檔　　號:
保存年限:

衛生福利部食品藥物管理署 函

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密等及解密條件或保密期限：
附件：原料藥廠違反GMP警訊乙份（A21020000I_1141100102_doc1_Attach1.pdf）

主旨：美國FDA發布印度原料藥廠Warning Letter乙案，詳如說明段，請轉知所屬會員知照。

說明：

一、美國衛生主管機關Food and Drug Administration（FDA）查核印度原料藥廠「Bhargava Phytolab Private Limited」（廠址：E-1216 Extn Ghatal, Phase-1, Bhiwadi, Rajasthan, India），判定違反CGMP，並於113年12月18日發布Warning Letter（詳附件，美國FDA業於113年12月31日公布於其官網）。

二、鑑於上述原料藥廠未符合GMP之規定，恐具藥品製造品質之風險，請轉知所屬會員釐清相關國產及輸台製劑產品是否使用上述原料藥廠所生產原料藥，並應依風險管理原則執行相關後續處置。

正本：中華民國西藥商業同業公會全國聯合會、中華民國西藥代理商業同業公會、台北市西藥代理商業同業公會、中華民國開發性製藥研究協會、台灣藥品行銷暨管理協會、台灣製藥工業同業公會、中華民國學名藥協會、中華民國製藥發展協會

副本：電子公文交換章 2025/01/07 16:58:57

WARNING LETTER

Bhargava Phytolab Private Limited

MARCS-CMS 691610 — DECEMBER 18, 2024

Delivery Method:

VIA UPS

Reference #:

320-25-26

Product:

Drugs

Recipient:

Mr. Rajeshwar Sahai Bhargava

Managing Director

Bhargava Phytolab Private Limited

E - 1216 Extn Ghatal, Phase - 1

Bhiwadi 301019 Rajasthan

India

Issuing Office:

Center for Drug Evaluation and Research (CDER)

United States

Warning Letter 320-25-26

December 18, 2024

Dear Mr. Bhargava

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Bhargava Phytolab Private Limited, FEI 3012809762, at E - 1216 Extn Ghatal, Phase – 1, Bhiwadi, Rajasthan, India, from July 22 to July 26, 2024.

This warning letter summarizes significant violations of Current Good Manufacturing Practice (CGMP) regulations for finished pharmaceuticals, Title 21 Code of Federal Regulations (CFR), parts 210 and 211 (21 CFR parts 210 and 211), and significant deviations from CGMP for active pharmaceutical ingredients (API).

Because your methods, facilities, or controls for manufacturing, processing, packing, or holding do not conform to CGMP, your drugs 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 16, 2024, response to our Form FDA 483 in detail and acknowledge receipt of your subsequent correspondence.

During our inspection, our investigator observed specific violations and deviations including, but not limited to, the following:

Active Pharmaceutical Ingredient CGMP Deviations

1. Failure to ensure that, for each batch of API, appropriate laboratory tests are conducted to determine conformance to specifications.

You manufacture **(b)(4)** active pharmaceutical ingredients (**(b)(4)**) that you use in your finished drug product production or distribute to other **(b)(4)** drug product manufacturers. These **(b)(4)** are produced from numerous ingredients that pose potentially toxic effects (e.g., **(b)(4)**, etc.). You do not perform adequate testing for your **(b)(4)**. For example, **(b)(4)** limit testing was not performed on **(b)(4)**. By not adequately analyzing your **(b)(4)**, you failed to determine conformance to appropriate specifications.

In your response, you state your results meet acceptance criteria and you rely on your supplier COA for **(b)(4)**. Your response does not adequately describe whether each lot of **(b)(4)** will be fully and adequately tested for appropriate quality attributes prior to use in drug product manufacturing or distribution to other **(b)(4)** drug product manufacturers.

Furthermore, during the inspection, you stated process validation was not performed for the production of **(b)(4)**. Therefore, you lack assurance that the process is reproducible and able to produce an active pharmaceutical ingredient (API) meeting its predetermined specifications and quality attributes.

In response to this letter, provide:

• A comprehensive, independent assessment of the design and control of your firm's manufacturing operations, with a detailed and thorough review of all hazards that may impact chemical and microbiological attributes of your APIs.
• Your supplier qualification procedure (e.g., clearly predefined specifications, periodic revalidation).
• A timeline for performing appropriate performance process qualification (PPQ) for each of your marketed API. Include your process performance protocol(s), and written procedures for qualification of equipment and facilities.

2. Failure to ensure that all specifications test procedures are scientifically sound and appropriate to ensure that your raw materials conform to established standards of quality and purity.

Your firm did not demonstrate that you adequately test incoming lots of **(b)(4)**, which is used to manufacture **(b)(4)**. For example, you relied on your vendor's COA for **(b)(4)** testing that did not include potentially harmful impurities (e.g., **(b)(4)**).

Your response is inadequate. You indicate testing of impurities for **(b)(4)** will be performed for every lot by a contract test laboratory. However, you lack a plan to qualify the contract testing laboratory that will adequately perform the testing of your incoming lots of **(b)(4)** for potentially harmful impurities. Furthermore, there is no assurance that previously distributed lots are safe and free from harmful impurities.

(b)(4)

Without appropriate testing of incoming production materials and finished API, you cannot ensure that the identity, purity, strength, quality, and safety of the components used to manufacture your **(b)(4)** drug products meet specifications and are suitable for their intended uses.

In response to this letter, provide:

• A comprehensive, independent review of your material system to determine whether all suppliers of components, containers, and closures, are each qualified and the materials are assigned appropriate expiration or retest dates. The review should also determine whether incoming material controls are adequate to prevent use of unsuitable components, containers, and closures.
• The chemical and microbiological quality control specifications you use to test and release each incoming lot of components for use in manufacturing.
• A summary of results obtained from testing all components to evaluate the reliability of COA from each component manufacturer. Include your standard operating procedure (SOP) that describes this COA validation program.
• A description of how you will test each component lot for conformity with all appropriate specifications for identity, strength, quality, and purity. If you intend to accept any results from your supplier's certificate of analysis (COA) instead of testing each component lot for strength, quality, and purity, specify how you will robustly establish the reliability of your supplier's results through initial validation as well as periodic revalidation. In addition, include a commitment to always

conduct at least one specific identity test for each incoming component lot. In the case of **(b)(4)**, we note that this includes the performance of **(b)(4)** and other impurities as required per the USP monograph.
• If you intend to use a contract testing laboratory to test drug components, a summary of your program for qualifying and overseeing contract facilities that test the components should be included.

Finished Drug Product CGMP Violations

3. 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 **(b)(4)** system used to manufacture **(b)(4)** incorporated as a component of your drug products was not designed and maintained appropriately for its intended use. For example, your **(b)(4)** system included a dead leg and was not continuously circulating, which could foster the development of biofilms. You also failed to adequately monitor your **(b)(4)** system to ensure that the system is operating properly and continuously producing **(b)(4)** suitable for its intended use.

Your response regarding validation of your **(b)(4)** system is inadequate. You did not include how you will ensure that your **(b)(4)** system design is appropriate for its intended use, maintained and sampled appropriately, and subject to closer scrutiny to enable prompt detection when the system may be falling out of a state of control. You also fail to assure that the **(b)(4)** you use during concurrent remediation is suitable for intended use.

(b)(4) must be suitable for its intended use and routinely tested to ensure ongoing conformance with appropriate chemical and microbiological attributes. Routine monitoring of microbial counts and identity of contamination in the system is integral to ensuring oversight of ongoing state of control and suitability of **(b)(4)** for use in manufacturing operations.

In response to this letter, provide:

• A detailed summary of your validation program for ensuring a state of control throughout the product lifecycle, along with associated procedures. Describe your program for process performance qualification (PPQ), and ongoing monitoring of both intra-batch and inter-batch variation to ensure a continuing state of control.
• Include your process performance protocol(s), and written procedures for qualification of equipment and facilities.
• Provide a detailed program for designing, validating, maintaining, controlling, and monitoring each of your manufacturing processes that includes vigilant monitoring of intra-batch and inter-batch variation to ensure an ongoing state of control. Also, include your program for qualification of your equipment and facility.
• An assessment of each drug product process to ensure that there is a data-driven and scientifically sound program that identifies and controls all sources of variability, such that your production processes, will consistently meet appropriate specifications and manufacturing standards. This includes, but is not limited to, evaluating suitability of equipment for its intended use, sufficiency of detectability in your monitoring and testing systems, quality of input materials, and reliability of each manufacturing process step and control.
• Timelines for completed PPQ for marketed drug products for which a state of control has not been adequately/fully established.
• A comprehensive, independent assessment of your **(b)(4)** system design, control, and maintenance.
• A thorough remediation plan to install and operate a suitable **(b)(4)** system. Include a robust ongoing control, maintenance, and monitoring program to ensure the remediated system design consistently produces **(b)(4)** adhering to **(b)(4)**, USP monograph specifications, and appropriate microbial limits.
• The current action/alert limits for total counts and objectionable organisms used for your **(b)(4)** system. Ensure that the total count limits for your **(b)(4)** are appropriately stringent in view of the intended use of each of the products produced by your firm.
• A detailed risk assessment addressing the potential effects of the observed **(b)(4)** system failures on the quality of all drug product lots currently in U.S. distribution or within expiry.

Specify actions that you will take in response to the risk assessment, such as customer notifications and product recalls.

For general principles and approaches that FDA considers appropriate elements of process validation, see FDA's guidance document Process Validation: General Principles and Practices, at: https://www.fda.gov/downloads/drugs/guidances/ucm070336.pdf (https://www.fda.gov/downloads/drugs/guidances/ucm070336.pdf)

4. 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)).

Your firm supplied aseptically filled **(b)(4)** to the US without adequate validation of your aseptic process. For example, during the inspection you stated that you have not performed media fills. While your firm has not shipped **(b)(4)** drug products to the United States since 2021, FDA is concerned you lack adequate controls to ensure sterility.

To ensure the sterility of products purporting to be sterile, aseptic filling and closing operations must be adequately validated before manufacture and distribution.

See FDA's guidance document *Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice* to help you meet CGMP requirements when manufacturing sterile drugs using aseptic processing. This guidance is on the FDA website at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070342.pdf. (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070342.pdf.)

In response to this letter, provide:

• Details about the improvements you are making to your facility and process to ensure that all units you purport to be sterile are produced under appropriate aseptic processing conditions.
• A corrective action plan that includes use of **(b)(4)** for all your products, and specifies appropriate testing limits for microbiological and chemical quality.
• Describe how you will sterilize equipment utilized for the filling of sterile products. Provide a detailed sterilization method, a list of all equipment sterilized using this method, validation protocols, and validation reports for your processes.

Provide a comprehensive summary of your media fill program that ensures an appropriate simulation of the worst-case conditions of commercial manufacturing. In addition, describe in detail how you examine units for presence of growth and how you perform batch yield reconciliation. Include all related standard operating procedures (SOPs).

In your response to this letter:

• Describe how you will sterilize the **(b)(4)** manufacturing operation. Provide a detailed sterilization method, a list of all equipment sterilized using this method, validation protocols, and validation reports for your processes.
• Provide a comprehensive summary of your media fill program that ensures an appropriate simulation of the worst-case conditions of commercial manufacturing. In addition, describe in detail how you examine units for presence of growth and how you perform batch yield reconciliation. Include all related standard operating procedures (SOPs).

Drug Production Ceased

We acknowledge your commitment to cease production of **(b)(4)** at this facility for the U.S. market. In response to this letter, clarify whether you intend to resume manufacturing of sterile drugs for the U.S. market at this facility in the future.

If you plan to resume any manufacturing operations regulated under the FD&C Act, notify this office before resuming your drug manufacturing operations. You are responsible for resolving all deficiencies and systemic flaws to ensure your firm is capable of ongoing CGMP compliance. In your notification to the Agency, provide a summary of your remediations to demonstrate that you have appropriately completed all corrective action and preventive action (CAPA).

CGMP Consultant Recommended

Based upon the nature of the violations and deviations we identified at your firm, you should engage a consultant qualified to evaluate your operations and to assist your firm in meeting CGMP requirements if your firm intends to resume manufacturing drugs for the U.S. market. The qualified consultant should also perform a comprehensive six-system audit of your entire operation for CGMP compliance and evaluate the completion and efficacy of your corrective actions and preventive actions before you pursue resolution of your firm's compliance status with FDA.

See Quality System, Facilities & Equipment System, Materials System, Production System, Packaging & Labeling System, and Laboratory Control System per FDA's guidance document *Quality Systems Approach to Pharmaceutical CGMP Regulations* https://www.fda.gov/media/71023/download. (https://www.fda.gov/media/71023/download.)

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.

Cosmetics Manufactured for Distribution in the United States

You stated during FDA's inspection that you intend to distribute cosmetics to the U.S. within the next 9-12 months. Any cosmetics you distribute to the U.S. must comply with applicable statutory and regulatory requirements, including the FD&C Act. We note that under section 301(a) of the FD&C Act [21 U.S.C. 331(a)], it is a prohibited act to introduce or deliver for introduction into interstate commerce a cosmetic that is adulterated or misbranded. Further, your facility may be subject to requirements of the Modernization of Cosmetic Regulations Act of 2022 (MoCRA). Information on MoCRA requirements may be found at https://www.fda.gov/cosmetics/cosmetics-laws-regulations/modernization-cosmetics-regulation-act-2022-mocra. (https://www.fda.gov/cosmetics/cosmetics-laws-regulations/modernization-cosmetics-regulation-act-2022-mocra.)

Conclusion

The violations and deviations cited in this letter are not intended to be an all-inclusive list of violations and deviations that exist at your facility. You are responsible for investigating and determining the causes of any violations and deviations and for preventing their recurrence or the occurrence of other violations and deviations.

FDA placed products offered for import into the U.S. from your firm on Import Alert 66-40 on November 15, 2024.

Correct any violations and deviations promptly. FDA may withhold approval of new applications or supplements listing your firm as a drug manufacturer until violations and deviations are completely addressed and we confirm your compliance with CGMP. We may re-inspect to verify that you have completed corrective actions to any violations and deviations.

Failure to address any violations and deviations may also result in the FDA continuing to refuse admission of articles manufactured at Bhargava Phytolab Private Limited, at E - 1216 Extn Ghatal, Phase – 1, Bhiwadi, Rajasthan, India 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 that appear to be adulterated may be detained or refused 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).

This letter notifies you of our findings and provides you an opportunity to address the above deficiencies. After you receive this letter, respond to this office in writing within 15 working days. Specify what you have done to address any violations and deviations and to prevent their recurrence. In response to this letter, you may provide additional information for our consideration as we continue to assess your activities and practices. 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. Identify your response with FEI 3012809762 and ATTN: Reba Gates.

Sincerely,
/S/

Francis Godwin
Director
Office of Manufacturing Quality

Office of Compliance

Center for Drug Evaluation and Research

More Warning Letters (/inspections-compliance-enforcement-and-criminal-investigations/compliance-actions-and-activities/warning-letters)