DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
Food and Drug Administration 12420 Parklawn Drive Room 2032 Rockville, MD 20857 Industry Information: www.fda.gov/oc/industry	December 4-8 and 11-12, 2023
	FEI NUMBER 3011524794

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: V.N Prasad Patibandla, General Manager Manufacturing

FIRM NAME	STREET ADDRESS
Laurus Synthesis Private Limited	Plot No. 74B, Jawaharlal, Nehru Pharma City Parawada
CITY, STATE AND ZIP CODE	TYPE OF ESTABLISHMENT INSPECTED
Anakapalli, Andhra Pradesh, 531021, India	API Intermediate Manufacturer

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

OBSERVATION #1
Investigation of unexpected occurrences are not adequately conducted.

Specifically,

A. Investigations into damage of (b) (4) which are used in the manufacturing of key starting materials and API intermediates intended for the US market, are inadequate. In the past three years, five deviations involving (b) (4) damage were initiated with three deviations being deficient. For example:

1) Deviation investigations DEV-SV1-22-0002, DEV-SV1-23-0002, and DN/LSV1/MFG/019/21 for (b) (4) damage did not document the size and/or location of the (b) (4) damage.

2) Deviation investigation DEV-SV1-22-0002 was initiated on January 10, 2022 to investigate damage of the (b) (4) (b) (4) of (b) (4) 202. The (b) (4) was observed during batch-to-batch cleaning on January 10, 2022. The damage was not present during preventive maintenance done on November 21, 2021. A total of (b) (4) batches were manufactured since the last Preventive Maintenance, including (b) (4) batches of (b) (4) (b) (4) and (b) (4) batches of (b) (4) (b) (4) The investigation did not include screening al (b) (4) batches for (b) (4) particles. Only (b) (4) lots of product (b) (4) manufactured after product changeover were sampled and inspected for (b) (4) particles by filtration. The complete bulk lot was not visually inspected for particles and there was no scientific rationale for taking (b) (4) g of sample from a (b) (4) bulk batch for screening for (b) (4) particles. The key starting material (b) (4) is used in the manufacture of API (b) (4) intended for the US and Global markets.

3) Deviation investigation DEV-SV1-23-0002 was initiated on January 07, 2023 to investigate damage of the (b) (4) (b) (4) on the (b) (4) 221. The damage was observed during Preventive Maintenance done on January 07, 2023. The damage was not identified during product change over cleaning on January 05, 2023 and

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during prior Preventive Maintenance on October 07, 2022. A total of (b) (4) lots of (b) (4) were manufactured since the last passing Preventive Maintenance on October 07, 2022 and were likely impacted. The investigation stated that there was no impact on the executed batches (b) (4) as they met specification and were consumed in the subsequent stage (b) (4) The investigation did not include screening of any of these batches for (b) (4) particles. These batches were further processed and dispatched. The customer (b) (4) was not informed about the deviation.

4) Deviation investigation for damaged (b) (4) ncluding DN/LSV1/MFG/019/21 (for (b) (4) 05) and DEV-SV1-23-0002 (for (b) (4) 221) were inadequate in tracking (b) (4) particle contaminants. It was stated that there was no impact to products manufactured due to downstream filtration steps that could remove (b) (4) particles. However, the capability of the filtration steps to remove (b) (4) particles was not scientifically justified, proven, or documented within the investigation report.

B. Non-Conformance Investigation NCM/LSV1/003/22 was initiated for non-conforming assay and purity results by HPLC during (b) (4) hold-time study of key starting material (b) (4) One out of (b) (4) batches on hold time study (2 of (b) (4) samples) analyzed failed for assay and impurities. The investigation concluded that it was an isolated case and no further actions were documented.

C. OOS investigation OOS/LSV1/001/22 identified improper in-process sampling as suspected cause for impurity by HPLC for key starting material (b) (4) The investigation infers that the operator collected samples only from the (b) (4) in process material and therefore the assay passed during in-process testing and failed for impurity during finished testing. However, procedure MFG/027, "In-process sampling", does not specify the correct sampling procedure to account for (b) (4) in-process materials. In addition, the (b) (4) material within the (b) (4) was not scientifically justified or proven.

D. Non-Conformance Investigation NCM-LSV1-001 was initiated for OOS results for (b) (4) water TOC. The investigation is inadequate as it did not document/correlate the OOS result with other test results including TAMC and conductivity.

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OBSERVATION #2
Sampling plans for intermediates are inadequate.

Specifically,

The current sampling plan for the intermediate (b) (4) fails to ensure that a representative sample is obtained for assay and impurities. (b) (4) is (b) (4) which is then (b) (4) (b) (4) After (b) (4) the product is packaged and a (b) (4) sample is taken from each drum of packaged intermediate and analyzed for loss on drying, assay, and impurities. Although (b) (4) validation (b) (4) LSV1/ (b) (4) has been performed to assess the uniformity of (b) (4) for (b) (4) the critical quality attributes of assay and impurities were not assessed in any study to ensure that these quality attributes are also uniformly distributed within the material and therefore the sample is representative of the batch.

OBSERVATION #3
Equipment is not maintained, cleaned, and stored in a manner to prevent contamination.

Specifically,

During the walkthrough of (b) (4) on December 04-05, 2023, the following were observed related to the equipment used in the manufacturing of API intermediate (b) (4)

A. The interior of (b) (4) 104 and (b) (4) 109, which are used during the manufacture of (b) (4) had apparent rust on the (b) (4) Furthermore, (b) (4) (b) (4) 116, which is also used in the manufacturing of (b) (4) had apparent product residue remaining in the (b) (4) even though the (b) (4) was identified as cleaned.

B (b) (4) 201 used in the (b) (4) had apparent white residue contained on and around the (b) (4) In addition, outside light was observed from the inside of the (b) (4) (b) (4) room where product is final packaged through gaps surrounding the (b) (4) Furthermore, the (b) (4)

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covering the (b) (4) had apparent dirt and dark residue embedded on the (b) (4) (b) (4) This (b) (4) was stated to have been inspected as clean on December 02, 2023 during the (b) (4) preventive maintenance.

C. Product contact transfer hoses used to transfer (b) (4) during production and non-product contact transfer hoses are stored in the accessory room on a shelf with the hose ends covered with bags. These hoses were not stored in a way to ensure that any residual solvent or moisture after use and cleaning does not remain within the hoses. In addition, debris were found in at least two of the hoses that were identified as clean in the area. Furthermore, these hoses do not have an associated equipment ID nor did all hoses have an associated cleaning tag attached.

OBSERVATION #4

Batch production records do not contain complete information related to the production and control of the batch.

Specifically,

A. Portable gauges, such as the (b) (4) used to (b) (4) process water, and product and non-product contact transfer hoses are not identified or recorded within the batch production record for traceability and to ensure they are adequate for use.

B. The use of process water in the manufacture of (b) (4) is not adequately documented, including the required performance of the sample port and transfer hose (b) (4) prior to use according to procedure MFG/024 (b) (4) of Materials into (b) (4).

C. (b) (4) pressure is applied and maintained up to (b) (4) cm2 to the (b) (4) during the (b) (4) The pressure reading during these steps is not recorded even though your manufacturing personnel stated that the gauge has a numeric reading.

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OBSERVATION #5
The issuance of documents is not adequately controlled.

Specifically,

Batch product record annexure pages that contain batch-related information and data are not adequately issued and controlled. For example, during the manufacture of (b) (4) batches (b) (4) (b) (4) five, six, and five annexure pages, respectively, were used in the manufacture to document weights obtained during (b) (4) These pages are printed by production personnel as outlined in procedure QA/086, "Procedure for Operation of Document Management System (DMS) Software", and can be used for any purpose as part of the execution of the batch record. These pages are not issued, controlled, or reconciled in a way to ensure that the data and records are complete and that all pages printed are accounted for as part of batch record execution and documentation.

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