WARNING LETTER

Antaria Pty. Ltd.

MARCS-CMS 674495 — MARCH 22, 2024

Delivery Method:

VIA UPS

Reference #:

320-24-27

Product:

Drugs

Recipient:

Mr. Geoffrey B. Acton

Managing Director

Antaria Pty. Ltd.

1821 Ipswich Rd
Rocklea QLD 4106
Australia

Issuing Office:

Center for Drug Evaluation and Research | CDER

United States

Warning Letter 320-24-27

March 22, 2024

Dear Mr. Acton:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Antaria Pty. Ltd., FEI 3025978151, at 81 Shettleston St, Units 1 & 2 Rocklea, Queensland, Australia, from November 13 to 17, 2023.

This warning letter summarizes significant deviations from Current Good Manufacturing Practice (CGMP) for active pharmaceutical ingredients (API).

Because your methods, facilities, or controls for manufacturing, processing, packing, or holding do not conform to CGMP, your API 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 December 7, 2023 response to our Form FDA 483 in detail and acknowledge receipt of your subsequent correspondence.

During our inspection, our investigator observed specific deviations including, but not limited to, the following.

1. Failure to adequately investigate and document out-of-specification results and implement appropriate corrective actions.

Your firm manufactures API **(b)(4)** USP, labeled in part to be the active ingredient used in **(b)(4)**. You failed to adequately investigate out-of-specification (OOS) test results. Specifically, your firm lacked adequate investigations and corrective actions for numerous OOS results obtained during laboratory testing of your API, including assay and loss on ignition (LOI)

testing. The root causes were not clearly defined nor adequately documented, and lots with OOS results were released by your quality unit (QU).

In your response, you state that staff turnover and insufficient staff training attributes to the lack of competency in good laboratory practices. Additionally, you state that you will revise your OOS procedures. You also state that you will review historical LOI OOS to identify a root cause and retrain your laboratory staff. Your response is inadequate because you failed to describe a holistic review of all investigations' root cause analyses and corrective actions for adequacy. In addition, you did not inform your customers who received OOS lots for assay nor perform a retrospective assessment of retain samples.

Inadequate investigations can lead to unidentified root causes, ineffective corrective action and preventive action (CAPA), and recurring problems that compromise the ability to manufacture safe and effective drugs.

For more information about handling OOS results and documentation of your investigations, please refer to the FDA guidance for industry publication Investigating Out-of-Specification at https://www.fda.gov/media/158416/download.

In response to this letter, provide:

- A retrospective, independent review of all invalidated OOS (including in-process and release/stability testing) results for U.S. products irrespective of whether the batch was ultimately distributed in the United States and a report summarizing the findings of the analysis, including the following for each OOS:

o Determine whether the scientific justification and evidence relating to the invalidated OOS result conclusively or inconclusively demonstrates causative laboratory error.
o 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.
o 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 (e.g., 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). Provide a summary of potential manufacturing root causes for each investigation, and any manufacturing operation improvements.

- A comprehensive, independent assessment of your overall system for investigating deviations, discrepancies, complaints, OOS results, and failures. Provide a detailed action plan to remediate this system. Your action plan should include, but not be limited to, significant improvements in investigation competencies, scope determination, root cause evaluation, CAPA effectiveness, QU oversight, and written procedures. Address how your firm will ensure all phases of investigations are appropriately conducted.

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

Based on review of your laboratory results, you failed to appropriately perform analytical testing (assay and LOI) of your **(b)(4)** USP in accordance to the current version of United States Pharmacopeia (USP) monograph, nor did you have data to support that your test method was equivalent or better than the USP method. In your response, you state that you will revise your **(b)(4)** USP assay and LOI test methods to better align with the USP.

Without adequate testing, there is no scientific evidence to assure that your APIs conform to appropriate specifications before release.

See FDA's guidance document, *Analytical Procedures and Methods Validation for Drugs and Biologics*, for general principles and approaches that FDA considers appropriate elements of analytical method validation at https://www.fda.gov/media/87801/download.

In response to this letter provide:

- A list of chemical and microbial test methods and specifications used to analyze each lot of your API before making a lot disposition decision, and the associated written procedures.
- A comprehensive, independent assessment of your laboratory practices, procedures, methods, equipment, documentation, and analyst competencies. Based on this review, provide a detailed plan to remediate and evaluate the effectiveness of your laboratory system.

3. Failure to have laboratory control records that include complete data derived from all laboratory tests conducted to ensure your API complies with established specifications and standards.

You failed to include complete data in your laboratory records for all laboratory analyses, and accordingly relied on incomplete information to determine whether your **(b)(4)** USP met established specifications. For example, you lacked documentation of the preparation of stock solutions, sample solutions, diluents, mobile phases, and reagents used during testing of your API. You also failed to document the instruments and equipment used when performing analytical testing.

In your response, you acknowledge that your laboratory records lack complete testing information. You also state that you update your worksheets to record pertinent information. Your response is inadequate because it does not address the overall lack of traceability of previous analytical data, nor does it include a comprehensive strategy to confirm the validity of the previous analytical data used to release your **(b)(4)** USP.

Without adequate documentation of analytical tests and equipment used, you lack basic data to support that each API product batch conforms to appropriate specifications before release and distribution.

In response to this letter provide a complete assessment of documentation systems used throughout your manufacturing and laboratory operations to determine where documentation practices are insufficient. Include a detailed CAPA plan that comprehensively remediates your firm's documentation practices to ensure you retain attributable, legible, complete, original, accurate, contemporaneous records throughout your operation.

4. Failure to design an adequate documented, on-going stability testing program to monitor the stability characteristics of API and to use the results to confirm appropriate storage conditions and retest or expiry dates.

Your firm's stability program is inadequate. Your firm failed to place at least one lot of your API manufactured in 2019, 2020, or 2021 on stability annually.

In your response, you acknowledge that your stability procedure lacks specificity regarding appropriate testing. Additionally, you acknowledge that your stability study only consists of lots manufactured in 2015 and that you only establish your annual, ongoing stability program in 2022. Your response is inadequate because you did not discuss a retrospective review of API lots in distribution that were manufactured without appropriate stability testing.

Without an adequate stability program, you cannot ensure that your APIs meet established specifications and all pre-determined quality criteria throughout the APIs' assigned shelf-life.

In response to this letter provide:

- A comprehensive, independent assessment and CAPA plan to ensure the adequacy of your stability program. Your remediated program should include, but not be limited to:

o Stability-indicating methods.
o Stability studies for each drug product in its marketed container-closure system before distribution is permitted.
o 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.
o Detailed definition of the specific attributes to be tested at each station (timepoint).

- All procedures that describe these and other elements of your remediated stability program.

Additional API CGMP Guidance

FDA considers the expectations outlined in ICH Q7 when determining whether API are manufactured in conformance with CGMP. See FDA's guidance document *Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients* for guidance regarding CGMP for the manufacture of API at https://www.fda.gov/media/71518/download.

Conclusion

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

Correct any deviations promptly. FDA may withhold approval of new applications or supplements listing your firm as a drug manufacturer until any 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 deviations.

Failure to address any violations may also result in the FDA refusing admission of articles manufactured at Antaria Pty. Ltd.81 Shettleston St, Units 1 & 2 Rocklea, Queensland, Australia 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 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 3025978151 and ATTN: Daniel W. Brisker.

Sincerely,
/S/

Francis Godwin
Director
Office of Manufacturing Quality
Office of Compliance
Center for Drug Evaluation and Research

CC:
Registered US Agent
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