Teva Pharmaceutical Works Private Limited Company 10/13/16

Department of Health and Human Services

Public Health Service
Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

Warning Letter 320-17-01

Via UPS
Return Receipt Requested

October 13, 2016

Mr. Erez Vigodman
President & CEO
Teva Pharmaceutical Works Pvt. Ltd.
5th Basel Street
P.O. Box 3190
Petah Tikva 4951033
Israel

Dear Mr. Vigodman,

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Teva Pharmaceutical Works Pvt. Ltd. at 2100 Godollo, Tancsics Mihaly ut 82, Godollo, Hungary, from January 21 to 29, 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 firm's February 22, 2016, response in detail and acknowledge receipt of your subsequent correspondence.

Our investigators 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)

You did not adequately investigate media fill and sterility test failures. These failures indicate that there is a lack of adequate sterility assurance in your manufacturing facility.

a. Media Fills
You did not adequately investigate media fill contamination in your aseptic manufacturing lines. For example, media fill run **(b)(4)**, performed September 14-16, 2015, in the closed Restricted Access Barrier System (RABS) small volume parenteral line in **(b)(4)**, yielded 31 contaminated units. In addition, media fills for other filling lines at your facility yielded one or more contaminants.

You attributed the contamination in these media fills to aseptic technique breaches by different operators. Various breaches were identified relating to set-up, filling, and changing of the filling tank. However, your investigations were insufficient. For example, you failed to identify the microorganisms found in the contaminated units.It is imperative that you determine the identity of microorganisms found in media filled units in order to adequately understand the potential sources and scope of the contamination.

Any contamination in a media fill run indicates a potentially significant sterility assurance problem and should be thoroughly investigated.

b. Sterility Test Positive Investigations
You also did not thoroughly investigate sterility test positives. For example, your investigation of a sterility test failure for **(b)(4)** injection (batch **(b)(4)**) did not adequately assess the hazards in the aseptic manufacturing operation that led to the sterility failure. You also did not determine whether other batches made on the same production line were affected.

In addition, you invalidated multiple sterility test positive results obtained during batch release testing. However, we note that your firm uses a sterility test **(b)(4)** as well as a sterility testing kit that minimizes potential for adventitious contamination that could cause false positives.

Your response is inadequate. In response to this letter, provide the following information:

- a comprehensive review of all sterility positive and media fill failure investigations since January 2014 to reassess your root causes, corrections, conclusions, and effect of your lack of aseptic processing control on the sterility of marketed commercial batches.
- revised media fill contamination investigation standard operating procedures (SOP), including but not limited to identification of microorganisms from each contaminated unit, thorough assessment of possible causes, and assurance of appropriate corrective actions to prevent contamination.
- revised sterility failure investigation SOP, including but not limited to a thorough assessment of potential manufacturing root causes, identification of actions to prevent contamination, and assurance that invalidation of a sterility positive does not occur unless there is a robust and conclusive laboratory root cause.

- a retrospective evaluation of videos of your aseptic manufacture of all in-date batches distributed to the United States to determine contamination hazards posed by deficient aseptic practices. Also review the video of the production activities associated with the **(b)(4)** injection sterility failure to help identify the source of contamination in that batch.
- a thorough assessment of the adequacy of your facility, equipment, and process. Determine failure modes relating to design, control, and maintenance. Include a comprehensive corrective action and preventive action (CAPA) plan that fully identifies microbial contamination risks throughout your operation and describes improvements to assure high confidence in the sterility of your products.

2. Your firm failed to establish and 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))

a. Poor Aseptic Behavior

During the inspection, our investigators observed poor aseptic processing techniques that had been previously videotaped at your facility. For example, video from September 8 and 9, 2015, showed the following during the set-up and filling of the sterile injectable drug **(b)(4)**:

- an operator passing a pen directly over the stopper bowl to another operator.
- an operator sitting on the clean room floor during set-up of the filling line and not changing the gown after standing up.
- operators leaning against the cleanroom walls.
- an operator leaving the RABS **(b)(4)** open for extended periods of time during filling line set-up, even when he was not working in the immediate area.

Your response is inadequate. In response to this letter, provide the following:

- a risk assessment of the poor aseptic techniques observed during the inspection.
- a broader evaluation of any additional aseptic technique breaches that have occurred in your operation (e.g., through review of videos).
- updated information to demonstrate that each of your aseptic processing lines is in a state of control.

In addition to implementing enhancements to your aseptic processing operation design, describe how you will improve staff competencies, supervisory oversight of daily operations, and other controls.

b. Mechanical Failure During Media Fill

Your firm rejected numerous integral vials during media fill batches due to mechanical problems or other causes without appropriate justification. For example, media fill batch **(b)(4)** was aborted due to a mechanical failure of the conveyor belt motor. Although 3,696 integral vials had been filled, the vials were not incubated, and the media fill was invalidated without adequate justification. Your firm indicated that it would have released a commercial batch as a sub-lot under these circumstances.

You also did not have a procedure describing production and disposition practices after such a mechanical failure.

Your response is inadequate. In response to this letter, provide the following:

- a list of commercial batches rejected as a result of mechanical problems or other reasons and the CAPA that was implemented in each case.
- a list of all media fills conducted since January 2011 with fill date, number of units run, number of units incubated, number of positive units, and annotation of whether the fill was aborted.
- descriptions of circumstances under which any portion of a media fill batch was incubated as a separate segment, and whether you detected any positive units.
- changes made to your written procedures to ensure that media fills accurately simulate actual production practices and to address when it is appropriate to abort a media fill run.

3. Your firm failed to establish an adequate system for monitoring environmental conditions in aseptic processing areas. (21 CFR 211.42(c)(10)(iv))

Your SOP *G010291 System of Microbiological Environment Monitoring* includes microbial alert and action levels. Per the SOP, no more than **(b)(4)** colony forming unit (CFU) is permitted on two hands in Grade A (ISO 5) areas where personnel perform critical interventions during filling, line set-up, and other aseptic activities. In Grade B (ISO 7) areas, which are described as filling, filtration, capping, or changing rooms, no more than **(b)(4)** CFUs are permitted on two hands, and there is an alert level at **(b)(4)** CFUs.

However, when our investigators observed operators performing activities which should adhere to Grade A levels (hands in open RABS and under laminar air flow), your firm officials stated that the operators were held to Grade B levels. Furthermore, your firm failed to justify allowing **(b)(4)** CFU on the **(b)(4)** of operators who perform Grade A interventions without any potential follow-up. Such instances should trigger an alert or action condition that, at a minimum, should lead to trending and may indicate the need for further investigation.

In response to this letter, provide a comprehensive retrospective review and risk assessment of personnel and environmental monitoring data since January 1, 2015. In addition, describe how future monitoring will be conducted in different classified aseptic processing areas to ensure that action and alert levels are commensurate with the operations being performed in the specified area.

4. Your firm failed to establish laboratory controls that include scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that components, drug product containers, closures, in-process materials, labeling, and drug products conform to appropriate standards of identity, strength, quality, and purity. (21 CFR 211.160(b))

The suitability test you performed in **(b)(4)** failed to meet acceptance criteria for sterility testing. Specifically, a positive control sample did not exhibit growth of **(b)(4)** during sterility testing for **(b)(4)** mg/mL solution **(b)(4)**. Your firm did not investigate this failure of media to support growth. Unsuitable sterility test methods increase the probability that your quality control test will not detect a non-sterile product.

Your response is inadequate. In response to this letter, provide the following:

- a thorough investigation into the root cause of the positive control test failure, including your CAPA plan.
- a comprehensive investigation of each of your sterility test methods and their ability to reproducibly promote microbial growth in the presence of product.
- your latest plans for performing microbial testing (which was suspended during the inspection).

5. 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))

Our investigators observed colony counts for environmental and personnel monitoring that did not match your official records. For example, one contact plate from a Grade B area had a reported result of **(b)(4)** CFU, but our investigator counted **(b)(4)** CFUs on the plate. Five other plates had reported results of **(b)(4)** CFU, although our investigator counted **(b)(4)** CFU on each plate.

Inaccurate reporting of environmental and personnel monitoring data undermines your ability to evaluate and maintain a state of control in your aseptic processing operation.

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))

Your stand-alone computer systems lacked controls, such as routine audit trail review and full data retention, to prevent analysts from deleting data. Although you implemented a procedure to begin reviewing audit trails of your high performance liquid chromatography (HPLC) Empower system on January 11, 2016, you had not performed any reviews prior to our inspection. Furthermore, the procedure you implemented on January 11 required **(b)(4)** random audit trail review **(b)(4)**.

We acknowledge your commitment to strengthening your procedures to assure user access restrictions and implement audit trails for computerized systems. However, simply activating audit trail functions and instituting user controls are insufficient to correct the data integrity problems observed at your facility and to prevent their recurrence. In response to this letter, provide details of your retrospective review of the HPLC and other laboratory data, such as Fourier transform infrared spectroscopy, gas chromatography, UV spectrophotometry, and **(b)(4)** analyzer data. Indicate the period covered in your review and your rationale for selecting that timeframe.

7. Your firm failed to follow adequate written procedures for the preparation of master production and control records designed to assure uniformity from batch to batch. (21 CFR 211.186(a))

Our investigators found quality-related documents in a waste bin. Among these documents were an incomplete sterility test data sheet, a form used to track the movement of **(b)(4)** samples, a media fill incubation card, and others. The incomplete sterility test data sheet had been filled out to track information about a "**(b)(4)**" sterility check. After an error was observed on the original data sheet, the record was torn and discarded with no written explanation.

CGMP Consultant Recommended
Based upon the nature of the violations we identified at your firm, we strongly recommend that your consultant, who should be qualified as set forth in 21 CFR 211.34, assist your firm in meeting

CGMP requirements. Your consultant should provide a thorough assessment of your entire operation to identify contamination hazards, assist in remediation of sterility assurance in your facility, improve your quality system, and certify readiness. 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.

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, online at http://www.fda.gov/downloads/Drugs/.../Guidances/ucm070342.pdf.

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 and record retention policies 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, including but not limited to investigation into your laboratory testing raw data, reported results, and quality oversight for all products and process lines. We recommend that a qualified third party with specific expertise in the area where potential breaches were identified should evaluate all data integrity lapses. Provide a detailed report from your consultant.

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 (both microbiology and chemistry), 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 (for example, 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 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, 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.

FDA placed your firm on Import Alert 66-40 on May 27, 2016.

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 continuing to refuse admission of articles manufactured at Teva Pharmaceutical Works Private Limited Company, located at 2100 Godollo, Tancsics Mihaly ut 82, Godollo, Hungary, 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 (mailto:CDER-OC-OMQ-Communications@fda.hhs.gov)** or mail your reply to:

Lixin (Leo) Xu, M.D., Ph.D.
Compliance Officer
U.S. Food and Drug Administration

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Silver Spring, MD 20993
USA

Please identify your response with FEI 3002875215.

Sincerely,
/S/
Francis Godwin
Acting Director
Office of Manufacturing Quality
Center for Drug Evaluation and Research

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