DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
12420 Parklawn Drive, Room 2032 Rockville, MD 20857 ORAPHARMInternationalresponses@fda.hhs.gov Industry Information: www.fda.gov/oc/industry	11/13-17/2023
	FEI NUMBER 3025978151

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Geoffrey B. Acton, Managing Director

FIRM NAME	STREET ADDRESS
Antaria Pty Ltd	81 Shettleston Street/Unit 1 & 2
CITY, STATE AND ZIP CODE	TYPE OF ESTABLISHMENT INSPECTED
Rocklea, Queensland, Australia 4106	API and Drug Manufacturer

THIS DOCUMENT LISTS OBSERVATIONS MADE BY THE FDA REPRESENTATIVE(S) DURING THE INSPECTION OF YOUR FACILITY. THEY ARE INSPECTIONAL OBSERVATIONS; AND DO NOT REPRESENT A FINAL AGENCY DETERMINATION REGARDING YOUR COMPLIANCE. IF YOU HAVE AN OBJECTION REGARDING AN OBSERVATION, OR HAVE IMPLEMENTED, OR PLAN TO IMPLEMENT CORRECTIVE ACTION IN RESPONSE TO AN OBSERVATION, YOU MAY DISCUSS THE OBJECTION OR ACTION WITH THE FDA REPRESENTATIVE(S) DURING THE INSPECTION OR SUBMIT THIS INFORMATION TO FDA AT THE ADDRESS ABOVE. IF YOU HAVE ANY QUESTIONS, PLEASE CONTACT FDA AT THE PHONE NUMBER AND ADDRESS ABOVE.

DURING AN INSPECTION OF YOUR FIRM (I) (WE) OBSERVED:

QUALITY SYSTEM

OBSERVATION 1

The responsibilities and procedures applicable to the quality control unit are not in writing and fully followed.

Specifically, your Quality Unit (QU) failed to fulfill its duties and responsibilities. Examples include the following.

a) There is a failure to conduct an appropriate investigation into out of specification (OOS) test results. There is a failure to assess and address all possible root causes for these failures and to identify and implement appropriate corrective actions to prevent their reoccurrence.

b) There is a failure of the Quality Unit to review and approve all written procedures. For example, your firm uses some documents, including checklists, to supplement approved procedures that do not show review and approval (signature and date) by QA. Examples include
- POS206.142_R0 Lab Checklist – Data Processing for HPIC Issue Date: 27FEB2023
- POS201.27_R0 Issue Checklist for CoA Generation/ Checklist for CoA Review Issue Date: 14JAN2022

c) Annual product quality reviews are not being performed in a timely manner. As of the date of this inspection, your firm has not completed an annual product quality review for products manufactured in 2022.

d) The annual product quality review for products manufactured in 2021 states: "no records were found for products being tested for stability in 2021 for the Brisbane site". The annual product quality review for products manufactured in 2020 states: "no records were found for products being tested for stability in 2020 for the Brisbane site". These reports were approved by QA however, the lack of stability studies and stability data for

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2020 and 2021 did not trigger an investigation.

e) Your firm is not following SOP 206.113 Brisbane Stability Oven Operation, Rev 0 issued 08AUG2022 regarding (b) (4) downloading and review of the temperature and humidity readings from the data loggers for the stability chambers. The data loggers reached their maximum storage capacity on October 6, 2022 and has not recorded temperature or humidity in the stability chambers since that date.

OBSERVATION 2

There is a failure to thoroughly review any unexplained discrepancy or the failure of a batch or any of its components to meet any of its specifications, whether or not the batch has been already distributed.

Specifically, your firm's Quality Unit failed to adequately investigate Out of Specification (OOS) test results, determine root cause, and implement corrective actions. Approximately 146 OOS results were obtained in 2023 for (b) (4) API for all countries, including for assay and Loss on Ignition (LOI). At the time of testing all lots of (b) (4) API have the potential to be shipped to US and all are labeled as USP grade. There is no documentation of root cause or any specific information regarding investigations to justify attributing the failure to such items as not following SOP, issue with sample amount or sample unity, and/or technician error. Many OOS investigations are simply a re-testing of the product by a different analyst. There is limited to no documentation of the preparation of the initial samples and standards or of the re-tested sample nor is there documented justification for invalidating the initial result except to state the product passed when tested by a different analyst. Sometimes the re-testing is performed by a third analyst as the initial and re-test results are both OOS.

Examples of OOS investigations in 2023 that were not adequately investigated for product shipped to the US include the following:

• Lot # (b) (4) (OOS 125B) – failed (b) (4) assay at (b) (4) % (specification is (b) (4) %-(b) (4) %). The product was re-tested by a second analyst and passed. OOS was attributed to an issue with the SOP not being followed but contains no documentation of what aspect of the SOP was not followed. The product was released by QA on July 13, 2023.

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• Lot #(b) (4) (OOS 856) – failed(b) (4) assay a(b) (4)%. The product was re-tested twice by two different analysts as the first re-test was also OOS. The third re-test has passing results and the OOS was attributed to an issue with "sample amount or sample unity". There is no documentation to show issue with sample. The product was released by QA on March 13, 2023.
• Lot #(b) (4) (OOS 18B) – failed Loss on Ignition (LOI) at(b) (4)% (specification is ≤(b) (4)%). The product was re-tested twice. The first re-test was performed by a different analyst and was also OOS. The third re-test was performed by the original analyst and has passing results. The OOS was attributed to an issue with the SOP not being followed but contains no documentation of what aspect of the SOP was not followed. The product was released by QA on June 8, 2023.
• Lot #(b) (4) (OOS 102B) - failed Loss on Ignition (LOI) at(b) (4)%. The product was re-tested by a second analyst and passed. OOS was attributed to an issue with the SOP not being followed but contains no documentation of what aspect of the SOP was not followed. The product was released by QA on May 26, 2023.
• Lot #(b) (4) (OOS 105B) - failed Loss on Ignition (LOI) at(b) (4)% (one of two values was OOS). The product was re-tested by a second analyst and passed. OOS was attributed to an issue with the SOP not being followed but contains no documentation of what aspect of the SOP was not followed. The product was released by QA on June 14, 2023.

LABORATORY SYSTEM

OBSERVATION 3

Laboratory records are deficient in that they do not include a complete record of all data obtained during testing and do not always include documentation of pertinent information related to the preparation and testing of a sample. For example,

a) There is no documentation of the preparation of standard stock solutions, working standards, reference standard solutions, sample solutions, diluents, mobile phases, reagents, and other preparations used for performing testing of drug samples including for assay, elemental impurities, and other required USP tests for testing of drug products to include(b) (4) API.

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b) The "calibration standard" listed in the template for the assay of (b) (4) via (b) (4) chromatography shows a date of preparation as 14FEB23. The bottle of working standard currently being used is dated 12SEP23. Per your technician, the date of 12SEP23 is also incorrect. The technician stated they had prepared the working standard several days earlier but did not change the date on the bottle.

c) There is no documentation of the (b) (4) of the sample as required by your test methods.

d) Your firm does not document the lot numbers and/or quantity used of reference standards, diluents, reagents and other laboratory consumables used in the preparation and testing of drug products to include (b) (4) USP (API). This includes items used for assay, elemental impurities, and other required USP tests.

e) Your firm does not document the instruments and equipment used when performing testing. For example, your firm has (b) (4) different kilns, at least (b) (4) different balances, and various pipettors that can be used during testing.

OBSERVATION 4

Your firm does not assign an expiration date for prepared working standards, mobile phases, diluents and other preparations used for performing testing of drug products, including (b) (4) API. Test methods include testing for assay, elemental impurities, and other required USP tests. For example, the bottle of working standard (b) (4) ug/mL (b) (4) standard solution) that is currently being used for assay by (b) (4) chromatography is marked with a prepared date of 12SEP23 but does not have an expiration date listed.

SOP 200.02 Shelf Life of Laboratory Reagents and Samples, rev 03 issued 07JUL2021 defines recommended expiration dates for laboratory prepared reagents and calibration standards however, your firm has no documentation of any validation work to justify these recommended expiration dates.

OBSERVATION 5

There is no written testing program designed to assess the stability characteristics of drug products.

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Specifically, your firm has not placed at least one lot of (b) (4) API (b) (4) on stability annually. For example, you currently have (b) (4) lots on long term stability; (b) (4) lot placed on stability in 2022 and (b) (4) in 2023. No lots have been placed on stability for product manufactured at the Brisbane site in 2019, 2020, or 2021. In addition, your firm uses (b) (4) starting material) from (b) (4) different suppliers however, your firm has not evaluated the need to place lots made from each supplier on stability.

The stability study conducted on (b) (4) lots of (b) (4) API manufactured at your Perth facility in 2015 does not have an approved written protocol. Your firm did not define the tests to be performed at each time point. The spreadsheet indicates all release tests however, your firm only tested for Loss on Ignition (LOI) and BET (surface area) at each time point after time point 0. The test results are not signed/approved. In addition, there was an OOS at the 60 month time point for LOI for lot# (b) (4) Your firm did not perform an adequate investigation and provided no documented justification for invalidating the original result. Your firm simply had a second analyst re-test the product and then passed it. Your firm is using this study to justofy placing a (b) (4) expiration date on the (b) (4) USP (API).

OBSERVATION 6

Calibration of balances used in the QC Laboratory are not calibrated appropriately. For example, the balances are not calibrated over the operating range and there is a failure to demonstrate that the balance meets the requirements defined for repeatability, accuracy, and linearity.

OBSERVATION 7

Your firm is not always following the approved test method. For example,

a) SOP206.15 USP (b) (4) Monograph Test Methods, rev 8 issued 09AUG2023, requires the use of a (b) (4) (b) (4) for the performance of the test for (b) (4) and colour of solution. This is consistent with the USP test method. Your firm is using a (b) (4)

b) SOP206.15 USP (b) (4) Monograph Test Methods, rev 8 issued 09AUG2023, requires drying of the (b) (4) and sample at (b) (4) C for a minimum of (b) (4) for Loss on Ignition. Your drying oven has a knob (no

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digital display) and does not have a mark for (b) (4) C. On November 15, 2023, I observed the technician performing the test setting the drying oven to over (b) (4) C as that is the closest mark to (b) (4) C.

OBSERVATION 8

Your firm has no documentation to show the test methods used for stability testing of (b) (4) USP (API) and other drug products are stability indicating.

FACILITY AND EQUIPMENT SYSTEM

OBSERVATION 9

Your firm has not fully qualified the stability chambers used for long term (30°C/65%RH – Oven ID O-0007) and accelerated stability studies. The chambers were installed in April 2022. The Operational Qualification (OQ) report approved on August 15, 2022 by QA contains no information about the actual operation of the chambers including no temperature and humidity readings, no verification documentation that the digital read out of the temperature and humidity is correct, no documentation of the placement of the temperature and humidity probes that feed the digital read out, no temperature mapping of the chambers, and no documentation of any alarms for the chambers. The Performance Qualification (PQ) for the chambers has not been completed. There is no approved protocol and the draft protocol provided does not call for verification or qualification of the chambers when full (or at any specific capacity); only (b) (4) monitoring of temperature and humidity of the empty chamber. Your firm brought storage of stability samples in house when these chambers were installed, and you currently have (b) (4) stability samples for the (b) (4) USP) stored in the long term chamber as well as other samples related to (b) (4) dispersions and (b) (4) being contract tested. Your firm has no temperature or humidity data from October 6, 2022 to present except for a (b) (4) note in a logbook. There are several recent entries noting the temperature and/or humidity was out of specification however, no investigation was initiated.

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The observations of objectionable conditions and practices listed on the front of this form are reported:

1. Pursuant to Section 704(b) of the Federal Food, Drug and Cosmetic Act, or

2. To assist firms inspected in complying with the Acts and regulations enforced by the Food and Drug Administration.

Section 704(b) of the Federal Food, Drug, and Cosmetic Act (21 USC 374(b)) provides:

"Upon completion of any such inspection of a factory, warehouse, consulting laboratory, or other establishment, and prior to leaving the premises, the officer or employee making the inspection shall give to the owner, operator, or agent in charge a report in writing setting forth any conditions or practices observed by him which, in his judgement, indicate that any food, drug, device, or cosmetic in such establishment (1) consists in whole or in part of any filthy, putrid, or decomposed substance, or (2) has been prepared, packed, or held under insanitary conditions whereby it may have become contaminated with filth, or whereby it may have been rendered injurious to health. A copy of such report shall be sent promptly to the Secretary."

mmA 11/17/2023