates.

In response to this letter, provide:

- A comprehensive assessment with corrective actions and preventive actions (CAPA) to ensure your QU is given the needed authority and resources to effectively discharge its functions. The assessment should also include, but not be limited to:
    - a determination of whether procedures used by your firm are robust and appropriate
    - provisions for QU oversight throughout your operations to evaluate adherence to appropriate practices
    - complete and final review of each batch and its related information prior to the QU disposition decision
    - oversight and approval of investigations and discharging of all other QU duties to assure identity, strength, quality, and purity of all products
- A comprehensive, independent assessment of your overall system for investigations of deviations, atypical events, complaints, out-of-specification results, and failures. Your CAPA should include but not be limited to improvements in investigation competencies, root cause analysis, written procedures, and quality unit oversight. Also include your process for evaluating CAPA effectiveness.

2. **Failure to adequately validate written procedures for the cleaning and maintenance of equipment.**

You failed to conduct cleaning validation studies to demonstrate that your cleaning procedures for non-dedicated production equipment are adequate to prevent potential cross-contamination between your API, which include highly potent drugs such as testosterone, progesterone, estrogen, and opioids.

During the inspection, you provided a cleaning validation study conducted in 2008 at a different location using equipment, cleaning methods, and cleaning agents that differ from those used at your facility. In addition, this study did not justify hold times for your equipment.

In your response, you committed to revising your cleaning procedures and conducting a cleaning validation study.

Your response is inadequate because you did not include a comprehensive risk assessment to determine the potential cross-contamination of various API and solvents into the API you distributed. In addition, you failed to provide a plan to ensure that your equipment is adequately cleaned in the interim.

In response to this letter, provide:

- A comprehensive retrospective review of the adequacy of your cleaning procedures and practices, cleaning validation strategy, and adequacy of any validation studies conducted, for each piece of manufacturing equipment used to manufacture more than one product.
- A summary of updates to your cleaning validation protocol to better incorporate conditions identified as worst case. This should include, but not be limited to:
    - evaluating API that are of highest toxicity

- assessing API of the lowest solubility in your cleaning solvents
- evaluating API with characteristics that make them difficult to clean
- swabbing equipment locations that are most difficult to clean

- A summary of the revisions you made to SOPs, or new SOPs that ensure an appropriate program is in place to verify and validate cleaning procedures for new products, processes, and equipment.

- A risk assessment to determine the effect of inadequate cleaning practices on all potentially affected lots of API you distributed. This assessment should include, but not be limited to, an analysis of retains of all lots at risk for potential cross-contamination. Specify what actions you will take, such as notifying customers and recalling products, if your risk assessment indicates that your drug products may be compromised by your inadequate cleaning procedures.

3. **Failure to transfer all quality or regulatory information received from the API manufacturer to your customers.**

You omitted the name and address of the original API manufacturers on the certificates of analysis (COA) you issued to your customers and did not include copies of the original batch certificate. For multiple API, you generated COA by copying and pasting analytical results from the original API manufacturers, replacing the manufacturers' information with your letterhead, then issuing these COA to your customers. You omitted critical information, including the original manufacturers' names and addresses.

In your response you stated that you will reference the name of the original manufacturer on the COA you provide to your customers. Your response is inadequate because you should provide the name and address of the original manufacturer and a copy of the original batch certificate.
Customers and regulators rely on COA for information about the quality and sourcing of drugs and their components. Omitting information from COA compromises supply chain accountability and traceability and may put consumers at risk.

See *Guidance for Industry: Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients* and *Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients—Questions and Answers* for more information on how API, from original manufacturers as well as API repackagers and relabelers, should be labeled and should clearly identify the original API manufacturer as the API moves through the supply chain. The guidance can be found at: https://www.fda.gov/media/71518/download (https://www.fda.gov/media/71518/download) and https://www.fda.gov/media/112426/download (https://www.fda.gov/media/112426/download).

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.

Quality Systems

Your firm's quality systems are inadequate. See FDA's guidance document Quality Systems Approach to Pharmaceutical CGMP Regulations for help implementing quality systems and risk management approaches to meet the requirements of CGMP regulations 21 CFR, parts 210 and 211 at https://www.fda.gov/media/71023/download (https://www.fda.gov/media/71023/download).

CGMP consultant recommended

Based upon the nature of the deviations we identified at your firm, we strongly recommend engaging a third party qualified with expertise in the operations you perform 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 resolving all deficiencies and systemic flaws to ensure ongoing CGMP compliance.

Drug Listing Violation

Your firm manufactures drugs (including repackaging and relabeling) for commercial distribution in the U.S. According to the data collected at the time of inspection, the list of repackaged API at this establishment includes NANDROLONE DECANOATE POWDER (NDC 63275-9989) and TESTOSTERONE PROPIONATE POWDER (NDC 63275-9878) that are not listed with FDA. Under section 510 of the FD&C Act, as amended, and 21 CFR, all drugs manufactured, prepared, propagated, compounded, or processed for U.S. commercial distribution must be listed with FDA. See 21 U.S.C. 360(j)(1); see also 21 CFR 207.17 and 207.41. Failure to properly list a drug product is prohibited and will render the drug misbranded under 21 U.S.C. 331(p), 352(o).

Conclusion

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

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

Until these deviations 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 15 working days. Specify what you have done since our inspection to correct your deviations 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 written responses to:

CDR Steven E. Porter, Jr.

Director, Division of Pharmaceutical Quality Operations IV

19701 Fairchild Road

Irvine, CA 92612

Please identify your response with unique identifier 570613.

If you have questions regarding any issues in this letter, please contact CAPT Matthew R. Dionne, Compliance Officer, at (303)-236-3064, or Matthew.Dionne@fda.hhs.gov (mailto:Matthew.Dionne@fda.hhs.gov).

Sincerely,

/S/

CDR Steven E. Porter, Jr.

Director, Division of Pharmaceutical Quality Operations IV

CC:

Rafael Padilla, Chief Executive Officer

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The Netherlands

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