WARNING LETTER

Rxhomeo Private Limited

MARCS-CMS 575889 — JUN 13, 2019

Delivery Method:

VIA UPS

Product:

Drugs

Recipient:

Mr. Shiv Shanker Asthana

Director

Rxhomeo Private Limited

Indradhanush, 4-1-424 to 426, Bank Street, Abids
Hyderabad 500001 Telangana
India

Issuing Office:

Center for Drug Evaluation and Research

10903 New Hampshire Avenue
Silver Spring, MD 20993
United States

Via UPS **Warning Letter** 320-19-26

Return Receipt Requested

June 13, 2019

Mr. Shiv Shanker Asthana

Director

Rxhomeo Private Limited

Indradhanush, 4-1-424 to 426, Bank Street, Abids

Hyderabad, Telangana, 500001

India

Dear Mr. Asthana:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Rxhomeo Private Limited (FEI 3005269310) at Indradhanush, 4-1-424 to 426, Bank Street, Abids, Hyderabad, Telangana, from January 28 to February 1, 2019.

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 February 21, 2019, 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 test samples of each component for identity and conformity with all appropriate written specifications for purity, strength, and quality. Your firm also failed to validate and establish the reliability of your component supplier's test analyses at appropriate intervals (21 CFR 211.84(d)(1), (2) and (3)).

You purchased components such as bulk homeopathic drug **(b)(4)** tablets, and containers and closures from outside suppliers, but you did not test these incoming materials for identity and other quality attributes upon receipt nor had you verified the accuracy of certificates of analysis (COA).

Your firm receives components, homeopathic drug **(b)(4)**, that contain constituents that, if at improper concentrations, can be especially toxic, such as **(b)(4)** contains **(b)(4)** is a highly toxic, well-studied poison that is used as a rodenticide. You failed to establish the reliability of your homeopathic drug **(b)(4)** supplier according to your supplier qualification procedures. You utilized these homeopathic **(b)(4)** of toxic materials for drug product manufacturing without COA and without testing to ensure that the components did not contain levels of **(b)(4)** at potentially toxic concentrations.

In your response, you provided revised procedures that include collection of raw material samples for testing and wrote new procedures to address the receipt, storage, and labelling of raw material and packing material. Your response is inadequate because you did not address impact of the lack of component testing on marketed drug products within expiry.

You also stated that you plan to discontinue purchasing bulk homeopathic active pharmaceutical ingredient (API) and drug **(b)(4)** from outside suppliers and instead plan to manufacture them yourself using homeopathic starting materials. However, you did not provide details on your homeopathic API and drug **(b)(4)** manufacturing process and your validation plans.

As a reminder, your API manufacturing process must also conform to 21 U.S.C. 351(a)(2)(B); for expectations, you may refer to the *Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients Guidance for Industry*, which can be found at https://www.fda.gov/media/71518/download (https://www.fda.gov/media/71518/download).

In response to this letter, provide:

- A detailed description of how you plan to test each component, container, and closure for conformity with all appropriate written specifications for identity, purity, strength and quality. If you accept your suppliers' COA in lieu of testing components, describe in detail how you plan to establish the reliability of your suppliers' test results through periodic validation.
- A risk assessment for any drugs within expiry and distributed within the United States that were manufactured from inadequately tested and controlled components. Include your plan to test your retention samples to ensure that drugs do not contain any active ingredient levels that may increase the risks of patient exposure to toxic effects.
- If you plan to manufacture your own API, a comprehensive plan for how you will produce and test the API.

- A description of the process validation to be used for your various drug products. Include details of the in-process tests and controls to be employed.

2. Your firm failed to prepare batch production and control records with complete information relating to the production and control of each batch of drug product produced (21 CFR 211.188).

Your batch records lack appropriate details, including but not limited to the following: line clearance information, the identity of major equipment and lines used in production, batch-specific information for components used, weights and measures of components used, in-process test results, a statement of yield, labeling control records, a description of the final container closures, sampling performed, identification of person(s) performing each significant step and/or directly supervising each step, any investigations related to the batch, and limits related to hold times or equipment control settings.

Furthermore, more than **(b)(4)** of your homeopathic drug products share a single master batch record. The single master batch record has large sections of free-form space with no pre-determined statements of weight or measure of components used to manufacture homeopathic drug products.

Having incomplete records deprives you of traceability of actions necessary for investigational purposes. Furthermore, having a master batch record with no product-specific instructions, information, and calculations could potentially lead to mix-ups and errors in drug production.

In your response, you provided revised procedures for your batch records. However, your response is inadequate because your new batch records still do not contain adequate details including appropriate limits for equipment settings, yield, component specifications, or labeling specifications. Also, it is not clear from your response whether you intend to implement product-specific master batch records for all your drug products.

In response to this letter, perform a global review of the production processes for all your drug products and establish appropriately detailed master batch records that capture all significant manufacturing steps for each specific drug product and contain validated formulas to avoid mix-ups and errors.

3. Your firm's quality control unit failed to exercise its responsibility to ensure drug products manufactured are in compliance with CGMP, and meet established specifications for identity, strength, quality, and purity (21 CFR 211.22).

Your quality unit (QU) failed to provide adequate oversight over your manufacturing processes. Your Quality Assurance QA-004-00 procedure does not define and describe the structure, function and responsibilities for the QU.

Furthermore, your production operators also belong to the QU. The same production operators that manufacture your homeopathic drug products also authorize component review and release. Under a CGMP compliant quality system, it is expected that the manufacturing units and the QU remain independent.

Your QU also failed to release labels, control access to labels, and adequately qualify suppliers. Adequate labeling controls are important to prevent mix-ups, which is a concern as your firm manufactures more than **(b)(4)** different homeopathic drug products.

Your firm also failed to establish procedures for many essential quality and production operations, including but not limited to the following:

- Receiving drug components
- Sampling and release of incoming materials
- Investigating out-of-specification results and rejects
- Process validation and cleaning validation
- Master production records and batch production records

- Annual product reviews
- Equipment qualification

In your response, you provided new written procedures for operations cited above. Your response is inadequate because you did not assess the impact that your lack of an independent QU and procedures could have on distributed drug within expiry.

In response to this letter:

- Provide a comprehensive assessment with corrective actions and preventive actions (CAPA) to ensure your QU is given the authority and resources to effectively and independently function. 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
    - A complete and final review of each batch and its related information before the QU disposition decision
    - Oversight and approval of investigations and discharging of all other QU duties to ensure identity, strength, quality, and purity of all products
- Conduct a risk assessment of the batches of your drug products within expiry which were manufactured and released to the market without proper QU oversight.
- Provide a timeline for implementation of your new procedures, as well as metrics for compliance.

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 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 if your firm intends to resume manufacturing drugs for the U.S. market. We also recommend that the qualified consultant perform a comprehensive audit of your entire operation for CGMP compliance and that the consultant evaluates the completion and efficacy of your corrective actions and preventive actions before you pursue resolution of your firm's compliance status with FDA.

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.

FDA placed your firm on Import Alert 66-40 on May 22, 2019.

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 Rxhomeo Private Limited, Indradhanush, 4-1-424 to 426, Bank Street, Abids, Hyderabad, Telangana, 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:

William Yang

Consumer Safety 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 3005269310.

Sincerely,

/S/

Francis Godwin

Director

Office of Manufacturing Quality

Office of Compliance

Center for Drug Evaluation and Research

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