WARNING LETTER

Thibiant International, Inc.

MARCS-CMS 555921 — MARCH 06, 2019

Product:

Drugs

Recipient:

Ms. Lorena G. Frost

VP, Commercial Affairs

Thibiant International, Inc.

2585 Azurite Circle
Newbury Park, CA 91320
United States

Issuing Office:

Division of Pharmaceutical Quality Operations IV

19701 Fairchild
Irvine, CA 92612-2506
United States

WARNING LETTER

VIA SIGNATURE CONFIRMED DELIVERY

CMS 555921

March 6, 2019

Ms. Lorena G. Frost
VP, Commercial Affairs
Thibiant International, Inc.
2585 Azurite Circle
Newbury Park, CA 91320

Dear Ms. Frost:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Thibiant International, Inc. FEI-3003411151, at 2585 Azurite Circle, Newbury Park, California from March 6 to March 15, 2018.

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 April 5, 2018, response in detail.

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

1. 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).

Your firm did not adequately investigate drug product failures to ensure that you did not release defective drug product.

From August 24, 2015, to July 24, 2017, batch **(b)(4)** of your **(b)(4)** over-the-counter (OTC) drug product failed at multiple stability timepoints for pH and viscosity. At one timepoint, the batch failed for specific gravity. Your out-of-specification (OOS) investigation concerning this batch dated **(b)(4)**, concluded that the drug product formulation was unstable.

Your customer declined your proposed changes to correct the deficient drug product formulation. However, despite knowing the formulation was flawed, you manufactured a second batch, **(b)(4)**, on **(b)(4)**, using the same formulation. Samples taken before and after filling batch **(b)(4)** failed for quality attributes (viscosity and pH). You initiated a deviation that noted that the "safety, quality, and performance of the product is unaffected" and that "the customer's perception of the product will not be compromised." You released the batch with failing test results, and when analyzing the batch on stability it failed at multiple timepoints for pH, viscosity, and specific gravity.

In your response, you stated that you will update your investigation procedure. If you identify any deviation or OOS, the quality unit will initiate an investigation into the root cause and assess the impact.

Your response was inadequate. Following our inspection, batch **(b)(4)** was recalled based on our investigator's findings; although batch **(b)(4)** was not recalled, it had expired. You failed to determine whether additional nonconforming drug products have been released. Also, your OOS procedure which allows you to release nonconforming drug product "**(b)(4)**" is not acceptable. Even a manufacturer who performs contract manufacturing is responsible for meeting CGMP and cannot distribute substandard, adulterated drugs.

In response to this letter, provide the following.

• A comprehensive, independent assessment of your system for investigating deviations, atypical events, complaints, OOS results, and failures. Your corrective action and preventive action (CAPA) plan should include, but not be limited to, improvements in investigations, root cause analysis, written procedures, and quality unit oversight. Also include your process for evaluating CAPA plan effectiveness.

• A retrospective, independent review of all OOS in-process and finished testing results for products currently on the U.S. market within expiry. Assess whether OOS results were properly investigated. Include scientific justification and evidence whether any invalidated OOS results were conclusive. For investigations that

establish laboratory root cause, ensure that you have identified other laboratory methods vulnerable to the same root cause for remediation.

• A thorough review of production (e.g., batch manufacturing records, adequacy of the manufacturing steps, raw materials, process capability, deviation history, batch failure history) for any OOS results with inconclusive or unidentified root causes.

• A review and remediation of your system for investigating OOS results. Provide a CAPA plan to improve OOS handling. Your CAPA plan should ensure that your revised OOS investigation procedure does not allow the release of OOS drug product and includes:

o Enhanced quality unit oversight of laboratory investigations
o Identification of adverse laboratory control trends
o Resolution of potential causes of laboratory errors
o Investigations of potential manufacturing root causes when a laboratory root cause cannot be conclusively identified
o A CAPA plan that specifies meaningful improvements when you identify manufacturing root causes

For more information about handling failing, out-of-specification, out-of-trend, or other unexpected results and documenting your investigations, see FDA's guidance document, Investigating Out-Of-Specification (OOS) Test Results for Pharmaceutical Production, at https://www.fda.gov/downloads/drugs/guidances/ucm070287.pdf (https://www.fda.gov/downloads/drugs/guidances/ucm070287.pdf).

2. Your firm failed to 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)).

You lack adequate stability data to demonstrate that your **(b)(4)** OTC drug product remains acceptable throughout its labeled two-year expiry period.

Batch **(b)(4)** manufactured in **(b)(4)** failed long-term stability testing specifications for pH, viscosity, and specific gravity at multiple time points. Long-term stability test results for batch **(b)(4)**, manufactured in **(b)(4)**, were also found to be OOS at multiple time points. Both the 2015 Annual Product Review and Investigation INV-**(b)(4)** (initiated in **(b)(4)**) concerning **(b)(4)** concluded that the drug product's formulation was unstable.

In your response, you stated that new stability specifications were generated from development studies, two production stability studies have been conducted to date, and specific gravity should be for information only.

Your response was inadequate. You failed to provide the reports from development and production stability studies to support changes to your stability specification. You also did not provide sufficient details to indicate that your firm will remediate your operations to ensure compliance with CGMP.

In response to this letter, provide the following.

• A comprehensive, independent assessment and CAPA plan to ensure the adequacy of your stability program. Your CAPA plan should include, but not be limited to:

o A remediated SOP describing your stability program
o Stability indicating methods
o Stability studies for each drug product in its container-closure system before distribution is permitted
o An ongoing program in which representative batches of each drug product are added each year to the program to determine if the shelf-life claims remains valid
o Specific attributes to be tested at each station

• The development study report and rationale which support the new stability specifications.
• The scientific reason why specific gravity is for information only.

3. Your firm failed to establish the reliability of the component supplier's analysis through appropriate validation of the supplier's test results at appropriate intervals (21 CFR 211.84(d)(2)).

Your firm failed to test incoming components, including the active ingredient zinc oxide, for their purity, strength, and other appropriate quality attributes. Instead, your firm relied on certificates of analysis (COA) from unqualified suppliers.

In your response, you stated that your raw material supplier qualification procedure has been drafted and will be finalized in May 2018. The procedure requires **(b)(4)**. The supplier's COA will be verified every **(b)(4)** thereafter.

Your response was inadequate. You failed to provide a timeline for supplier qualification and evidence you will perform ID testing on each incoming component lot. Your response did not include a retrospective assessment of your OTC drug products that have been manufactured with components that have not been adequately tested to ensure adherence to quality attribute specifications.

In response to this letter, provide the following.

• The chemical and microbiological specifications you use to approve release of each incoming lot of components for use in manufacturing.
• A description of how you will conduct at least one specific identity test for each incoming component lot, regardless of a COA validation program.
• A summary of your procedures to establish the reliability and consistency of your supplier's results through initial validation, followed by periodic re-validation.
• A summary of results obtained from testing all components to evaluate the reliability of the COA from each component manufacturer. Include your SOP that describes this COA validation program.
• A summary of your procedures for qualifying and overseeing contract facilities that test the OTC drug products you manufacture.
• A comprehensive review of your material system to determine whether all containers, closures, and ingredients from each supplier are qualified and assigned appropriate expiration or retest dates. The review should also determine whether incoming material controls are adequate to prevent use of unsuitable containers, closures, and components.
• Your procedures to ensure that you test all glycerin lots for diethylene glycol (DE) and ethylene glycol (EG).
• Tests results for DEG and EG in retain samples of all glycerin lots in your glycerin-containing drug products. For lots of drug products within expiry made with glycerin lots containing DEG or EG, include detailed risk

assessments, including corrective actions. See FDA's Guidance Document, Testing of Glycerin for Diethylene Glycol, at https://www.fda.gov/downloads/Drugs/Guidances/ucm070347.pdf (https://www.fda.gov/downloads/Drugs/Guidances/ucm070347.pdf)

4. Your firm failed to establish adequate written responsibilities and procedures applicable to the quality control unit and to follow written procedures applicable to the quality control unit (21 CFR 211.22(d)).

Your quality unit failed to follow your procedures, SOP LPM-898 Handling of Out-Of-Specification Test Results and SOP FP-221 Out-of-Specification Investigations. Both require completing all investigations within **(b)(4)** from date of initiation. Investigation INV-**(b)(4)** was initiated for stability OOS results on **(b)(4)**, but was not approved or closed by the time of our inspection in March 2018. Your quality unit also failed to establish a procedure to ensure that you reviewed **(b)(4)** charts and investigated any excursions you found.

In your response, you stated that your OOS procedure will be revised to include a **(b)(4)** quality management review to ensure the timely review and approval of all open investigations. You also stated that your SOP FP-237, which governs the **(b)(4)** operation, has been updated to include instructions for replacing, monitoring, and reviewing **(b)(4)** charts on a **(b)(4)** basis.

Your response was inadequate. You did not provide sufficient evidence that all investigations have been reviewed, approved, and closed. You also failed to assess the **(b)(4)** to ensure that they are functioning properly and within specification ranges.

In response to this letter, provide the following.

• A comprehensive assessment, with CAPA, to ensure your quality unit (QU) is given the authority and resources to effectively function. The assessment should also include, but not be limited to:

o A determination of whether procedures used by your firm are robust and appropriate
o Provisions for oversight throughout your operations to evaluate adherence to appropriate procedures
o A complete and final review of each batch and its related information before the disposition decision
o Oversight and approval of investigations, and discharging all other quality unit duties, to ensure identity, strength, quality, and purity of all drug products

• An assessment of any **(b)(4)** excursions and the impact to the stability studies. Also determine if the **(b)(4)** require re-qualification or re-mapping.
• Procedures that ensure your quality unit reviews stability data before it assigns expiration dates to drug products to assure that expiration dates are appropriate.

Quality Unit Authority

Significant findings in this letter indicate that your quality unit is not fully exercising 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.

See FDA's guidance document, Quality Systems Approach to Pharmaceutical CGMP Regulations, at https://www.fda.gov/downloads/Drugs/.../Guidances/UCM070337.pdf (https://www.fda.gov/downloads/Drugs/.../Guidances/UCM070337.pdf)

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 resolving all deficiencies and systemic flaws to ensure 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 in your facility.

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

Until these violations 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.

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.

Your written response should refer to the Warning Letter number above (555921). Please address your reply to:

CDR Steven E. Porter, Jr.
Director, Division of Pharmaceutical Quality Operations IV
United States Food and Drug Administration
19701 Fairchild
Irvine, CA 92612

If you have any questions about the content of this letter, please contact Jessica Mu, Compliance Officer, at 949-608-4477 and reference unique identifier CMS 555921 on all correspondence.

Sincerely,
/S/
CDR Steven E. Porter, Jr.
Director, Division of Pharmaceutical Quality Operations IV

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