WARNING LETTER

Mylan Laboratories Limited – Unit 7

MARCS-CMS 607508 — AUGUST 20, 2020

Delivery Method:

VIA UPS

Reference #:

320-20-44

Product:

Drugs

Recipient:

Ms. Heather Bresch

Chief Executive Officer

Mylan Laboratories Limited – Unit 7

1000 Mylan Boulevard
Canonsburg, PA 15317
United States

Issuing Office:

Office of Manufacturing Quality

10903 New Hampshire Avenue
Silver Spring, MD 20993
United States

Dear Ms. Bresch:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Mylan Laboratories Limited, Unit 7, FEI 3003227156, at Plot No. 14, 99, & 100, Phase-II, IDA, Pashamylaram, Patancheru (M), Sangareddy District, India, from February 24 to 28, 2020.

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 March 20, 2020, response to our Form FDA 483 in detail and acknowledge receipt of your subsequent correspondence.

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

1. Failure to have adequate cleaning procedures to prevent contamination or carry-over of a material that would alter the quality of the API.

Inadequate Cleaning Records for Bulk Storage Tanks
Your firm manufactures **(b)(4)** and other **(b)(4)**. You use numerous storage tanks to hold various materials, including mother liquids, fresh solvents, and recovered solvents.

Your firm did not have adequate cleaning records for approximately **(b)(4)** non-dedicated bulk storage tanks. You used these tanks in numerous API manufacturing processes across your **(b)(4)** non-dedicated manufacturing blocks. Our investigators requested cleaning records for these tanks. Your firm management provided some records for activities conducted after October 2019 but stated that cleaning, storage, and usage records for storage tanks were not documented or maintained prior to October 2019.

During the inspection our investigators queried your firm on the quality of recovered solvents held in these storage tanks. Your firm management stated that complete impurity profiles of recovered solvents were not performed during the initial evaluation of your solvent recovery contract manufacturing organizations (CMO). Coupled with inadequate cleaning records, there are limited assurances that your non-dedicated equipment would not contribute to cross-contamination or carry-over of residual impurities.

Some recovered solvents used at your site are processed by CMOs. One CMO you used for solvent recovery is **(b)(4)** which was added to Import Alert 66-40 on **(b)(4)** and was issued Warning Letter **(b)(4)**. The firm was cited for inadequate impurity profiles of recovered solvents, which included unknown peaks observed in more than **(b)(4)** lots of **(b)(4)** between 2018 and 2019. Your firm received, stored in non-dedicated bulk tanks, and used multiple **(b)(4)** lots from this CMO, including one lot in which an unknown peak was identified by your firm. You used these lots in the manufacturing of **(b)(4)** API in one of your **(b)(4)** non-dedicated API manufacturing blocks. Numerous other API intended for the United States market were also manufactured in these non-dedicated blocks.

Inadequate Cleaning Validation and Verification Program
In addition to your lack of cleaning records, your cleaning validation and verification program for non-dedicated manufacturing and storage equipment are inadequate. Specifically, during the review of cleaning method validation of **(b)(4)** our investigator observed that your method was not adequately validated to ensure it was capable of detecting and appropriately quantitating **(b)(4)** impurities such as **(b)(4)**. An inadequate scope of impurity analysis, in combination of non-dedicated equipment, lack of cleaning records, and introduction of elevated unknown impurities, increase the risk potential for API and API intermediate cross-contamination.

In your response, you referred to corrective actions implemented as a result of Warning Letter 320-20-06 issued on November 5, 2019, to your Mylan Unit 8 facility. We still remain concerned with some of the practices found in your facility both at the time of the inspection and after that Warning Letter was issued, particularly around control of recovered solvents.

You determined that the cleaning validation and verification program was adequate based upon the absence of out-of-specification investigations, lack of complaints, and undetected impurity testing. Your response is inadequate. Cross-contamination cannot be assumed to be uniformly distributed. Testing alone is insufficient to mitigate the observed contamination hazards.

In response to this letter, provide the following:

- Written confirmation that you no longer use **(b)(4)** to supply materials for your drug manufacturing operations.
- A comprehensive, third-party 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.

2. Failure to control and monitor procedures to recover solvents to ensure that they meet appropriate standards before reuse.

Your firm failed to implement procedures to evaluate and control impurity risks associated with solvents used in your API manufacturing operations. This includes adequate testing of all incoming raw materials to confirm their suitability for manufacturing processes in which they may be used, establishing an impurity profile for solvents to ensure that they meet appropriate standards, and maintaining an ongoing program for monitoring process controls to ensure stable manufacturing and prevent unanticipated impurities.

For example, during a review of incoming raw material acceptance testing between 2015 to 2019, the impurity profiles did not match for multiple lots of recovered **(b)(4)** from **(b)(4)** when compared to the impurity profile of **(b)(4)** solvent. Specifically, unknown peaks were detected in the recovered solvent. Your firm management stated that only the main peak is evaluated during analysis. Your firm failed to evaluate the unknown peaks observed during analytical testing of recovered solvents. Unknown peaks observed in chromatograms may represent unanticipated impurities and should be thoroughly evaluated, and if necessary, investigated.

In your response, you provided some corrective actions and improvements that were implemented prior to this inspection. You state these were based upon learnings from Mylan Unit 8 which had similar issues. You determined the recovered solvents utilized at this facility had minimal impact on API and API intermediates based upon the absence of out-of-specification investigations, lack of complaints, and undetected impurity testing. Your response is inadequate. Your evaluation of the unknown peaks observed in recovered solvent chromatograms was not comprehensive and did not include a thorough manufacturing evaluation to determine if your solvent recovery process contributed impurities to the recovered solvent.

In response to this letter, provide the following:

- A detailed plan describing how you will implement an ongoing program for monitoring unknown impurities from fresh solvents (e.g., stabilizers/additives, contaminants from transport, etc.) which may pose a risk for carry over into the API.
- A detailed plan describing how you will implement an ongoing program for monitoring process control to ensure stable manufacturing and prevention of unanticipated impurities during solvent recovery operations.
- A procedure requiring an impurity profile analysis and risk assessment for all solvent recovery operations. The scope of the procedure should include recovered solvents for internal and external use.
- An updated procedure for evaluating unknown peaks in chromatograms, including a discussion on the level at which an impurity would need to be identified. Provide scientific justification for your decision.

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 API 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).

Repeat Deviations at Multiple Sites

FDA cited similar CGMP deviations at another facility in your company's network.

On November 5, 2019, Mylan Laboratories Limited – Unit 8, FEI No. 3002785310, was issued Warning Letter 320-20-06 for, among other things, failure to have adequate written procedures for receipt, identification, testing, and handling of raw materials and a failure to clean equipment and utensils to prevent contamination or carry-over of material. The poor controls of recovered solvents at this facility led to contamination of drugs with **(b)(4)** impurities.

We observed similar deficiencies related to inadequate storage and handling of recovered solvents utilized at your Unit 7 API manufacturing operations. These repeated failures at multiple sites manufacturing API demonstrate that your company's oversight and control over the manufacture of drugs is inadequate. You should immediately and comprehensively assess your company's global manufacturing operations to ensure that systems and processes, and ultimately, the products manufactured, conform to FDA requirements at all your sites.

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 (mailto: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 drug applications or supplements listing your firm as a drug manufacturer.

Failure to correct these deviations may also result in the FDA refusing admission of articles manufactured at Mylan Laboratories Limited, Unit 7, at Plot No. 14, 99, & 100, Phase-II, IDA, Pashamylaram, Patancheru (M), Sangareddy District 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 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).

Please identify your response with FEI 3003227156 and ATTN: Joseph Lambert, Pharm.D.

Sincerely,
/S/
Francis Godwin
Director
Office of Manufacturing Quality
Office of Compliance
Center for Drug Evaluation and Research

cc:
Mr. P. Jayachandra Prasad, Vice President of Manufacturing Services
Mylan Laboratories Limited – Unit 7
Plots 14, 99, 100; IDA
Pashamylaram II, Patancheru Medak District, Hyderabad Telangana, 502319
India

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