Mylan Laboratories Limited, (Nashik FDF) 4/3/17

10903 New Hampshire Avenue
Silver Spring, MD 20993

Certified Mail
Return Receipt Requested

Warning Letter 320-17-32

April 3, 2017

Mr. Rajiv Malik
President
Mylan Pharmaceuticals, Inc.
1000 Mylan Boulevard
Canonsburg, PA 15317

Dear Mr. Malik:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Mylan Laboratories Limited at F-4 & F-12, MIDC, Malegaon Taluka, Sinnar District, Nashik 422 113, Maharashtra, India, from September 5 to 14, 2016.

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 October 5, 2016, 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 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).

From January 1 to June 30, 2016, your firm invalidated 101 out of 139 (about 72 percent) initial out-of-specification (OOS) assay results without sufficient investigation to determine the root cause of the initial failure.

For example, you opened laboratory investigation report PR 908027 for an initial OOS six-month stability assay result of **(b)(4)** percent (specification **(b)(4)**–**(b)(4)** percent) for **(b)(4)** mg tablets, lot **(b)(4)**. You invalidated the initial failing result without adequate investigation, performed re-testing, and then reported the **(b)(4)** results of these replicate re-tests (**(b)(4)** percent). Your investigation did not reach an assignable cause, nor did you take appropriate corrective actions and preventive actions to ensure that the significant "analytical bias" to which you ultimately attributed the initial failure would not affect other analytical work in your laboratory.

In your response, you state that laboratory decisions are to be made on the basis of scientific evaluation, and that they are to determine whether OOS laboratory results are the result of the laboratory process or the manufacturing process. However, in the example above, your investigation assumed "analytical bias" in your laboratory process but failed to determine how this apparently significant error in your analyses could be eliminated or mitigated in the future.

Your response is inadequate because you failed to implement a corrective action and preventive action (CAPA) plan to mitigate errors that you attribute to laboratory process. Further, you did not include these improperly invalidated OOS results in your analysis of laboratory investigation trends. According to your *Laboratory Investigation Report* procedure MLLNSK-SOP-QA-GMP-0138, version 6, only "confirmed" root causes are to be identified and trended in laboratory investigation reports. Because your laboratory investigations frequently invalidate initial failures without cause, your laboratory trending excludes a large proportion of data that would otherwise alert you to problems in your laboratory system. Failure to identify trends in OOS investigations is a repeat observation from the previous FDA inspection, March 19 to 26, 2015.

In response to this letter, conduct and provide the results of a trend analysis of all your OOS results that includes both "confirmed" root causes and the initial OOS results that you have previously excluded as invalid without assignable root causes. For each invalidated result, indicate the product tested, date of analysis, type of analysis, purpose of the test, original result, retest results, and your unconfirmed assignable root cause. Revise and provide your updated *Laboratory Investigation Report* procedure. Specify how your revised procedure ensures that all OOS investigations are included in your trending.

2. Your firm failed to establish an adequate quality control unit with the authority to review production records to assure that no errors have occurred or, if errors have occurred, that they have been fully investigated (21 CFR 211.22(a)).

Your quality unit failed to monitor and investigate error signals generated by the computerized systems that you use for high performance liquid chromatography and gas chromatography. These signals indicated the loss or deletion of original CGMP analytical data. However, your quality unit did not comprehensively address the error signals or determine the scope or impact of lost or deleted data until after these problems were reviewed during our inspection.

For example, our investigator reviewed audit trails from August 2016 assay testing on **(b)(4)** batch **(b)(4)** and dissolution testing for **(b)(4)** tablets batch **(b)(4)**. The audit trail for these tests included the message, "deleted result set," but neither of these two incidents were recorded in the analytical packages for these batches of drug products, nor were they reviewed or investigated by the quality unit.

In addition, during the inspection, our investigator observed that your Empower 3 system audit trail displayed many instances of a "Project Integrity Failed" message, which indicates that injections were missing from the results of analytical testing. For example, in **(b)(4)** analysis for **(b)(4)** tablets batch **(b)(4)** conducted on June 20, 2016, no chromatogram was rendered for the initial run of testing. The data package for this testing clearly shows that the initial run is missing, but your quality unit did not investigate the incident.

Although you showed our investigator isolated examples of interrupted, missing, deleted, and lost data for which you had opened investigations, you reached similar conclusions in many of these investigations regarding the root cause of your loss of data integrity but failed to take appropriate corrective action and preventive action in response. Our investigator observed that you attributed numerous incidents to power interruptions, connectivity problems (disconnection of the Ethernet or power cord), and instrument malfunctions. You could not explain why these events occurred with frequency in your laboratory, nor had you undertaken a comprehensive investigation into the problem or sought to correct it and prevent its recurrence.

In your written response dated February 17, 2017, you identified seven samples from a single week of testing for which original results were lost following data acquisition interruptions at the time of initial analysis. Instead of uniformly initiating an investigation into the root cause of each interruption when it occurred or even documenting it for later review and investigation by the quality unit, you explained in your response that you retested the samples immediately after the interruptions.

Your response is inadequate because you have not identified and investigated each instance in which data acquisition was interrupted. While you assessed a limited number of error codes from a seven day period, you did not evaluate the effects of other error codes identified in your simulation exercise report on the reliability, accuracy, or completeness of the data you use to evaluate the quality of your drugs. Although you have submitted multiple responses, you have not yet:

- shown exactly how widespread these problems are;
- evaluated their full effects on the quality of your drugs;
- explained why these events occurred with frequency in your laboratory;
- or demonstrated how you will ensure that your quality unit reviews, investigates, and acts upon codes that affect the reliability of your CGMP data.

In response to this letter, provide your validation of laboratory instrument error codes. Identify the specific codes that may impact product quality and the reliability of CGMP

data, and provide your procedures to demonstrate how your quality unit will review, investigate, and respond to these specific codes.

Data Integrity Remediation

Your quality system does not adequately ensure the accuracy and integrity of data to support the safety, effectiveness, and quality of the drugs you manufacture. We acknowledge that you are using a consultant to audit your operation and assist in meeting FDA requirements. In response to this letter, provide the following.

A. A comprehensive investigation into the extent of the inaccuracies in data records and reporting. Your investigation should include:

- A detailed investigation protocol and methodology; a summary of all laboratories, manufacturing operations, and systems to be covered by the assessment; and a justification for any part of your operation that you propose to exclude.
- An assessment of the extent of data integrity deficiencies at your facility. Identify omissions, alterations, deletions, record destruction, non-contemporaneous record completion, and other deficiencies. Describe all parts of your facility's operations in which you discovered data integrity lapses.
- A comprehensive retrospective evaluation of the nature of the testing data integrity deficiencies.

B. A current risk assessment of the potential effects of the observed failures on the quality of your drugs. Your assessment should include analysesof the risks to patients caused by the release of drugs affected by a lapse of data integrity, and risks posed by ongoing operations.

C. A management strategy for your firm that includes the details of your global corrective action and preventive action plan. Your strategy should include:

- A detailed corrective action plan that describes how you intend to ensure the reliability and completeness of all of the data you generate, including analytical data, manufacturing records, and all data submitted to FDA.
- A comprehensive description of the root causes of your data integrity lapses, including evidence that the scope and depth of the current action plan is commensurate with the findings of the investigation and risk assessment.

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.

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) and 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 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 refusing admission of articles manufactured at Mylan Laboratories Limited at F-4 & F-12, MIDC, Malegaon Taluka, Sinnar District, Nashik 422 113, Maharashtra, 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 or mail your reply to:

Joseph Lambert, Pharm.D.
Compliance Officer
U.S. Food and Drug Administration
White Oak Building 51, Room 4359
10903 New Hampshire Avenue
Silver Spring, MD 20993

Please identify your response with FEI 3005587313.

Sincerely,
/S/
Thomas J. Cosgrove, J.D.
Director
Office of Manufacturing Quality
Office of Compliance
Center for Drug Evaluation and Research