Morton Grove Pharmaceuticals, Inc. 2/17/17

Chicago District Office
550 W. Jackson Blvd., 15th Floor
Chicago, IL 60661
Telephone: (312) 353-5863
Fax: (312) 596-4187

February 17, 2017

WARNING LETTER

CHI-3-17

UPS NEXT DAY
SIGNATURE REQUIRED

Mr. Sunil Khera
President
Morton Grove Pharmaceuticals, Inc.
6451 Main Street
Morton Grove, IL 60053

Dear Mr. Khera:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Morton Grove Pharmaceuticals, Inc., at 6451 Main Street, Morton Grove, Illinois, from January 4 to February 5, 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).

In addition, the inspection revealed that you failed to submit field alert reports (FAR) to FDA as required by section 505(k) of the FD&C Act, 21 U.S.C. 355(k), 21 CFR 314.98(b) (abbreviated new drug applications (ANDA)). Failure to comply with regulations promulgated under section 505(k) is a prohibited act under section 301(e) of the FD&C Act, 21 U.S.C. 331(e).

We reviewed your firm's March 7, 2016 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.

Current Good Manufacturing Practice Violations

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).

Our investigators documented that your investigations into out-of-specification (OOS) test results were not thorough, timely, or based on scientific rationales. Your investigations did not adequately determine root cause.

*Stability Failure: Investigation **(b)(4)***

Two different batches of your triamcinolone acetonide lotion USP 0.1% failed stability testing at **(b)(4)**. On July 25, 2015, batch **(b)(4)** failed for **(b)(4)**, and batch **(b)(4)** failed both **(b)(4)**. During the inspection, we reviewed your initial OOS investigation **(b)(4)**, in which you determined that the stability failures were caused by **(b)(4)** in **(b)(4)**, an excipient used to manufacture triamcinolone acetonide lotion.

In the same investigation, you also concluded, without performing a science-based health hazard evaluation, that such impurities do not pose health risks. You continued to distribute other batches of the same product while your OOS investigation remained open for more than five months. During the inspection, your management told our investigators that your investigation "… fell through the cracks."

In your response, you provided a copy of your updated investigation into this problem. Your response was inadequate in the following ways:

- You failed to explain the basis for your original determination that **(b)(4)** in **(b)(4)** caused the stability failures in finished products.
- You also failed to extend the investigation to all potentially-affected batches of drugs made with the **(b)(4)**.
- You **(b)(4)** perform a health hazard analysis, but the analysis did not identify the specific **(b)(4)** related to the failures.

In response to this letter:

- Detail both phases of your investigation and how you determined the root cause.
- Update your efforts to identify the **(b)(4)**, and assess each **(b)(4)**.

- Detail your actions to ensure that all your product/quality-related investigations are thorough, timely, and scientifically sound.
- **(b)(4)**
- Justify why you did not take additional actions with respect to batches of potentially-affected products that were distributed and remain on the market.

2. Your firm failed to ensure that laboratory records included complete data derived from all tests necessary to assure compliance with established specifications and standards (21 CFR 211.194(a)).

Your records showed that multiple in-process and finished batches of fluticasone propionate nasal spray USP failed assay for **(b)(4)**. For example, in-process batches **(b)(4)** and **(b)(4)** initially failed release criteria for **(b)(4)**, as did their respective finished product batches **(b)(4)** and **(b)(4)**.

When our investigator reviewed your investigation into these initial **(b)(4)** failures, we found that your investigation protocol **(b)(4)** assigned the cause of the failures to analyst error if repeat tests delivered passing results. The original results were invalidated without scientific justification under the protocol and only re-test results were reported as part of batch release decisions. The original results were not reported or considered in evaluating the quality of your drugs for release.

3. Your firm failed to follow written procedures applicable to the quality control unit (21 CFR 211.22(d)).

In multiple instances, we found that you conducted investigations into quality-related problems outside of the quality unit's oversight and authority. Although your quality unit has numerous procedures that govern investigations (e.g., S-100-341 *Laboratory Investigation, Initiation, and Reporting Procedure,* S-100-351 *Deviation Procedure*, S-100-375 *Corrective Actions/Preventive Actions Follow-Up System (CAPA)*, and QC-102-027 *Investigation and Evaluation of* **(b)(4)** *Out of Specification (OOS) Results*), your firm conducted investigations as "internal audits" so that the investigations would not be governed by those procedures and by your quality unit.

For example, after an FDA inspection from January 22 to March 26, 2014, you conducted a retrospective "MGP Gap Assessment" regarding "trial injections" performed in your facility. Instead of initiating an investigation and CAPA under the supervision and authority of the quality unit, you performed this assessment as part of an **(b)(4)** and identified at least **(b)(4)** analytical methods that used trial injections.

In addition to the fact that you conducted your "MGP Gap Assessment" outside the authority of the quality unit, your assessment was inadequate in the following ways:

- You limited your assessment to a review of data pertaining to **(b)(4)** batches representing **(b)(4)** finished drug products produced at your facility during 2013 and 2014.Over the same period, you manufactured more than **(b)(4)** batches representing **(b)(4)** drug products, but you did not include the majority of these batches or products in the assessment.
- You did not provide the methodology on which you relied to determine the scope of your assessment.
- You did not provide the criteria on which you relied to determine whether the quality of your products had been affected by the practice of using "trial injections."
- You did not evaluate the extent of your practice of performing trial injections, such as type of products, number of release, stability, and application submission batches affected.

In response to this letter:

- Explain why you performed and documented quality-related investigations without quality unit oversight.

- List your CAPA(s) to ensure that all investigations and deficiencies from your internal audits are overseen by your quality unit.
- List all quality-related investigations and CAPA generated during the last three years initiated as a result of an internal audit or any other mechanism. Refer to your procedure governing each of these investigations and CAPA.
- Justify why you limited your review to only **(b)(4)** batches representing **(b)(4)** finished drug products and did not extend the assessment to include API and excipients.

4. Your firm failed to establish and follow adequate control procedures to monitor the output and to validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product (21 CFR 211.110(a)).

During our inspection, we observed that your manufacturing process for fluticasone propionate nasal spray USP relied on an unvalidated and experimental manufacturing process in which you **(b)(4)**.

In January 2013, multiple in-process and finished product batches of fluticasone propionate nasal spray USP failed to meet release specification for **(b)(4)**. Failure to meet **(b)(4)** specifications may reduce the effectiveness of products administered as nasal sprays. You rejected these batches and corresponding finished products and undertook an investigation into the **(b)(4)** failures. Your investigations **(b)(4)** and **(b)(4)** stated that "the root cause can be attributed to the raw material . . . **(b)(4)** . . ." but offered no further explanation for the failures and did not specify the basis for your conclusion.

Following these investigations, you began manufacturing **(b)(4)**. However, you have never revalidated your manufacturing process to account for the variability in your finished product that you initially attributed to **(b)(4)**.

When significant variability is observed in one or more stages of pharmaceutical production, it is essential that executive management support and implement effective actions to address the source(s) of the variation and provide for a continued state of control. Your firm does not have an adequate ongoing program for monitoring process control to ensure stable manufacturing operations and consistent drug quality.

See FDA's guidance document, *Process Validation: General Principles and Practices*, for general principles and approaches that FDA considers appropriate elements of process validation, at **http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070336.pdf (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070336.pdf**

In response to this letter, provide scientific data supporting the validated status of the fluticasone propionate nasal spray USP manufacturing process.

5. Your firm's quality control unit failed to test in-process materials during the production process (21 CFR 211.110(c)).

Contemporaneous in-process testing ensures the manufacturing process remains within its validated parameters and in a continued state of control. Our investigators documented that your manufacturing process did not subject materials to in-process testing as required. For example, the FDA investigator found that assay testing for fluticasone propionate nasal spray USP in-process batch **(b)(4)** and the corresponding finished product batch **(b)(4)** were performed simultaneously on January 4, 2015. The investigator also found that your firm routinely tested in-process materials and their corresponding finished products simultaneously for **(b)(4)** additional drug products.

This practice violated not only the applicable regulatory requirements but also the express terms of your own regulatory filings with FDA where you described required in-process testing. See ANDA 78792, section 2.3.P, page 7: **(b)(4)**

In response to this letter:

- Retrospectively review every instance where you did not conduct in-process testing at the appropriate time.
- List all OOS, invalidated OOS, unexpected, and out-of-trend (OOT) in-process test results for products within expiration.
- Investigate your previous assessments of the quality standards of each drug product to determine the need for changes in drug product specifications, manufacturing, or control procedures as required by 21 CFR 211.180(e).

6. Your firm failed to exercise appropriate controls over computer or related systems to assure that only authorized personnel institute changes in master production and control records, or other records (21 CFR 211.68(b)).

Our investigators observed that information technology (IT) staff at your facility share usernames and passwords to access your electronic storage system for **(b)(4)** data. Your IT staff can delete or change directories and files without identifying individuals making changes.After a previous inspection in which FDA observed similar deficiencies, you committed to eliminate these and other data integrity vulnerabilities.

In response to this letter:

- Provide your detailed plan to ensure that each current and future employee will have a unique username and password to allow traceability of changes to electronic data back to specific authorized personnel.
- Describe the specific changes made to your software and electronic systems to ensure the effectiveness of your corrective actions.
- Include a detailed description of the role of your quality unit to ensure that the corrections are appropriately implemented and sustainable.

Post-Market Reporting Violations

During the inspection, we found that your firm failed to submit FAR to FDA as required by section 505(k) of the FD&C Act, 21 U.S.C. 355(k), 21 CFR 314.98(b) (ANDA).

Specifically, your firm did not submit a FAR within three working days when fluticasone propionate nasal spray USP batch **(b)(4)** was OOS for assay at the **(b)(4)** stability test interval. You discovered the OOS assay result on June 11, 2015. Later you discovered additional OOS stability values for multiple batches and initiated an investigation on August 3, 2015. You did not submit a FAR until the second day of FDA's inspection, January 5, 2016, more than six months after you discovered the initial OOS.

Repeat violations and deviations at multiple sites

Since 2013, FDA has taken the following actions in response to CGMP violations and deviations at other Wockhardt facilities.

1. Wockhardt Waluj, FEI 3005289335, was placed on Import Alert on May 22, 2013 and was issued a Warning Letter dated July 18, 2013, for, among other things, limiting an FDA inspection and manipulating and deleting data.
2. Wockhardt Chikalthana, FEI 3002808503, was issued a Warning Letter on November 25, 2013, and was placed on Import Alert on November 26, 2013 for, among other things, manipulating and deleting data.
3. Wockhardt Waluj, FEI 3004540156, was issued a Warning Letter on November 25, 2013 for, among other things, manipulating and deleting data and deficient in-process testing practices.

4. CP Pharma, FEI 3003369660, was issued a Warning Letter on November 16, 2016, for poor aseptic practices and environmental monitoring in the manufacture of sterile drugs.
5. Wockhardt Ankleshwar, FEI 3002808500, was placed on Import Alert on August 5, 2016, and received a Warning Letter on December 23, 2016 for data manipulation and destruction, and poor aseptic practices in the manufacture of sterile drugs.
6. Wockhardt Shendra, FEI 3009278506, received an Untitled Letter on January 27, 2017, for manipulating and deleting data and poor aseptic practices in the manufacture of sterile drugs.

At this time, seven Wockhardt facilities (including Morton Grove) are considered out of compliance with CGMP. These repeated failures at multiple sites demonstrate your company's inadequate oversight and control over the manufacture of drugs.

In your responses to the various actions listed above, including during multiple meetings with FDA, you have repeatedly discussed and promised corporate-wide corrective actions. Yet, when FDA inspects or returns to other Wockhardt facilities, similar violations are shown to persist.

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 manufactured, conform to FDA requirements.

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.
- Interviews of current and former employees to identify the nature, scope, and root cause of data inaccuracies. We recommend that these interviews be conducted by a qualified third party.
- 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. We recommend that a qualified third party with specific expertise in the area where potential breaches were identified should evaluate all data integrity lapses.

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. Indicate whether individuals responsible for data integrity lapses remain able to influence CGMP-related or drug application data at your firm.
- Interim measures describing the actions you have taken or will take to protect patients and to ensure the quality of your drugs, such as notifying your customers, recalling product, conducting additional testing, adding lots to your stability programs to assure stability, drug application actions, and enhanced complaint monitoring.
- Long-term measures describing any remediation efforts and enhancements to procedures, processes, methods, controls, systems, management oversight, and human resources (e.g., training, staffing improvements) designed to ensure the integrity of your company's data.
- A status report for any of the above activities already underway or completed.

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 in all of your facilities.

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

Russell K. Riley, Compliance Officer
U.S. Food and Drug Administration
Chicago District
550 W. Jackson Boulevard
15th Floor
Chicago, IL 60661