Akorn, Inc. 2/4/19

Division of Pharmaceutical Quality
Operations III
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January 4, 2019

WARNING LETTER

Case# 558914

UPS NEXT DAY
SIGNATURE REQUIRED

Mr. Rajat Rai
Chief Executive Officer
Akorn, Inc.
1925 West Field Court
Suite 300
Lake Forest, IL 60045

Dear Mr. Rai:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Akorn, Inc. at 1222 West Grand Avenue, Decatur, IL, from April 9 to May 16, 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 June 7, 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 follow appropriate written procedures that are designed to prevent microbiological contamination of drug products purporting to be sterile, and that include validation of all aseptic and sterilization processes (21 CFR 211.113(b)).

Poor Aseptic Behavior

Operators displayed poor aseptic practices during aseptic set-up and filling operations. For example:

a. Operators placed their head and upper torso inside the filling cabinet during interventions and performed interventions over open vials without clearing them.
b. Operators excessively handled sterile stopper bags before introduction into the stopper chute in the ISO 5 filling cabinet. Specifically, operators removed the outer secondary layer (sterility barrier) and manually handled the sterile single-layer bag. These stopper bags were then re-placed on the non-sterile shelving units located in the ISO 7 area for extended periods of time. During this time, operators unnecessarily touched and manipulated the bags. These bags are subsequently introduced into the stopper chute located in the ISO 5 filling cabinet. Notably, your procedures specifically prohibit manipulation of the stoppers once the outer bag has been removed.

In addition, operators shook stopper bags inside the ISO 5 area and the bag also contacted the interior of the stopper chute (critical product contact surface) during the loading process. Your procedures specifically prohibit agitating and shaking during loading.

Personnel also failed to disinfect stopper bags prior to their introduction into the ISO 5 area, again, as required per your procedure.

c. Operators placed sterile wipes on a ledge below the filling line and later used the same wipes to clean the interior of the ISO 5 filling area cabinet doors and part of the filling area machine where open sterile vials were exposed.

d. Interventions require a large door to be opened. When opened, the door is exposed to the ISO 7 area, and when being closed, there is a significant risk of the lower quality room air sweeping into the ISO 5 filling cabinet. Empty sterile vials are located extremely close to the door. In addition, although operators wiped the open door after interventions were complete, the wiping was vigorous, only disinfected part of the door, and was performed while closing the door. The line design and operator practices both contribute to an unacceptable risk of contamination of the open sterile vials.

In addition, certain interventions performed on the ISO 5 filling line were not documented in your intervention log records, as per your procedures.

Non-Integral Cleanroom Materials

Our investigators observed non-integral packages containing sterile gloves. Packages were also observed to contain foreign matter, such as fibers. These gloves, purported to be sterile, are worn by aseptic manufacturing operators who perform critical interventions and can present a contamination hazard to your products. Examples of such interventions include making aseptic connections, clearing jammed and fallen vials, adjusting sterile production equipment, and changing environmental monitoring plates.

In another instance, our inspection found holes in the secondary packaging layer of your sterile wipes. Your firm assumed the outer layer provided a sterile barrier for the primary, interior package. Only by contacting the supplier during our inspection did you learn that the outer layer is not a sterile barrier. Firm management acknowledged the primary layer is never disinfected before use in the cleanroom. Further, your supplier qualification protocol remains insufficient, and your supplier qualification program does not require you to ensure the suitability of this supplier.

Inadequate Cleanroom Design and Smoke Study Deficiencies

Your stopper hopper leans diagonally over the top of the filling line during stopper loading operations, thereby blocking first air over open, exposed sterile vials.

In addition to this inadequate design, your smoke studies performed for your ISO 5 areas also lacked simulation of multiple critical interventions that occur during aseptic manufacturing operations.

Thorough smoke studies are essential to evaluate the effects of such interventions on unidirectional airflow and to ensure design modifications are made wherever necessary.

The ISO 5 area is critical because sterile product is exposed and therefore vulnerable to contamination. Your aseptic filling process should be designed, and operations executed, to prevent contamination hazards to your sterile product. The flawed design of the filling line and execution of the aseptic operations promote influx of contamination into the critical filling areas.

Your firm's response is inadequate. We acknowledge you engaged a third party to assist in efforts to re-train personnel and provide additional oversight of aseptic practices, and that you are revising procedures. You also stated that you are installing restricted air barrier systems (RABS), as previously committed in 2016. You state that you plan to perform supplemental smoke studies for interventions not captured in the current studies and additional smoke studies once you install the new RABS.

However, you did not provide a sufficient evaluation of all batches produced under inadequate conditions. You also did not commit to extensive redesign of your aseptic process operation.

In response to this letter, provide:

- A comprehensive, independent identification of all contamination hazards with respect to your aseptic processes, equipment, and facilities. Include an independent risk assessment that covers, among other things, all human interactions with the ISO 5 area, equipment placement and ergonomics, air quality in the ISO 5 area and surrounding room, facility layout, personnel flow, and material flow.
- A detailed corrective action and preventative action (CAPA) plan, with timelines, to address the findings of the contamination hazards risk assessment. Describe how you will significantly improve aseptic processing operation design and control and personnel qualification.
- Your plan to ensure appropriate aseptic practices and cleanroom behavior during production. Include specific steps to ensure routine and effective supervisory oversight for all production batches. Describe the frequency of quality assurance oversight (e.g., audit) during aseptic processing and other operations. Also, provide your protocol and

an update on your third party's independent assessment of your aseptic practices. As part of your assessment, summarize your review of past processing videos.
- A thorough risk assessment that evaluates how poor aseptic technique and cleanroom behavior, such as those observed during the inspection, may have affected quality and sterility of your drugs.
- A description of the extent of the missing batch record entries for interventions performed. Detail how you will remediate your system for recording interventions while also not adding further contamination risks to your products.
- A review of your supplier qualification, monitoring, and maintenance program to ensure you adequately address the quality of the materials brought into the cleanroom. Include a review of all materials, including but not limited to, disposable materials (e.g., sterile gloves and wipes) to ensure integrity and prevent contamination in the aseptic processing operation.
- A copy (e.g., a video file) of your new smoke study recordings and a detailed description or schematic of the RABS extension used to provide local protection of the stopper hopper area. Provide an independent assessment of the smoke studies.

2. Your firm failed to perform operations within specifically defined areas of adequate size and to have separate or defined areas or such other control systems necessary to prevent contamination or mix-ups in aseptic processing areas (21 CFR 211.42(c)(10)).

Environmental and Personnel Monitoring

Your environmental monitoring program is deficient. Your procedures allowed personnel performing aseptic interventions in the ISO 5 cabinet to have one colony-forming unit (CFU) on their gloves on a repeated basis without triggering an appropriate response. Your action limit for this location was two CFUs, and you had no alert limit. You lacked scientific justification for your limit and the associated procedure.

In addition, personnel were observed sanitizing their hands with isopropyl alcohol prior to personnel monitoring. Sanitizing gloved hands just before sampling is unacceptable because it can prevent microbial recovery and it undermines the reliability of personnel monitoring data.

Your response is inadequate. While you commit to evaluate your environmental monitoring program, your target completion date is December 31, 2019. You commit to tighten the glove limit for personnel monitoring, but only after "critical" interventions in the ISO 5 areas. Growth observed on glove samples taken from personnel performing any activities within the ISO 5 area should trigger an alert or action condition that, at a minimum, should lead to trending and may indicate the need for further investigation. Notably, your SOP identifies numerous interventions, defined as major and minor, which require extensive activities within the ISO 5 zone. Any personnel who perform activities within the ISO 5 area should meet your tightened glove limit.

In response to this letter, provide:

- A comprehensive, independent, retrospective review of your personnel and environmental monitoring program. Include a risk assessment of personnel and environmental monitoring data since April 2015. Indicate the changes you will make to your program to ensure it provides meaningful information by robustly detecting and responding to microbial data from your classified areas. Provide an updated timeline for implementation of your program and procedural changes.

- The most recent revision of your "Environmental Site Selection and Justification" document.

Cleaning Operations

Your cleaning program is deficient. While operator entries in sanitization records state that all required sanitization steps were completed in cleanrooms, many steps were actually skipped, and various pieces of equipment were not sanitized.

Your operators did not ensure the mop makes proper contact with the floor. Mops were not wetted frequently to ensure adequate coverage. For example, an operator cleaned the walls surrounding Line AH for several minutes without rewetting the mop.

In your response, you stated that you have performed targeted training on sanitization procedures. Further, you note that your disinfectant efficacy program demonstrates the ability of your agents to reduce bioburden. Your response is inadequate. You are not consistently following your validated procedures.

Although you acknowledge that all disinfection activities had not been completed, you have not determined the scope of these poor practices observed at your facility, including identifying employees involved and how long this has been occurring. You did not extend your investigation to determine if complete disinfection activities and proper documentation practices were followed.

In response to this letter, provide:

- The investigations and CAPAs initiated in response to the cleaning and disinfection observations by our investigators. Provide updated cleaning and disinfection forms.
- A comprehensive evaluation of the design, control, maintenance, and oversight of your cleaning and disinfection program.
- An overall management strategy that describes how your executive management will oversee improvements in design and execution of manufacturing operations and ensure ongoing scrutiny to enable sustainable quality assurance.

3. Your firm failed to follow a written testing program designed to assess the stability characteristics of drug products and to use results of such stability testing to determine appropriate storage conditions and expiration dates (21 CFR 211.166(a)).

You cannot ensure the stability of your product, acetylcysteine injection 200 mg/mL, because you have not performed L-Cystine and L-Cysteine impurity testing on stability samples since 2016. At the time of the inspection, you also did not have a validated test method.

Your 2016 annual report for acetylcysteine injection 200 mg/mL to the agency notes that the L-Cystine and L-Cysteine impurity tests are pending for stability samples. However, the tests are not included in the 2017 annual report. Your 2017 internal stability report states "NO TEST" for both impurity tests.

We acknowledge that you filed a field alert report during the inspection and initiated a recall of all lots of acetylcysteine injection 200 mg/mL on June 22, 2018, because the specification could not be confirmed over the shelf-life. We also acknowledge you filed a supplement to revise the test method.

In your response, you state no other stability testing issues were noted with FDA-approved test methods. Your response is inadequate. You did not include such an evaluation for your other marketed products (irrespective of whether you hold a drug application).

In response to this letter, provide a comprehensive assessment and CAPA to ensure the adequacy of your stability program. Your CAPA should include, but should not be limited to, a remediated standard operating procedure (SOP) describing your stability program; stability-indicating methods; stability studies to support each drug product in its container-closure system before distribution is permitted; an ongoing program in which representative batches of each product are added each year to the program to determine if the shelf-life claim remains valid; and specific attributes to be tested at each station. The stability program should ensure the suitability and validation of your analytical methods, and requirements to assess impact of insufficient methods on marketed products.

Additional Guidance on Aseptic Processing

See FDA's guidance document, *Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Practice*, to help you meet the CGMP requirements when manufacturing sterile drugs using aseptic processing, at https://www.fda.gov/downloads/Drugs/Guidances/ucm070342.pdf.

Quality Systems

Your firm's quality systems are inadequate. For guidance on establishing and following CGMP compliant quality systems, see FDA's guidance for industry:

- *Q8(R2) Pharmaceutical Development*, at https://www.fda.gov/downloads/drugs/guidances/ucm073507.pdf;
- *Q9 Quality Risk Management*, at https://www.fda.gov/downloads/Drugs/Guidances/ucm073511.pdf; and
- *Q10 Pharmaceutical Quality System*, at https://www.fda.gov/downloads/drugs/guidances/ucm073517.pdf.

CGMP Consultant Recommended

Because you failed to correct repeat violations, we strongly recommend engaging a consultant qualified as set forth in 21 CFR 211.34, to assist your firm in meeting CGMP requirements. We recommend that the qualified consultant perform a comprehensive audit of your entire operation for CGMP compliance and evaluate the completion and effectiveness of corrective actions and preventive actions. Your use of a consultant does not relieve your firm's obligation to comply with CGMP. Your firm's executive management remains responsible for resolving all deficiencies and systemic flaws to ensure ongoing CGMP compliance.

Data Integrity Remediation

As detailed above, FDA has concerns regarding the accuracy of intervention, sanitization, and other records produced at this facility. 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. See FDA's guidance document, *Data Integrity and Compliance With Drug CGMP*, for guidance on establishing and following CGMP compliant data integrity practices at https://www.fda.gov/downloads/drugs/guidances/ucm495891.pdf.

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, including results of the data review for drugs distributed to the United States. Include a detailed description of the scope and root causes of your 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 analyses of the risks to patients caused by the release of drugs affected by a lapse of data integrity and analyses of the risks posed by ongoing operations.

C. A management strategy for your firm that includes the details of your global CAPA plan.

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 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, and the Center for Veterinary Medicine (CVM) at AskCVM@fda.hhs.gov, or by telephone to 1-888-INFO-FDA (1-888-463-6332) 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.

Please send your electronic reply to: ORAPHARM3_RESPONSES@fda.hhs.gov.

Attn: Russell K. Riley
Compliance Officer
U. S. Food and Drug Administration
Division of Pharmaceutical Quality Operations III

Refer to the Unique Identification Number (Case# 558914), and FEI 1450114 when replying. If you have questions regarding the contents of this letter, please contact Mr. Russell K. Riley by phone at (630) 323-1101

Sincerely,
/S/
Jeffrey Meng
Program Division Director (Acting)
Division of Pharmaceutical Quality Operations III