WARNING LETTER

Mayon's Pharmaceuticals Pvt Ltd

MARCS-CMS 607388 — SEPTEMBER 04, 2020

Delivery Method:

VIA UPS

Product:

Drugs

Recipient:

Mr. Yusuf MH Chimthanawala

Chief Executive Officer

Mayon's Pharmaceuticals Pvt Ltd

576 Quaemi Bagh, Near Itwari Railway Station
Nagpur 440002 Maharashtra
India

Issuing Office:

Center for Drug Evaluation and Research | CDER

United States

Warning Letter 320-20-46

September 4, 2020

Dear Mr. Chimthanawala:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Mayon's Pharmaceuticals, Pvt. Ltd., FEI 3010910756, at Old Kamptee Road, Behind Octroi Naka No. 4, Kalamna, Nagpur, Maharashtra from February 17 to 20, 2020.

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

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 March 14, 2020, response and subsequent responses to our Form FDA 483 in detail.

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

Finished Drug Violations

1. Your firm failed to conduct at least one test to verify the identity of each component of a drug product. Your firm also failed to test each component for conformity with all appropriate specifications for purity, strength, and quality (21 CFR 211.84(d)(1) and (2)).

Your firm failed to test incoming components used to manufacture your in-process homeopathic materials and finished homeopathic drug products to determine identity, purity, strength, and quality. For example, you did not test **(b)(4)**, which contains **(b)(4)**, used in your **(b)(4)**, for identity. You also failed to perform appropriate identity testing of **(b)(4)** used in products such as **(b)(4)**.

Furthermore, you failed to determine whether each component, such as **(b)(4)**, conformed with all appropriate specifications for purity, strength, and quality before using them. Your firm did not qualify the suppliers of the components used in your products and you could not provide scientific evidence that your components are compliant with appropriate specifications. Your drug products have been used in the development of **(b)(4)** homeopathic **(b)(4)** products.

In response to this letter, provide:

• The chemical and microbiological quality control specifications you use to test and release each incoming lot of component for use in manufacturing.

• A description of how you will test each component lot for conformity with all appropriate specifications for identity, strength, quality, and purity. If you intend to accept any results from your supplier's Certificates Of Analysis (COA) instead of testing each component lot for strength, quality, and purity, specify how you will robustly establish the reliability of your supplier's results through initial validation as well as periodic re-validation. In addition, include a commitment to always conduct at least one specific identity test for each incoming component lot.

• A summary of results obtained from testing all components to evaluate the reliability of the COA from each component manufacturer. Include your Standard Operating Procedure (SOP) that describes this COA validation program.

• A summary of your program for qualifying and overseeing contract facilities that test raw material you use and the drug products you manufacture.

2. Your firm failed to establish written procedures for production and process control designed to assure that the drug products you manufacture have the identity, strength, quality, and purity they purport or are represented to possess (21 CFR 211.100(a)).

You released numerous batches of drugs, some of which contain ingredients with toxic components, without validating your manufacturing process. For example, you manufactured and distributed **(b)(4)** to the United States without data that supports the product quality and homogeneity.

Your response stated you developed a process validation master plan, but you provided only a validation protocol for your **(b)(4)** products. You did not provide a timeline or detailed plan to ensure all products are manufactured using validated processes.

In response to this letter, provide:

• A detailed summary of your validation program for ensuring a state of control throughout the product lifecycle, along with associated procedures. Describe your program for process performance qualification, and ongoing monitoring of both intra-batch and inter-batch variation to ensure a continuing state of control.

• A timeline for performing appropriate process performance qualification for each of your marketed drug products. Include your process performance protocols, and written procedures for qualification of equipment and facilities.

3. Your firm failed to use equipment in the manufacture, processing, packing, or holding of drug products that is of appropriate design, adequate size, and suitably located to facilitate operations for its intended use and for its cleaning and maintenance (21 CFR 211.63).

Your **(b)(4)** system, which provides **(b)(4)** for the formulation of some of your homeopathic drug products, was not designed to consistently produce **(b)(4)**. Our investigator observed dead legs, dripping **(b)(4)**, and threaded piping. There should be no threaded fittings in a pharmaceutical **(b)(4)** system.

In your response, you provided photographs showing adjustments to your **(b)(4)** system design that appear to lessen the severity of the design flaws, but do not resolve them. You also stated that you initiated a detailed gap and impact assessment but did not provide supporting documentation.

In response to this letter, provide:

• A comprehensive remediation plan for the design, control, and maintenance of the **(b)(4)** system.

• Validation report for the **(b)(4)** system obtained after all identified design issues have been fully corrected and any maintenance repairs have been completed. Include the system validation protocol, the complete test results, and the final validation report.

• A detailed risk assessment addressing the potential effects of the observed **(b)(4)** system failures on the quality of all drug product lots currently in U.S. distribution. Specify actions that you will take in response to the risk assessment, such as customer notifications and product recalls.

• The current action/alert limits for total counts and objectionable organisms used for your **(b)(4)** system. Ensure that the total count limits for your **(b)(4)** are appropriately stringent in view of the intended use of each of the products produced by your firm.

• A procedure governing your program for ongoing control, maintenance, and monitoring that ensures the remediated system consistently produces **(b)(4)** that is suitable for its intended use.

API Deviations

1. Failure to clean equipment and utensils to prevent contamination or carry-over of a material that would alter the quality of the API beyond the official or other established specifications.

Your firm manufacturers homeopathic in process materials and **(b)(4)** from various raw materials. Our investigator observed unidentified debris in the **(b)(4)** of your **(b)(4)** equipment, which is used to process multiple raw materials for homeopathic **(b)(4)**, including **(b)(4)** containing **(b)(4)**. This equipment was marked as clean.

Your response states that you filed a deviation and re-trained your staff. This response is inadequate because you failed to identify the observed debris and perform an impact assessment for the drugs that were manufactured using this dirty equipment.

In response to this letter, provide:

• A comprehensive, independent retrospective assessment of your cleaning effectiveness to evaluate the scope of cross-contamination hazards. Include the identity of residues, other manufacturing equipment that may have been improperly cleaned, and an assessment whether cross-contaminated products may have been released for distribution. The assessment should identify any inadequacies of cleaning procedures and practices, and encompass each piece of manufacturing equipment used to manufacture more than one product, including both API and finished products.

• A corrective and preventive action plan, based on the retrospective assessment of your cleaning program, that includes appropriate remediations to your cleaning processes and practices, and timelines for completion. Provide a detailed summary of vulnerabilities in your process for lifecycle management of equipment cleaning. Describe improvements to your cleaning program, including enhancements to cleaning effectiveness, improved ongoing verification of proper cleaning execution for all products and equipment, and all other needed remediations.

2. Failure to establish adequate written procedures for cleaning equipment and its release for use in manufacture of API.

You do not have adequate cleaning procedures for the equipment you use to manufacture multiple homeopathic products. You did not validate the methods you used to clean your equipment. Inadequate removal of raw materials and residues from manufacturing equipment during cleaning can lead to cross-contamination of material used in your homeopathic **(b)(4)**.

Your response states that you revised your cleaning procedure, but the cleaning procedure provided in your response is the same as the one collected during our inspection and is not indicative of any revisions. You also failed to provide a plan or supporting documentation for a cleaning validation program. This response is inadequate because it does not establish systemic procedures and controls for your cleaning program to prevent cross-contamination.

In response to this letter, provide:

• Appropriate improvements to your cleaning validation program, with special emphasis on incorporating conditions identified as worst case in your drug manufacturing operation. This should include, but not be limited to, identification and evaluation of all worst-case:

o Drugs with higher toxicities
o Drugs with higher drug potencies
o Drugs of lower solubility in their cleaning solvents
o Drugs with characteristics that make them difficult to clean
o Swabbing locations for areas that are most difficult to clean
o Maximum hold times before cleaning

• In addition, describe the steps that must be taken in your change management system before introduction of new manufacturing equipment or a new product.

• A summary of updated SOPs that ensure an appropriate program is in place for verification and validation of cleaning procedures for products, processes, and equipment.

Conclusion

The violations and deviations cited in this letter are not intended to be an all-inclusive list of violations and deviations that exist at your facility. You are responsible for investigating and determining the causes of these violations and deviations and for preventing their recurrence or the occurrence of other violations and deviations.

FDA placed your firm on Import Alert 66-40 on July 13, 2020.

Until you correct all violations and deviations completely and we confirm your compliance with CGMP, FDA may withhold approval of any new drug applications or supplements listing your firm as a drug manufacturer.

Failure to correct these violations and deviations may also result in the FDA continuing to refuse admission of articles manufactured at Mayon's Pharmaceuticals Pvt. Ltd., Old Kamptee Road, Behind Octroi Naka No. 4, Kalamna, Nagpur, Maharashtra into the United States under section 801(a)(3) of the FD&C Act, 21 U.S.C. 381(a)(3). Articles under this authority 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 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.

If you have evidence or information that you believe demonstrates that your products are not in violation of the FD&C Act and FDA regulations, include that evidence or information for our consideration.

Send your electronic reply to CDER-OC-OMQ-Communications@fda.hhs.gov.

Identify your response with FEI 3010910756 and ATTN: Marisa Heayn.

Sincerely,
/S/

Francis Godwin
Director
Office of Manufacturing Quality
Office of Compliance
Center for Drug Evaluation and Research

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