Mylan Pharmaceuticals Inc. 11/9/18

U.S. Food and Drug Administration
Division of Pharmaceutical Quality Operations I
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WARNING LETTER
CMS # 557903

November 9, 2018

Ms. Heather Bresch
Chief Executive Officer
Mylan Pharmaceuticals, Inc.
1000 Mylan Boulevard
Canonsburg, PA 15317

Dear Ms. Bresch:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Mylan Pharmaceuticals, Inc. at 781 Chestnut Ridge, Morgantown, West Virginia, from March 19, 2018, to April 12, 2018.

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 May 3, 2018, response in detail and acknowledge receipt of your subsequent correspondence.

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

1. Your firm failed to clean, maintain, and, as appropriate for the nature of the drug, sanitize and/or sterilize equipment and utensils at appropriate intervals to prevent malfunctions or contamination that would alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements (21 CFR 211.67(a)).

Your cleaning validation and verification program for manufacturing equipment is inadequate to prevent cross contamination.

A. Your firm has had many recurring incidents in which visible drug residues were found on non-dedicated equipment after the equipment was deemed clean by multiple staff.

For example, on January 10, 2018, your firm opened an investigation after a technician found visible residues of nitrofurantoin in the form of a yellow powder on your encapsulation machine after you had already made **(b) (4)** batches of another drug, verapamil HCl extended release (ER) capsules, a white powdered drug product.

You had cleaned the encapsulation machine after you finished manufacturing the yellow nitrofurantoin and before you started to manufacture the white verapamil HCl ER capsules. The machine was cleaned **(b) (4)** more times between different capsule dosage strength changes of verapamil HCl ER. Although both manufacturing and quality personnel performed visual inspections after these cleanings, visible yellow powder residue of nitrofurantoin was not detected on the encapsulation machine**(b) (4)** until many verapamil batches had been exposed to a significant risk of cross-contamination with nitrofurantoin.

B. Your firm continued to experience cleaning swab failures related to detergent residue across numerous pieces of non-dedicated equipment and surfaces. In your 2013 cleaning assessment, you noted several cleaning swab failures and difficulties in recovering your detergent, **(b) (4)**, from equipment surfaces. This assessment culminated in the decision to replace **(b) (4)** with a pharmaceutical-grade detergent. However, our inspection noted that you continued to use **(b) (4)**. You also continued to obtain failing cleaning swab results in 2018 for residual **(b) (4)** after equipment was deemed visually clean.

C. Your cleaning program was insufficient, including, but not limited to, the following.

- The selection process for equipment, location, and number of swab samples collected was not justified or consistently documented (e.g., sufficient pieces of equipment, demonstration of reproducibility).
- The cleaning procedures used in your validation and verification protocols were not always documented.
- Protocols were not consistently followed (e.g., obtaining successful samples from **(b) (4)**).
- For periods as long as 6 years, cleaning validation and verification study reports were not finalized for drug products you deemed “high risk.” The lengthy delay in producing your October 2016 report to evaluate the capability of your cleaning procedures for these critical products was attributed to “misplacement of the protocol and associated data.”
- Adequate validation or verification studies were not always performed when introducing a new high-risk (e.g., difficult to clean, low solubility, potent) active ingredient into the manufacturing operation.

• Initial equipment surface cleaning swab results with unknown or extraneous peaks were sometimes invalidated (without meaningful investigation) by re-collecting a swab from the failed location after a re-clean, or from another equipment location.

• You lacked a system to trigger timely and effective investigations when multiple visual checks failed to detect visible drug residues remaining on a piece of equipment.

• Cleaning swabs were sometimes lost or not accounted for in your data.

Your response was insufficient in that it lacked updated procedures and evidence to support a validated cleaning program. In addition, you provided only partial product impact assessments.

In response to this letter:

• Provide evidence of a validated program in which cleaning procedures used to remove active ingredients and detergents from production equipment can consistently meet predetermined and scientifically sound specifications.

• Justify the number, location, timing, and frequency of cleaning swabs on equipment, and the selection of products and equipment types for your cleaning matrix validation/verification activities.

• Assess all equipment (**(b) (4)**) in which drug product residues were discovered during manufacturing or cleaning operations at your facility.

• Provide a retrospective investigation into all cleaning swab failures and identify the root cause of the failures. Specify any swab failures for which the corrective action was to re-clean without investigating the root cause of the failure. Provide your corrective action and preventive action (CAPA) plan that details improvements to procedures for cleaning and equipment inspection that will be implemented as a result of your investigation.

• Describe your updated cleaning training program for your production and quality assurance employees. Include any objective competency and proficiency results to assess training effectiveness.

2. 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).

Your investigations into out-of-specification (OOS) results and process deviations were inadequate. Root causes did not consistently include scientifically supported conclusions.

A. Your firm opened Laboratory Investigation Report 1464472 on March 6, 2018, because of OOS assay test results for three separate batches of the active pharmaceutical ingredient (API) atenolol, USP. You also obtained OOS results during re-analysis. During the inspection, two quality directors stated that the OOS results were dismissed because the values were obtained when solution stability had exceeded the time limit **(b) (4)**. However, our investigators' review of the data provided by your firm indicated that standards and samples of this API can be stable **(b) (4)**. The unjustified invalidation of failing test results is a repeat violation **(b) (4)**.

B. Your firm opened two manufacturing investigation reports, No. 1071629 on December 12, 2016, and No. 1106258 on January 25, 2017, to investigate atypically high assay and high variability content uniformity results for three batches of prednisolone sodium phosphate 10 mg orally disintegrating tablets (ODT). The investigations identified a root cause of untrained or inexperienced operators **(b) (4)**. The investigation did not fully evaluate the processing factors that contribute to variability in your finished tablets. In particular, it did not evaluate the inherent

variability of the **(b) (4)** method used for charging **(b) (4)**, and identify more robust methods for performing this critical transfer that could prevent blend segregation and tablet dose non-uniformity. It also did not ensure improvements were adequately specified in batch records to enable an ongoing state of control. We acknowledge your firm's market recall on April 30, 2018, of all batches of prednisolone sodium phosphate ODT within expiry from the U.S. market.

C. Your firm opened multiple manufacturing investigation reports and trending assessments from July 2016 to October 2017 related to out-of-trend and OOS content uniformity results for metolazone 2.5 mg tablets. A scientifically justified root cause had not been identified, and effective CAPA plans had not been implemented. Despite substantial non-uniformity observed in multiple batches of metolazone 2.5 mg tablets, you continued to manufacture and release this drug product up to the time of the inspection.

Your response is inadequate because it lacked a comprehensive retrospective evaluation of all your investigations to ensure implementation of appropriate CAPA. Also, while you indicated that you are implementing controls to remediate your investigation system, you lacked a sufficient interim plan to ensure adequate oversight of investigations of manufacturing and quality issues.

In response to this letter, provide:

- A retrospective, independent review of all OOS (raw materials, in-process testing, and finished testing) results obtained for drug products currently within expiry. Assess whether the scientific justification and evidence were conclusive for each invalidated OOS result. For investigations that establish laboratory root cause conclusively, determine effectiveness of the CAPA and ensure that all laboratory methods vulnerable to the same root cause are identified for remediation. For any OOS results with inconclusive or no root cause identified in the laboratory, include a thorough review of production (e.g., batch manufacturing records, adequacy of manufacturing steps, raw materials, process capability, deviation history, batch failure history). Provide a CAPA plan that identifies manufacturing root causes and specifies meaningful improvements.

- A retrospective, independent evaluation of the adequacy of major manufacturing investigations (e.g., deviations, rejects) performed for products currently within expiry.

- A comprehensive, independent assessment of your overall system for investigations of deviations, atypical events, complaints, OOS results, and failures. Your CAPA should include, but not be limited to, improvements in investigation competencies, root cause analysis, written procedures, and quality unit oversight. Also include your process for evaluating CAPA effectiveness.

For more information about handling OOS results and conducting appropriate investigations, see FDA's guidance document, *Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production*, at **https://www.fda.gov/downloads/drugs/guidances/ucm070287.pdf (https://www.fda.gov/downloads/drugs/guidances/ucm070287.pdf)**.

3. Your firm failed to follow 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, and to record and justify any deviations from them (21 CFR 211.100(b)).

Changes in blend size, formulation, and manufacture of your drug products were not evaluated consistently, appropriately, or thoroughly before execution. In many cases, you failed to use your change management system for significant changes. Furthermore, numerous batches with major process changes were not included in your stability program.

During this inspection, our investigators identified numerous major changes that were not adequately managed to prevent substantial risks to drug quality, including, but not limited to, significant changes **(b) (4)**, and significantly modifying **(b) (4)** from validated production and process control procedures.

For example, to avoid potential contamination from a metal washer found **(b) (4)** carbidopa/levodopa 25 mg/100 mg tablets, Batch 3092534, by **(b) (4)**. You implemented this change without evaluating the effect it would have on your validated process. Following compression, you tested this batch and it failed the finished product dissolution specification.

Significantly, we note that recently you also submitted a field alert and recalled a batch of Maxide-25 Tablets 37.5 mg/25 mg for which equipment changes had been made to the manufacturing process without first adequately evaluating their impact. The batch (Batch 3087136) failed assay testing at the 3-month stability time point. Your investigation indicated that equipment changes and variability in **(b) (4)** likely played key roles in the failing assay results.

Your firm lacks an adequate ongoing program for monitoring process control to ensure stable manufacturing operations and consistent drug quality. Deviations from a validated process increase the likelihood of variation that can lead to product quality failures.

When significant variability is observed in one or more stages of pharmaceutical production, it is essential for executive management to support and implement effective actions that proactively address the source(s) of the variation and provide for a continued state of control.

In your response, you state that the combination of equipment controls, in-process testing, and verification of physical attributes **(b) (4)** provided a high degree of assurance of process control for compression operations. You also note that five batches of solid oral drug products, **(b) (4)** that were “authorized under a deviation” rather than the change control program, were rejected due to the failure to meet pre-defined quality attributes.

Your lack of rigorous oversight of manufacturing changes continues to be a major factor in the unexpected variation observed in your drug products. In response to this letter, provide the following:

- A comprehensive, independent evaluation of your change management system. This review should include, but not be limited to, a review of your procedure(s) to ensure that changes are sufficiently justified, adequately reviewed, and approved by your quality unit. The change management program should include such elements as adding lots to the stability program when there is a significant manufacturing change; provisions for qualification and validation; and a process for determining change effectiveness.

- An independent, retrospective review of any changes that may have significantly increased variation in manufacturing for all batches within expiry. This would include, but not be limited to, changes to your equipment, facility, materials, measurements, and process. Provide explanations and conclusions regarding how changes may have affected the identity, strength, quality, or purity of your drug products. This retrospective review should afford particular attention to all drug products **(b) (4)**.

- An assessment of the reliability of your manufacturing operations, with an emphasis on variation introduced by **(b) (4)**. Describe your plans to improve equipment and facility design **(b) (4)**, and to mitigate or eliminate human error.

- Detail your validation plan for ensuring a state of control throughout the product lifecycle. This should include, but not be limited to, a description of your program for vigilant monitoring of intra-batch and inter-batch variation to ensure an ongoing state of control.

Quality Unit Authority

Your inspectional history and significant findings in this letter indicate that your quality unit is not fully exercising its authority and/or responsibilities. For example, your quality unit failed to ensure that cleaning operations are adequate to prevent cross-contamination; manufacturing changes are appropriately evaluated; manufacturing processes are robust and capable of consistently delivering quality product; and investigations are effective. Your firm must provide the quality unit with the appropriate authority, sufficient resources, and staff to carry out its responsibilities and consistently ensure drug quality.

Quality Systems Guidance

Your firm's quality systems are inadequate. For guidance on establishing and following CGMP compliant quality systems to establish and maintain an ongoing state of control, see FDA's guidances: *Q8(R2) Pharmaceutical Development* at **https://www.fda.gov/downloads/drugs/guidances/ucm073507.pdf (https://www.fda.gov/downloads/drugs/guidances/ucm073507.pdf)**; *Q9 Quality Risk Management* at **https://www.fda.gov/downloads/Drugs/Guidances/ucm073511.pdf (https://www.fda.gov/downloads/Drugs/Guidances/ucm073511.pdf)**; and *Q10 Pharmaceutical Quality System* at **https://www.fda.gov/downloads/drugs/guidances/ucm073517.pdf (https://www.fda.gov/downloads/drugs/guidances/ucm073517.pdf)**.
Also see FDA's guidance document *Process Validation: General Principles and Practices* at **https://www.fda.gov/downloads/drugs/guidances/ucm070336.pdf (https://www.fda.gov/downloads/drugs/guidances/ucm070336.pdf)**.

Repeat Violations at Multiple Sites

FDA cited similar CGMP violations at this and other facilities in your company's network. Since 2015, FDA has taken the following actions in response to CGMP violations at Mylan facilities.

- On August 6, 2015, three Mylan facilities (FEI No. 3003813519, FEI No. 3007512701, and FEI No. 3007648351) were issued a combined Warning Letter for, among other things, inadequate controls for manufacturing sterile drugs; failure to establish scientifically sound and appropriate laboratory controls; and failure to thoroughly investigate unexplained discrepancies.

- On April 3, 2017, Mylan Laboratories, Ltd., FEI No. 3005587313, was issued a Warning Letter for, among other things, invalidating numerous initial OOS assay results without sufficient investigations to determine the root cause of the initial failure.

- **(b) (4)**

(b) (4). These repeated failures at multiple sites demonstrate that Mylan's management oversight and control over the manufacture of drugs is inadequate.

Your executive management remains responsible for fully resolving all deficiencies and ensuring ongoing CGMP compliance. You should immediately and comprehensively assess your company's global manufacturing operations to ensure that systems and processes, and ultimately, the products you manufacture, consistently conform to FDA requirements.

CGMP consultant recommended

Because you failed to correct repeat violations, we strongly recommend engaging an independent third party qualified as set forth in 21 CFR 211.34, 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 ensuring 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.

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) 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.

Correct the violations cited in this letter promptly. Failure to promptly correct these violations may result in legal action without further notice including, without limitation, seizure and injunction. Unresolved violations in this warning letter may also prevent other Federal agencies from awarding contracts.

Until these violations are corrected, we may withhold approval of pending drug applications listing your facility. We may re-inspect to verify that you have completed your corrective actions. We may also refuse your requests for export certificates.

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 **ORAPharm1_responses@fda.hhs.gov (mailto:ORAPharm1_responses@fda.hhs.gov)** or mail your reply to:

Maya Davis
Compliance Officer
FDA/OPQ Division I
One Montvale Avenue, Fourth Floor
Stoneham, MA 02180

Please identify your response with FEI No. 1110315.

Sincerely,
/S/
Diana Amador-Toro
Program Division Director/OPQ Division I
New Jersey District Office

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