WARNING LETTER

GPT Pharmaceuticals Private Ltd

MARCS-CMS 590938 — DECEMBER 17, 2019

Delivery Method:

VIA UPS

Product:

Drugs

Recipient:

Mr. Ashok Adityan

Managing Director

GPT Pharmaceuticals Private Ltd

11-1, C.I.E.E Hyderabad

Grandhinagar Balanagar 500037

India

Issuing Office:

Center for Drug Evaluation and Research

United States

Warning Letter 320-20-13

December 17, 2019

Dear Mr. Adityan:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, GPT Pharmaceuticals Pvt. Ltd., FEI 3008311641, at Plot No. 6/3, Road No. 11, Nacharam, Hyderabad, from June 24 to 28, 2019.

This warning letter summarizes significant violations of current good manufacturing practice (CGMP) regulations for finished pharmaceuticals. See Title 21 Code of Federal Regulations (CFR), parts 210 and 211 (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 July 17, 2019, response to our Form FDA 483 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's quality control unit failed to exercise its responsibility to ensure drug products manufactured are in compliance with CGMP, and meet established specifications for identity, strength, quality, and purity (21 CFR 211.22).

During the inspection, our investigators observed that your quality unit (QU) did not provide adequate oversight for the manufacturing of bulk **(b)(4)**. For example, your QU failed to ensure the following:

- Out-of-specification (OOS) test results for residual solvents were adequately investigated.
- Test methods for assay and impurities were validated.
- Adequate record and report documentation practices, including document control, were in place.

You receive active pharmaceutical ingredients (API) from suppliers and process them into **(b)(4)**. Your QU failed to adequately investigate OOS results for the residual solvent, **(b)(4)**, for API batches **(b)(4)**. You retested the API, obtained passing results, and released these API batches for use in production. You disregarded the initial OOS results without adequate scientific justification.

(b)(4) is a **(b)(4)** solvent and known **(b)(4)**. Solvents in **(b)(4)** should not be employed in the manufacture of drug substances, excipients, and drug products because of their unacceptable toxicity. However, if the use of **(b)(4)** solvents, such as **(b)(4)**, is unavoidable in order to produce a drug, then the levels should be restricted. For more information on residual solvents, see FDA's guidance document *Q3C—Tables and List* at https://www.fda.gov/media/71737/download (https://www.fda.gov/media/71737/download).

Your response stated that you retested each of the batches of **(b)(4)** API for **(b)(4)** content and all retest results were within specification. Your response also concluded the original failures for residual **(b)(4)** were not representative and did not compromise product quality. However, your response failed to provide justification to disregard the initial OOS results or a plan for how your QU will ensure OOS results are adequately investigated. You also did not provide adequate corrective action to ensure appropriate documentation of testing performed as part of your OOS investigations.

For more information about handling failing, out-of-specification, out-of-trend, or other unexpected results and documentation of your investigations, see FDA's guidance document *Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production* at https://www.fda.gov/media/71001/download (https://www.fda.gov/media/71001/download).

In response to this letter, provide a comprehensive assessment and remediation plan to ensure your QU is given the authority and resources to effectively function. The assessment should also include, but not be limited to:

- Residual solvents test of retains samples of API you received, as well as **(b)(4)** you distributed. If such testing reveals substandard quality drugs, take rapid corrective actions, such as notifying customers and product recalls.
- A list of all residual solvents used in your facility or at your suppliers, and your risk-based plans to strictly limit (or discontinue) any **(b)(4)** solvents in raw materials you receive and drugs you produce. Include specifications for all residual solvents used in API you receive.
- A retrospective, independent review of all invalidated OOS (including in-process and release/stability testing) results for U.S. drugs, irrespective of whether the batch was ultimately distributed in the U.S. and a report

summarizing the findings of the analysis, including the following for each OOS:

- Determine whether the scientific justification and evidence relating to the invalidated OOS result conclusively or inconclusively demonstrates causative laboratory error
- For investigations that conclusively establish laboratory root cause, provide rationale and ensure that all other laboratory methods vulnerable to the same or similar root cause are identified for remediation
- For all OOS results found by the retrospective review to have an inconclusive or no root cause identified in the laboratory, include a thorough review of production: batch manufacturing records, adequacy of the manufacturing steps, suitability of equipment/facilities, variability of raw materials, process capability, deviation history, complaint history, batch failure history. Summarize potential manufacturing root causes for each investigation, and any manufacturing operation improvements

- A comprehensive review and remediation plan for your OOS result investigation systems. The corrective action and preventive action (CAPA) plan should include but not be limited to the following:
  - Quality unit oversight of laboratory investigations
  - Identification of adverse laboratory control trends
  - Resolution of causes of laboratory variation
  - Initiation of thorough investigations of potential manufacturing causes whenever a laboratory cause cannot be conclusively identified
  - Adequately scoping of each investigation and its CAPA
  - Revised OOS investigation procedures with these and other remediations

- Provisions for QU oversight throughout your operations to evaluate adherence to appropriate practices.
- Oversight and approval of investigations and discharging of all other QU duties to ensure identity, strength, quality, and purity of all drugs you manufacture.

2. 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)).

Our investigator observed that your dedicated equipment such as the **(b)(4)** and **(b)(4)** used to manufacture **(b)(4)** had visible rust, dents, and scratches on product contact surfaces.

Your response stated that you did not verify the cleanliness of all surfaces because the manufacturing area and entire equipment train is dedicated. You also stated that your Quality Unit would verify equipment cleaning. However, your response did not provide a plan for ensuring routine maintenance of your facility, including equipment maintenance, repairs, and replacement.

In response to this letter, provide:

- Your CAPA plan to implement routine, vigilant operations management oversight of facilities and equipment. This plan should ensure, among other things, prompt detection of equipment/facilities performance issues, effective execution of repairs, adherence to appropriate preventive maintenance schedules, timely technological upgrades to the equipment/facility infrastructure, and improved systems for ongoing management review.

- A CAPA plan, based on the retrospective assessment, that includes appropriate remediations to your cleaning processes and practices, and timelines for completion. Provide a detailed summary of vulnerabilities in your process for lifecycle management of equipment cleaning. Describe improvements to your cleaning program, including enhancements to cleaning effectiveness; improved ongoing verification of proper cleaning execution for all products and equipment; and all other needed remediations.

3. 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 investigator observed your laboratory equipment lacked appropriate controls. For example, from January 1, 2018, to June 25, 2019, audit trails from **(b)(4)** Agilent 1260 Infinity Series II high-performance liquid chromatography (HPLC) instruments showed a pattern of aborted runs and single run entries for testing **(b)(4)**. Single run entries included analyses of multiple peaks or split peaks without documented investigations or adequate scientific justifications. Your employees used the Agilent Service Account login, with full administrative privileges, to abort HPLC testing runs without being attributable to a specific individual.

Your response identified the number of deleted, aborted, and single runs during your HPLC testing. However, your response did not provide adequate investigations or evidence of corrective actions put in place to prevent these data integrity issues from recurring.

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. 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/media/119267/download (https://www.fda.gov/media/119267/download).

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 and manufacturing 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 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 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 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.

Concerns with Drug Suppliers

You previously sourced **(b)(4)** API from **(b)(4)** who refused FDA inspection and was placed on Import Alert **(b)(4)** on **(b)(4)**. Accordingly, FDA placed your firm on Import Alert 99-32 until you no longer sourced drugs from **(b)(4)** and you committed to revise your API supplier qualification program.

Conclusion

The violations cited in this letter are not intended to be an all-inclusive list of violations that exist at your facility. You are responsible for investigating and determining the causes of these violations and for preventing their recurrence or the occurrence of 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). This also 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 December 16, 2019.

Until you correct all violations completely and we confirm your compliance with CGMP, FDA may withhold approval of any new drug applications or supplements listing your firm as a drug manufacturer.

Failure to correct these violations may also result in the FDA continuing to refuse admission of articles manufactured at GPT Pharmaceuticals Pvt. Ltd., FEI 3008311641, at Plot No. 6/3, Road No. 11, Nacharam, Hyderabad into the United States under section 801(a)(3) of the FD&C Act, 21 U.S.C. 381(a)(3). Articles under this authority 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:

Lynnsey Renn, Ph.D.

Compliance Officer

U.S. Food and Drug Administration

White Oak Building 51, Room 4235

10903 New Hampshire Avenue

Silver Spring, MD 20993

USA

Please identify your response with FEI 3008311641.

Sincerely,

/S/

Francis Godwin

Director

Office of Manufacturing Quality

Office of Compliance

Center for Drug Evaluation and Research

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