WARNING LETTER

Mylan Laboratories Limited - Unit 8

MARCS-CMS 589297 — NOVEMBER 05, 2019

Delivery Method:

VIA UPS

Product:

Drugs

Recipient:

Ms. Heather Bresch

Chief Executive Officer

Mylan Laboratories Limited - Unit 8

1000 Mylan Boulevard
Canonsburg, PA 15317
United States

Issuing Office:

Center for Drug Evaluation and Research

10903 New Hampshire Avenue
Silver Spring, MD 20993
United States

Warning Letter 320-20-06

November 5, 2019

Dear Ms. Bresch:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Mylan Laboratories Limited, Unit 8, FEI 3002785310, at G. Chodavaram Village, Vizianagaram, Andhra Pradesh, India, from May 27 to June 5, 2019.

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).

We reviewed your June 26, 2019, response to our Form FDA 483 in detail and acknowledge receipt of your subsequent correspondence. Your response is inadequate because it did not provide sufficient detail or evidence of corrective actions to bring your operations into compliance with CGMP.

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

1. Failure to have adequate written procedures for the receipt, identification, testing and handling of raw materials.

Your procedures for receiving, identifying, testing, and handling raw materials were inadequate to ensure suitability of materials used in manufacturing, including preventing contamination and cross-contamination with nitrosamine impurities such as N-nitrosodimethylamine (NDMA) and N-nitrosodiethylamine (NDEA). Your film had not anticipated the presence of NDMA or NDEA impurities based on your assessment of the API manufacturing process.

By December 2018, you recalled all your valsartan API batches after tests determined that the majority of batches contained NDEA contamination at levels above the limit. Your investigation dated November 21, 2018, with addendum dated January 1, 2019, concluded that NDEA contamination originated from recovered **(b)(4)** solvents. Your investigation into nitrosamine contamination also found that another recovered solvent, **(b)(4)**, contained NDEA at levels of 3.38 ppm, more than 40 times your limit of 0.08 ppm. Without adequate scientific justification, you concluded that the recovered **(b)(4)** solvent containing high levels of NDEA would not result in significant levels of NDEA in your API.

In addition, your firm found low levels of NDMA in your valsartan API. Your investigation concluded this nitrosamine impurity was introduced via contaminated **(b)(4)** recovered solvents. Notably, you stated in a Field Alert Report (FAR) submitted to FDA on September 13, 2019, that one likely root cause of the nitrosamine contamination found in rejected batches of valsartan API was recovered **(b)(4)** solvent containing NDMA at levels as high as 0.629 ppm.

Your firm used recovered solvents such as **(b)(4)** and **(b)(4)** from multiple external contract manufacturers, including **(b)(4)**. In January 2019 you restricted the procurement of all valsartan-related materials from **(b)(4)** and in March 2019, you removed **(b)(4)** from your approved manufacturing list. FDA placed **(b)(4)** on Import Alert 66-40 on **(b)(4)**, and issued Warning Letter **(b)(4)** on **(b)(4)**, due to CGMP deficiencies involving inadequate solvent recovery operations resulting in nitrosamine impurity contamination of solvents supplied to their customers.

Multiple contract manufacturers supplied solvents that were contaminated with nitrosamines, but your firm lacked documentation of which tanks were used to store these solvents. Although you acknowledged that there was no record of usage for each of the recovered solvent tanks, your response did not provide sufficient information on attempts to retrospectively reconcile the number, identification, and usage of the tanks. Furthermore, you did not provide an adequate investigation to determine whether other API could have been impacted by use of storage tanks that held recovered **(b)(4)** and other valsartan API process solvents.

After suspending the use of recovered solvents from contract manufacturers for valsartan API, your firm began relying on in-house solvent recovery of **(b)(4)**. While your firm maintained there was no opportunity to produce nitrosamine impurities with your current process, the process performance qualification report for your in-house solvent recovery of **(b)(4)** found that the solvent contained NDMA above your detection limit and NDEA at levels above your specification limit.

In your response, you explained the most probable reason for nitrosamine contamination was the use of **(b)(4)** that had been used to store material intended for destruction. You stated you switched to new **(b)(4)**, but your response did not address whether other similar equipment may also need to be replaced or remediated.

Furthermore, you stated that you will continue to use fresh solvents until you can validate your in-house solvent recovery process for control of nitrosamine impurities. Your response is inadequate because you did not commit to test fresh and recovered solvents for nitrosamine prior to release for use in API manufacturing.

See FDA's guidance document *M7 (R1) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk* for approaches to consider where appropriate regarding the presence of mutagenic impurities, at https://www.fda.gov/media/85885/download (https://www.fda.gov/media/85885/download).

In response to this letter, provide the following:

- An update on investigations involving recovered solvents, including but not limited to **(b)(4)** and **(b)(4)**, and corrective action and preventive action (CAPA) plans to avert the presence of NDMA, NDEA and other potential mutagenic impurities in all API manufactured at your firm.
- Your program for process performance qualification for API and recovered solvents, and ongoing monitoring of both intra-batch and inter-batch variation to ensure a continuing state of control. Include your program for ongoing lifecycle evaluation of impurity profiles for all API.
- Procedures for controlling incoming raw materials, including but not limited to ensuring that they are not co-mingled. In addition, provide an analysis of storage tanks that held contaminated **(b)(4)** and **(b)(4)** solvents, and whether material from those tanks was used to manufacture any other API produced by your firm.
- Specifications, including test methods, used to release fresh and recovered solvents in the API manufacturing process. Your response should address capability to detect and quantify a wide array of potential impurities or contaminants, including but not limited to nitrosamines.
- A comprehensive, third-party review of your material system. Provide a report that assesses the adequacy of this system, including but not limited to:
    - incoming lot controls to prevent use of unsuitable materials
    - assignment of appropriate expiration or retest dates
    - quality oversight of capability and acceptability of all material suppliers, including qualification standards for initial supplier selection and ongoing lifecycle evaluations to ensure continued supplier acceptability
    - all CAPA to be implemented, such as improvements to standard operating procedures (SOPs) and management oversight.

2. 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.

There is no assurance that your cleaning methods are adequate to clean and prevent contamination or carry-over of drugs manufactured on non-dedicated equipment. Our investigators observed that non-dedicated **(b)(4)**1102 and **(b)(4)**1506, were labeled as clean. However, when the interior surfaces of the **(b)(4)** chutes were wiped with lint-free cloths, **(b)(4)** stains were observed. Testing you conducted later determined the **(b)(4)** stains were residual valsartan API.

In your response, you attributed the adherence of residual deposits to rough surfaces on the equipment. Also, as an immediate action, the interior surfaces of the **(b)(4)** chutes of **(b)(4)**, which were also observed with **(b)(4)** stains, were ground and polished to smooth surfaces. You also implemented an update to your cleaning procedures.

You determined there was minimal impact on product quality based on a review of complaint and out-of-specification investigations. You also stated that all valsartan batches and other drugs manufactured were tested for “extraneous matter” and reported no failures. Your response is inadequate. Cross-contamination cannot be assumed to be uniformly distributed and testing alone is insufficient to mitigate the observed contamination hazards.

In response to this letter, provide the following:

- 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.
    - As one element of the risk assessment, describe whether you will be testing all API manufactured on non-dedicated equipment for impurities such as nitrosamines due to your deficient systems for cross-contamination prevention and cleaning. The risk assessment should support your response to this item.
- 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:

- drugs with higher toxicities
- drugs with higher drug potencies
- drugs of lower solubility in their cleaning solvents
- drugs with characteristics that make them difficult to clean
- swabbing locations for areas that are most difficult to clean
- 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.
- Your CAPA plan to implement routine, vigilant operations management oversight of facilities and equipment. This plan should ensure, among other things, prompt detection of equipment/facilities performance issues, effective execution of repairs, adherence to appropriate preventive maintenance schedules, timely technological upgrades to the equipment/facility infrastructure, and improved systems for ongoing management review.

CGMP Consultant Recommended

Based upon the nature of the deviations we identified at your firm, we strongly recommend engaging a consultant qualified to evaluate your operations 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 systemic flaws to ensure ongoing CGMP compliance.

Additional API CGMP Guidance

FDA considers the expectations outlined in ICH Q7 when determining whether API are manufactured in conformance with CGMP. See FDA's guidance document *Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients* for guidance regarding CGMP for the manufacture of API at https://www.fda.gov/media/71518/download (https://www.fda.gov/media/71518/download).

Conclusion

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

If you are considering an action that is likely to lead to a disruption in the supply of drugs produced at your facility, FDA requests that you contact CDER's Drug Shortages Staff immediately, at drugshortages@fda.hhs.gov, so that FDA can work with you on the most effective way to bring your operations into compliance with the law. Contacting the Drug Shortages Staff also allows you to meet any obligations you may have to report discontinuances or interruptions in your drug manufacture under 21 U.S.C. 356C(b). This also allows FDA to consider, as soon as possible, what actions, if any, may be needed to avoid shortages and protect the health of patients who depend on your products.

Until you correct all deviations 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 deviations may also result in FDA refusing admission of articles manufactured at Mylan Laboratories Limited, Unit 8 at G. Chodavaram Village, Vizianagaram, Andhra Pradesh, India 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 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 electronic reply to CDER-OC-OMQ-Communications@fda.hhs.gov (mailto:CDER-OC-OMQ-Communications@fda.hhs.gov) or mail your reply to:

Tamara Rosbury

Compliance Officer

U.S. Food and Drug Administration

White Oak Building 51, Room 4235

10903 New Hampshire Avenue

Silver Spring, MD 20993

USA

Please identify your response with FEI 3002785310.

Sincerely,

/S/

Francis Godwin

Director

Office of Manufacturing Quality

Office of Compliance

Center for Drug Evaluation and Research

cc:

Mr. Chinnikrishna Reddy

Head of API Site Operations

Mylan Laboratories Limited, Unit 8

G. Chodavaram Village

Vizianagaram 535204

Andhra Pradesh

India

More Warning Letters (/inspections-compliance-enforcement-and-criminal-investigations/compliance-actions-and-activities/warning-letters)