10903 New Hampshire Avenue
Silver Spring, MD 20993

February 1, 2019

Case #567857

WARNING LETTER

VIA UPS Overnight

Vance G. Russell, General Manager
Actavis Laboratories FL, Inc.
4955 Orange Drive
Davie, Florida 33314-3902

Mr. Russell:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Actavis Laboratories FL, Inc. at 4955 Orange Drive, Davie, Florida from July 9 to 19, 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 August 9, 2018 response in detail and acknowledge receipt of your firm's subsequent correspondence.

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

1. Your firm failed to establish adequate 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 (21 CFR 211.100(a)).

Your laser-drilled tablet manufacturing processes were insufficiently designed and managed to ensure an ongoing state of control. The laser drilling of your drug products is critical to ensure the appropriate drug delivery profile to patients. For example:

a) You failed to adequately validate critical parameters of your laser drilling machines for each drug product. **(b)(4)** for the drilling operation were modified by the engineering department in response to problems without review by the change management system, impact assessment, or change effectiveness verification.

b) Your firm failed to adequately evaluate the effect of changes made to visual inspection systems. These visual inspection systems are intended to conduct a 100% inspection of tablets for the presence and adequacy of a drill hole. These systems include "vision files" which define the acceptance criteria and parameter space used to accept or reject a tablet. However, the vision file for paliperidone extended-release tablets was modified multiple times by the engineering department in an attempt to fix problems (e.g., undrilled tablets not properly rejected) without documented change management, impact assessment, and validation of the capability to properly reject tablets with insufficient or no holes.

c) The Operational and Performance Qualification of your **(b)(4)** Laser Drill **(b)(4)** tested and challenged the visual inspection system for paliperidone extended-release tablets at a conveyor belt velocity of **(b)(4)**. However, numerous batches of paliperidone extended-release tablets produced on this equipment since 2015 were produced at a belt velocity significantly higher than the qualified range for this worst-case tablet size.

In your response, you commit to, in part, performing re-qualifications of pertinent manufacturing equipment, re-validating your laser-drilling processes, updating procedures, conducting studies to optimize drug product specific "**(b)(4)**," decommissioning **(b)(4)** Laser Drill **(b)(4)**, purchasing an additional **(b)(4)** Laser Drill, and re-opening applicable investigations before restarting manufacturing operations. However, you lacked sufficient details describing the extent of process redesign and new validation studies that you are planning for all drug products.

In addition, you did not indicate if both **(b)(4)** Laser Drills would be fully operational when you restart the manufacture of your laser drilled drug products.

Process validation evaluates the soundness of design and state of control of a process throughout its lifecycle. Each significant stage of a manufacturing process must be designed appropriately and assure the quality of raw material inputs, in-process materials, and finished drugs.

Process performance qualification (PPQ) studies determine whether an initial state of control has been established. Successful PPQ studies are necessary before commercial distribution. Thereafter, ongoing vigilant oversight of process performance and drug product quality is necessary to ensure you maintain a stable manufacturing operation throughout the drug product lifecycle.

In response to this letter, provide the following:

- Your validation plan for ensuring a state of control throughout the drug product lifecycle. Include a timeline for performing appropriate process performance qualification studies for each of your drug products and describe your program for vigilantly monitoring batch-to-batch variation to ensure an ongoing state of control. Also include your PPQ protocol(s) and your written procedures for qualification of equipment and facilities.
- A comprehensive, independent evaluation of your change management system. This evaluation should include, but not be limited to, review of your procedure(s) to ensure changes are sufficiently justified and adequately reviewed and approved by your Quality Unit

(QU). The change management program should also include specific provisions for evaluating change effectiveness.
- A scientific justification that your remaining laser drill, once qualified, will be able to adequately support the manufacture of all your laser drilled drug products until the second laser drill is qualified and the line validated.
- Characterization of the vision system used on your **(b)(4)** Laser Drill and discussion about the similarities and differences from the vision system used on your recently decommissioned **(b)(4)** Laser Drill. Also provide a comparison between **(b)(4)** and **(b)(4)** drilling mechanisms with emphasis on critical control parameters and any new risk mitigations that you will implement to improve process robustness and defect detectability.

2. Your firm failed to establish 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)).

Your firm failed to adequately qualify operators that perform in-process checks and acceptable quality level (AQL) inspections of your laser drilled drug products. Additionally, your firm failed to develop adequate written procedures for the in-process checks and AQL inspections of your firm's laser drilled drug products. Furthermore, you failed to ensure that operators undergo vision examinations, facilities had adequate lighting and magnification equipment, and plastic face shields worn by operators did not impede ability to inspect for critical drug product attributes.

In addition, during tightened AQL inspections, a single quality assurance (QA) inspector would document, during their shift, the inspection of approximately **(b)(4)** tablets for the presence of a laser drilled hole that can be as small as 0.3mm. These AQL inspections are intended to detect undrilled tablets (a critical defect) before the release of the batch. These defects can affect the release properties of your drug products, which are indicated for use in patients with diseases such as diabetes and schizophrenia.

In your response, you commit to improving lighting, performing vision examinations, providing operators with magnification equipment, and developing a qualification program for operators that perform in-process checks. Additionally, you state that QA inspectors can adequately inspect upwards of **(b)(4)** tablets per shift; however, your operators have not been adequately qualified at these conditions.

In response to this letter, provide the following:

- Details of your proposed qualification program for QA inspectors who perform in-process checks, including AQL sampling, for all your drug products.
- Evaluation to determine if an inspector can accurately, and robustly, determine the presence of a laser drilled hole which can be as small as 0.3mm in approximately **(b)(4)** tablets per shift. Include objective data (i.e., studies) and provide a science-based inspection process. This includes, but is not limited to, evaluating suitability of inspectional equipment for its intended use, and determining the capabilities and reliability of your QA inspectors through an effective qualification program.
- Data trends for all of your laser drilled drug products from September 1, 2016, to present. Include, at a minimum, the total number of units sampled (by drug product and lot), the results of all in-process, AQL (standard & tightened) and 100%/200% inspections, and the number of rejects and the reject type.

3. Your firm failed to establish an adequate quality control unit with the responsibility and authority to approve or reject all components, drug product containers, closures, in-process materials, packaging materials, labeling, and drug products (21 CFR 211.22(a)).

Your Quality Unit (QU) failed to fulfill its duties and responsibilities.

For example, your QU did not ensure robust oversight of your laser drilling process. They failed to ensure adequate validation of the laser drilling process, change management procedures, maintenance of critical manufacturing equipment, training of employees in their respective job functions, and investigations.

Regarding the latter, since 2015 your firm was aware of various process performance (e.g., no or misplaced hole in tablets) and drug product quality data (e.g., recall due to dissolution failure) that indicated a lack of control of your laser drilled drug products. However, your firm failed to ensure timely investigations and corrective and preventative actions (CAPA).

We acknowledge that, in response to our inspectional findings, you performed a risk assessment and have voluntarily recalled an additional **(b)(4)** batches of laser drilled drug products due to the potential for some tablets to lack laser drilled hole(s).

In your response you stated that you have **(b)(4)**. Also, in your fifth status report, dated January 10, 2019, you stated that you will be **(b)(4)**.

In response to this letter, provide the following:

- A comprehensive, independent assessment with CAPA to ensure your QU is given the needed authority and resources to effectively discharge its function. The assessment should also include, but not be limited to:

o A determination of whether procedures used by your firm are robust and appropriate

o Provisions for QU oversight throughout your operations to evaluate adherence to appropriate practices

o Complete and final review of each batch and its related information to support an appropriate final QU disposition decision

o Oversight and approval of investigations and discharging of all other QU duties to assure identity, strength, quality, and purity of all drug products

4. 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 firm did not adequately investigate drug product failures and significant defects. You lacked thorough investigations into root causes and failed to implement prompt and effective CAPA.

For example:

The Process Validation Report for paliperidone extended release tablets (No. 6516PTC Version #1.0 approved on September 22, 2015) showed that undrilled tablets or tablets drilled on the wrong side were accepted and not rejected by the vision system in two of the ten validation batches during the laser drilling stage. The root causes for these events were identified as dirty sensors and inadequate calibration of the grayscale accept limit due to human error by the maintenance mechanic, resulting in defective tablets not being rejected. However, the impact was considered "Minor" by your QU although issues with undrilled, or inadequately drilled, tablets continued.

Your firm performed an investigation on September 6, 2016 in response to undrilled tablets found in the "accepted drum" during the processing of a lot of paliperidone extended release tablets. The root cause of this event was considered to be a mechanical design flaw of the Laser Drill P-4130 accepted tablet discharge chute (which was in very close proximity to the reject tablet discharge chute) causing rejected tablets to fall into the accepted tablet drum. However, your firm conducted another investigation for the same batch on April 27, 2017, in response to a dissolution testing failure at the **(b)(4)** room temperature stability time point. You concluded that the dissolution failure was due to an undrilled tablet and the cause was considered to be a guide rail misalignment caused by an operator or maintenance mechanic. As a result, you state that tablets became off-center on the conveyor and missed the laser trigger sensor and vision system sensors. You also cited inadequate procedures for segregating rejected tablets. Two investigations identified two different possible root causes for undrilled tablets in the same batch of drug product. Neither sufficiently addressed the fundamental failure to adequately drill a hole in the tablet. Also, the QU failed to extend their investigation to other batches of laser drilled drug products previously processed on this equipment.

In your responses you commit to **(b)(4)**.

In response to this letter, provide the following:

- Results of your **(b)(4)**.
- Summary of how you will improve identification of potential human error risks in future process designs and root cause evaluations and enhance your overall risk reduction program in these areas.
- A comprehensive, independent assessment of your overall system for investigations of deviations, atypical events, complaints, out-of-specification results, and failures. Your CAPA should include but not be limited to improvements in investigation competencies, root cause analysis, written procedures, and QU oversight. Also include your process for evaluating CAPA effectiveness.

Repeat Observations at Facility
In previous inspections (December 2013, January 2016, and November 2017), FDA cited similar CGMP observations. You proposed specific remediation for these observations in your responses. These repeated failures demonstrate that executive management oversight and control over the manufacture of drugs is inadequate.

Process Controls
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

https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070336.pdf.

CGMP Consultant Recommended
In your response, you indicated that you have retained services of third-party consultants. Based upon the nature of the violations we identified at your firm, we strongly recommend engaging a third party and ensuring they are qualified as set forth in 21 CFR 211.34, to assist your firm in meeting CGMP requirements. It is important that the consultants have expertise in the specific areas of deficiency cited at your facility. 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, 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 drug 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 identify your response with FEI 3003194604.

Your written notification should refer to the Warning Letter Number above (Case #567857). Please electronically submit your signed reply on your firm's letterhead to CDR John W. Diehl, M.S., Director, Compliance Branch, at john.diehl@fda.hhs.gov and orapharm2_responses@fda.hhs.gov.

If you have questions regarding the contents of this letter, please contact H.L. Jamillah Selby, Compliance Officer, at 214-253-5218 or jamillah.selby@fda.hhs.gov.

Sincerely,

/S/
Monica R. Maxwell
Program Division Director
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