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Prequalification Team Inspection services
WHO PUBLIC INSPECTION REPORT
(WHOPIR)
Active Pharmaceutical Ingredient Manufacturer

Part 1	**General information**
Manufacturers details	
Name of manufacturer	**Laurus Labs Limited (Unit 4)**
Corporate address of manufacturer	Laurus Labs Limited 2nd Floor, Serene Chambers, Road No. 7, Banjara Hills, Hyderabad 500034, India
Inspected site	
Name & address of inspected manufacturing site if different from that given above	Laurus Labs Limited (Unit 4) Unit-4, Plot No.25, 25A to 25K, APSEZ De-Notified Area, Lalamkoduru Village, Rambilli Mandal Anakapalli, Andhra Pradesh 531011 India
Synthetic unit /Block/ Workshop	MB-2, MB-5, MB-6A, MB-7
Inspection details	
Dates of inspection	16-19 January 2024
Type of inspection	Routine GMP inspection
Introduction	
Brief description of the manufacturing activities	Laurus Labs Limited, Unit 4 manufactures a wide range of APIs, intermediates and ingredients corresponding to various therapeutic areas. No β-lactams or antibiotics are manufactured on-site. Contract manufacturing of products is performed on a campaign basis. The campus consisted of several buildings including several warehouses and 9 manufacturing blocks (MB). MB-6 and MB-8 consisted of sections A and B (separate buildings). MB-6B was dedicated to Digoxin manufacturing
General information about the company and site	Laurus is a research-driven pharmaceutical company mainly focusing in the areas of HIV, hepatis C and oncology. There are several Laurus manufacturing Units in the areas of Parawada and Atchutapuram, Andhra Pradesh. Laurus Unit 4 is located in the Atchutapuram area, approximately 70 Km from Visakhapatnam.
History	This was the first on-site WHO Prequalification inspection. A desk assessment of the site's GMP compliance was carried out in August 2020. The site had also been inspected by USFDA in July 2019. Laurus Unit 4 was

	periodically inspected by the national and local authorities. The last inspection by CDSCO was carried out in October 2023.
Brief report of inspection activities undertaken – Scope and limitations	
Areas inspected	Pharmaceutical Quality System Documentation Facilities and Equipment (warehouses, workshops) Utilities Production Packaging and labelling Product Release Quality Control laboratories
Restrictions	N/A
Out of scope	APIs not submitted to WHO Prequalification were excluded from the scope of this inspection
WHO APIs covered by the inspection	Lopinavir Lamivudine Tenofovir Disoproxil Fumarate (TDF)
Abbreviations	**Meaning**
AHU	Air handling unit
ALCOA	Attributable, legible, contemporaneous, original and accurate
API	Active pharmaceutical ingredient
APR	Annual product review
BMR	Batch manufacturing record
BPR	Batch production record
CC	Change control
CIP	Cleaning in place
CoA	Certificate of analysis
CpK	Process capability
DQ	Design qualification
EDI	Electronic deionization
EM	Environmental monitoring
FMEA	Failure modes and effects analysis
FPP	Finished pharmaceutical product
FTA	Fault tree analysis
GMP	Good manufacturing practices
HEPA	High efficiency particulate air
HPLC	High performance liquid chromatography (or high-performance liquid chromatography equipment)
HVAC	Heating, ventilation and air conditioning
IQ	Installation qualification
KF	Karl Fisher

LAF	Laminar air flow
LIMS	Laboratory information management system
MB	Microbiology
MBL	Microbiology laboratory
MR	Management review
NC	Non conformity
NRA	National regulatory agency
OQ	Operational qualification
PHA	Process hazard analysis
PLC	Programmable logic controller
PM	Preventive maintenance
PQ	Performance qualification
PQR	Product quality review
PQS	Pharmaceutical quality system
PW	Purified water
QA	Quality assurance
QC	Quality control
QCL	Quality control laboratory
QMS	Quality management system
QRM	Quality risk management
RA	Risk assessment
RCA	Root cause analysis
RO	Reverse osmosis
SMF	Site master file
SOP	Standard operating procedure
URS	User requirements specifications
UV	Ultraviolet-visible spectrophotometer

Part 2	**Summary of the findings and comments (where applicable)**

1. Quality management

The company had established a QMS based on ICHQ7, 21 CFR Parts 210 and 211, PIC/S and EU GMP, Schedule "M" of Drug and Cosmetics Act and ISO 9001:2015. The principles of the system were described in the Quality Manual and an Electronic Quality Assurance Management System (eQAMS) was implemented to handle the various areas of QMS such as change control, internal audits, deviations, complaints, CAPA etc. Similarly, an electronic Documentation Management System was implemented to handle quality documentation including but not limited to site-specific procedures and corporate procedures. The documentation system was divided into three levels: Level 1 (quality manual, SMF, VMP), Level 2 (SOPs, STPs), Level 3 (records). In general, personnel had the necessary experience and was appropriately trained. Facilities and equipment were adequately maintained and qualified. Quality risk management was integrated into all aspects of the QMS, and the basic concepts were aligned with ICH Q9. Senior management responsibilities and commitment were defined.

Management Review

Management review was described in the QM and in detail in a procedure. Management review meetings were held every 3 months. The Site QA was responsible for planning and scheduling the meeting. During the meeting, among others the following were discussed: follow up actions from the previous meeting, major changes, deviations, OOS, CAPAs, audits, complaints, returns, improvements, APQR, process performance, and effectiveness of actions. The minutes of the meeting covering the period July to September 2023 were reviewed.

Product Quality Review

PQRs were conducted based on a written procedure for batches manufactured between January and December every year. In case a new product was manufactured during the year, a rolling PQR was prepared annually. The QA department was responsible for establishing the PQR plan at the end of each year. The PQR Tracking Sheet was presented. Statistical evaluation and process capability were performed and calculated to evaluate the critical quality attributes and yield.

The PQR of Lamivudine for the period September 2022 to August 2023 was reviewed. 56 batches including 2 reprocessed batches were manufactured. The PQR included review of the synthetic route, manufacturing process, manufactured batches, key starting material and key intermediates quality data and suppliers, changes, OOS, deviations, IPC, CPP, QC evaluation of batches, yield results, validation studies, stability studies, complaints, recalls, and statistical evaluation.

Quality Risk Management

The principles of QRM were described at a high level, in the QM and SMF. Risk assessments for APIs were performed at the development, manufacturing, and distribution levels according to ICH Q9 principles. Examples of risk assessments regarding the manufacturing of Tenofovir Disoproxil Fumarate and the potential formation of N-nitrosamine impurities in Tenofovir Disoproxil Fumarate were reviewed.

Batch release

The batch release procedure (was reviewed and discussed in detail. The procedure addressed the release of intermediates (i.e., for internal use and for sale), and of finished products. All production related documentation along with the analytical report were sent to QA for review. A checklist was used. QA ensured that all documentation including batch records of intermediates had been reviewed and released, deviations and OOS had been fully investigated and closed out before giving their final approval for release. Furthermore, there was a procedure in place detailing the dispatch of materials to the market where it was described how a finished product was customized according to client specifications, sampled, tested, labelled, and released.

Root cause Investigations

A procedure was in place for carrying out investigations. The procedure was applicable to investigations of all non-conformities including but not limited to complaints, recalls, OOS/OOT, and deviations. Ishikawa/6M was usually used as a tool for investigations. As a result of the investigations, CAPA were identified and the effectiveness of CAPA was verified after implementation.

Deviations

A procedure for handling deviations was in place and was discussed in detail. The respective initiating department was responsible for the initiation, execution, and closure of the deviation. Head/Designee of the respective department was responsible for reviewing and conducting the investigation to identify the

root cause. Deviations were categorized as critical, major, or minor. The deviation was handled in eQAMS. Deviations were reviewed every three months and trended. The trending report for the period July to September 2023 was reviewed. At the end of each year, a consolidated report was prepared including a comparison of data with the previous two years. Examples of deviation handling were reviewed.

Any observations related to this section have been adequately addressed and the implementation of CAPA will be verified at the next inspection

2. Personnel

There were approximately 700 employees working on site. Production operated in three shifts while all other department operated in one shift. Key personnel responsibilities were described in job descriptions and the hierarchical and administrative structure were depicted in organization charts. The organogram and job descriptions were prepared according to a written procedure. Corporate Human Resources was responsible for compiling the organization chart. The job descriptions of the Head of Manufacturing the Head of QC, and the QA responsible for release of APIs were reviewed. Qualifications and delegation of duties were described in the job descriptions.

The procedure on personnel training was presented. There were several types of training including induction training, GMP training, on the job training, and SOP training. Training activities were handled electronically through the Learning Management System (LMS) software. Training evaluation was carried out for all training programs through an evaluation questionnaire. The trainee who scored less than 80% would undergo retraining until he/she could pass the exam.

Contract workers underwent training according to a written procedure. Each contract worker underwent induction training covering basic safety aspects, personal hygiene, basic GMP principles and training on specific duties before being involved in the day-to-day work activities. Evaluation of the training was performed by a questionnaire. The training record for contract worker on the SOP for personnel hygiene practices and personnel entry and exit was reviewed.

The procedure for personnel hygiene practices was discussed. There were pre-employment medical checks for all employees to ensure their fitness for the job. The Human Resources Department was responsible for the annual health check-ups of employees.
Contract workers also underwent medical checks according to a written procedure before employment and periodically thereafter.
Employees medical list was in place and monitored periodically by the Human Resources Department

Any observations related to this section have been adequately addressed and the implementation of CAPA will be verified at the next inspection

3. Buildings and facilities

The campus consisted of several buildings. There were two warehouses for raw materials including temperature-controlled rooms (<25°C) and cold storage, one warehouse for finished products and intermediates for sale including two cold rooms, a storage area for solvents in drums, a tank farm and 11 workshops (MB).

Layouts of the facilities were made available. In general, premises were constructed, designed, and maintained to suit the operations to be carried out and prevent the risk of contamination of materials and products. At large, the design of the premises was such as to minimize the risk of errors and permit effective cleaning and maintenance.

There were procedures in place for cleaning and maintenance of the facilities and logbooks were maintained. The SOP "Operation and preventive maintenance of AHU and dust collectors" was reviewed.

There were four Purified Water generation systems. The PW system (PWS-02), located on the first floor of Utility-1, supplying water to MB-2 and MB-5, was visited. The PW generation system consisted of the following stations: Sodium hypochlorite dosing, 100µm filter, 5µm cartridge filter, ultra-filtration unit, UV purifier. The output water was collected in a storage tank. Further, the treated water was passed through the RO and EDI Units, collected in an SS 316L storage tank, and distributed to various user points. Sanitization of the storage tank and the distribution loop was performed every 15 days by circulating hot water at above 80ºC, for 90 min. The Distribution System was spot-checked.

Any observations related to this section have been adequately addressed and the implementation of CAPA will be verified at the next inspection

4. Process equipment

Reactor systems, equipment, and utilities were installed to allow reflux, distillation, cooling, crystallization, centrifugation, drying, and milling required to make the APIs of interest. Materials of product contact were suitable. Tools and equipment were uniquely identified, and status labels were generally used. Similarly measuring equipment was labelled including the calibration status. In general, they were maintained according to written procedures and a plan for preventive maintenance was available. The procedure for handling, cleaning, and checking of sieves was presented. The integrity of the mesh was performed after cleaning. Spot-checks on equipment cleaning and maintenance records were made.

Any observations related to this section have been adequately addressed and the implementation of CAPA will be verified at the next inspection

5. Documentation and records

The company used an electronic documentation system to manage quality documentation including but not limited to site-specific procedures and corporate procedures. A procedure for the operation of the electronic documentation system was made available. There were procedures in place for issuance, approval, control, review, and withdrawal of procedures and quality documents. In general, all generated quality documentation including paper-based records were appropriately codified in accordance with the relevant procedures. There was a procedure in place defining the retention period of quality documentation. Material and product specifications were detailed in written form. Similarly, analytical methods for each material and product were documented.
A procedure for completing a batch production and control record, was in place and was discussed in detail.

<u>Batch numbering system</u>

The procedure for issuing batch numbers was presented. Initially, batches during manufacturing bared the same number as the Batch Production and Control Record (BPCR). Upon final release, the market batch number was generated through SAP. More specifically, upon completion of the analytical work by QC a stock intimation advice note would be sent to QA for issuing the BPR and commercial batch number in SAP. This intimation note would connect the BPCR number and the commercial batch number.

Any observations related to this section have been adequately addressed and the implementation of CAPA will be verified at the next inspection

6. Materials management

There were procedures in place for the receipt of raw materials, solvents in drums and bulk solvents in tankers. The receipt of bulk solvents was performed in an undercover area of the tank farm. The tanker and solvent documentation were checked upon receipt. The bulk solvent was sampled and tested, and the test results were taken into account before introducing the solvent in the tank using dedicated flexible hoses. Following mixing with the existing solvent in the tank a new sample was withdrawn and analyzed, and a new batch number was assigned following positive test results.
For the receipt of solvents in drums a check list was used to ensure the integrity of the drums and the quality of the solvents. There was a dedicated area in the solvent drum warehouse for sampling.
Similarly, the receipt of materials at warehouses 1 and 2 was performed based on a check list. Materials were stored in ambient temperature and relative humidity. However, both warehouse 1 and warehouse 2 had temperature-controlled rooms (<25^{o}C) and cold storage area in both warehouses. On the ground floor of warehouse 2 there were 3 sampling/dispensing rooms and there was a segregated area for rejected materials. The usage and cleaning record for sampling/dispensing room no. 3 was spot-checked. On the 1st floor of warehouse 2, packaging materials were stored, and a separate sampling room was established.
The procedure on sampling of materials was reviewed. The procedure was applicable to sampling of raw materials, packaging materials, solvents, and intermediates. Sampling of APIs and intermediates was performed on every container. Primary packaging materials were sampled according to ANSI/ASQC Z1.4-1993.

Any observations related to this section have been adequately addressed and the implementation of CAPA will be verified at the next inspection

7. Production and in-process controls

The production operated in three shifts. In general, production operations followed defined procedures. Process flows and routes of synthesis were available. Access to production premises was restricted to authorized personnel.

On 16th January 2024, the inspectors visited manufacturing block 7 (MB-7) where Lamivudine was manufactured. MB-7 consisted of three floors. Charging of materials took place on the second floor. Most of the reactors were installed on the 1st floor and the ground floor was used for filtration and final processing (clean area – crystallization, centrifugation, milling, packing etc.). Lamivudine was manufactured in four steps. Initially it was manufactured in MB-5 where process validation was performed in 2020. The product was transferred to MB-7 in 2023 scaling up the batch size, and process validation was completed the same year. During the tour, equipment usage logbooks and BPCRs were spot-checked. The inspectors continued

the tour of MB-7 on 17th January 2024 following the processing of Lamivudine intermediates and finished product and visiting the clean area.

MB-2 was also visited and processing of a Tenofovir Disoproxil fumarate(TDF) was followed. Similarly, to MB-7 charging of materials took place on the top floor, washing, extraction and distillation took place on the first floor and final processing took place in the clean area found on the ground floor. TDF was initially manufactured in MB-5 and was transferred to MB-2 in 2021 where scale up process validation was conducted.

On the afternoon of 17th January 2024, the inspection team visited MB-6A. This workshop was used for the manufacture of Lopinavir, however at the time of the inspection a different product was being manufactured. The inspectors visited the clean area and spot-checked the crystallization reactor, centrifuge, and drying oven logbooks.

Any observations related to this section have been adequately addressed and the implementation of CAPA will be verified at the next inspection

8. Packaging and identification labelling of APIs and intermediates

The API was packed in transparent LDPE bags. The bag was twisted and tied with a strip, placed in a secondary black LDPE bag and finally placed in a high-density polyethylene container.
Handling and labelling of intermediates and drug substances was done according to a written procedure. Production designated personnel were responsible for printing the quarantine labels, QA is responsible for printing the product & release labels and QC is responsible for approved labels.

Any observations related to this section have been adequately addressed and the implementation of CAPA will be verified at the next inspection

9. Storage and distribution

The dispatch of materials to the market SOP was reviewed and discussed. Handling of dispatch activities was carried out through SAP in accordance with a written procedure. The stock transfer order was issued by the Business Development department to the production personnel. Upon receipt, the production personnel would raise a stock intimation note to the QC and QA departments. The QC would check the batch specifications and complete the relevant information (i.e., expiry date) and forward the note to the QA department. In case further final processing was needed (e.g., micronization, packaging) then a BPCR would be issued, and the manufacturing personnel would proceed with the necessary activities. The QC personnel would sample and test the batch and finally all the documentation would be forwarded to the QA department for review and final decision. The QA department would issue the labels which would be affixed on the bags and containers by production personnel. In case there was a need for label reprinting, a justification had to be registered in SAP. The QA department would randomly verify container labels and gross weights against the packing list and observe the security sealing of the containers performed by the production personnel. The CoA would be issued at this stage. The QC personnel would prepare the CoA and send it to QA for review and printing. Two copies would be issued. One would be sent to the customer and the second one would be maintained by the QA department.

Any observations related to this section have been adequately addressed and the implementation of CAPA will be verified at the next inspection

10. Laboratory controls

Quality Control (QC) operations were independent from production. The QC was divided into different sections and included several areas/rooms like the HPLCs lab, the GC lab, the wet chemistry lab, the retention sample room, the sample preparation room, the glassware cleaning room, the chemicals storage room, and the balance room. The analytical laboratory was equipped with instruments like Karl Fischer Titrator, pH meter, Gas Chromatography, Conductivity meter, High Performance Liquid Chromatography, Polarimeter, Analytical balance, NIR spectrophotometer, UV spectrophotometer, Melting point, FTIR, Rotary evaporator distiller. Stability samples storage and Microbiological testing was contracted out to Unit 2. No microbiological specifications were established for the WHO Prequalification APIs.

Analytical method validation

The analytical method validation protocol for the determination of NDMA, NDEA, NDIPA, NEIPA, NDBA (Nitrosamines) content by GC and the Analytical method validation report were reviewed.
Eleven batches of TDF were randomly selected for analysis and no nitrosamine was detected.

OOS Handling

A procedure for handling OOS results was in place. The procedure was applicable to all type of samples. All the OOS results were trended quarterly including the identified root cause. The OOS trending report for the period July to September 2023, 30.10.2023 was discussed. Examples of OOS results handling were checked.

Stability studies

Stability studies were contracted out to Unit 2 in terms of sample storage. Sample analysis took place in Unit 4. The SOP "Stability chamber management and transportation of stability samples" (QC/030, effective date: 27.06.2022) was made available. Samples to be sent out to Unit 2 for stability had to be appropriately packed. A template was used to record the date, product, batch number, number of containers, stability conditions and transport conditions. For temperature sensitive materials (e.g., TDF) a qualified box with cold gel packs was used for the transport of the samples. Upon receipt at Unit 2, the responsible person checked, verified the receipt, and signed the template. Both sites maintained the stability plan. Samples had to be withdrawn up to 3 days after the due date and were sent back to Unit 4 for testing. Testing had to be completed within 15 days.
The stability protocol/report of Lamivudine (SSP/ALMD/VSP4/035/20, 11.2020) for the batches ALMD-2/VSP4/002/20 (MIL), ALMD-2/VSP4/003/20 (MIL) and ALMD-2/VSP4/004/20 (MIL) was reviewed. The batches were placed in accelerated conditions (40ºC/75%) and at 30ºC/75% and 25ºC/60%

Reference and Working Standards

There was a procedure in place describing the storage dispensing and inventory management of Reference and Working Standards. Spot-checks on the qualification and analytical data of the Lamivudine WS were made. Similarly, the Lamivudine WS use log was reviewed.

Retention samples

Retention samples were withdrawn and maintained according to a written procedure. The procedure was applicable to key starting materials, intermediates, and finished APIs. The quantity to be retained was included in the product specifications and was sufficient to perform two rounds of testing. The QC department was responsible for maintaining the inventory of retained samples. For withdrawal of a retention sample QA approval was necessary. The quantity to be used and remaining quantity were registered in a logbook. API and saleable intermediate retention samples were maintained for 1 year after their expiry date. Key raw materials and intermediates for internal use samples were maintained for 1 year after sampling.

Any observations related to this section have been adequately addressed and the implementation of CAPA will be verified at the next inspection

11. Validation

There was a procedure in place describing the principles of establishing the VMP and providing an overview of the validation operations, activities, organizational structure, and planning. QA was responsible for preparing the VMP. The VMP described the validation program into the following phases: preparation and approval of VMP, preparation and pre-approval of the validation protocols, execution of the tests, compilation of data collected during validation-review-and the preparation of the report, recommendations, on-going evaluation review, change control and revalidation. Calibration and preventive maintenance activities of the equipment were managed electronically using a dedicated software. A series of SOPs/schedules describing validation activities in different GMP areas were available and were spot-checked.

Cold room FG warehouse

A procedure for performing temperature mapping studies was in place. It provided details on the number of temperature loggers to be used, the frequency of recording temperatures, datalogger specifications, and duration of the study.

The temperature mapping study protocol and report were reviewed. The study was carried for 72 hours in empty conditions and for 72 hours in loaded conditions. 28 dataloggers were used and hot and cold points were identified. Open door study and recovery were performed as well as power failure study.

Qualification of Reactor SSR710 (MB07)

There was a procedure in place providing instructions on the qualification of equipment. The procedure described the steps for establishing URS, DQ, IQ, OQ and PQ and assigned responsibilities to key personnel and departments. The IQ, OQ, PQ protocols and reports for reactor SSR710 were checked.

HVAC clean area -workshop MB-6A (Lopinavir)

A procedure was in place for the qualification and validation of the HVAC system, LAF, RLAF isolators, biosafety cabinets, dynamic pass box and dust extraction systems.

The HVAC qualification for the clean area of the MB-6A (Lopinavir) was discussed. The area was supplied with filtered air by AHU-604, AHU-605, AHU-606 and AHU-607. The qualification was executed by a contractor and included the following tests:

Particle count test, HEPA filter integrity/filter leakage test, number of air changes/air velocity test, differential pressure test, particle count recovery test, visualization test/air flow pattern test, temperature, and relative humidity.

Cleaning Validation

There was a procedure in place for cleaning validation. Cleaning methodologies were adequately described. Similarly swab, rinse and reflux sampling processes were detailed. When there was a product change over (API to API) then MACO was calculated, and acceptance criteria were set based on HBEL. However, for batch-to-batch changes for the same intermediate or different intermediates the 10 ppm acceptance criteria were set.

Hold time studies

The dirty equipment hold-time study protocol for Tenofovir and the relative dirty equipment hold-time study report were reviewed. The equipment could remain for three days without any cleaning.

The dirty equipment hold-time study protocol for Lamivudine and the relative report were reviewed. The purpose of the study was to establish documented evidence on the hold-time of uncleaned equipment used in the manufacturing process of Lamivudine and also to provide a high degree of assurance and reliability on product degradation. The dirty hold time study was performed for 24h, 48h, 72h and 96h and carried out in Unit 3. A risk assessment was performed relating to the implementation of the study results to MB-07 facility.

Qualification of analytical instruments

The qualification of analytical instruments was carried out according to a written procedure. Analytical equipment/instruments were classified into three categories based on their criticality (Group A, B and C). Examples of HPLC qualifications/calibrations were discussed. The calibration included tests for flow rate accuracy, flow rate precision, gradient performance, system precision, injector accuracy, carry over test, injector linearity, carousel performance, detector linearity, detector sensitivity, wavelength accuracy, sample compartment temperature accuracy, and column oven temperature accuracy.

Any observations related to this section have been adequately addressed and the implementation of CAPA will be verified at the next inspection

12. Change control

A procedure for managing changes was in place. The scope covered all GMP areas affecting product quality including but not limited to materials, facilities, equipment, processes, specifications, analytical methods, and quality documentation. Changes were categorized in major or minor and temporary or permanent. The user was responsible for the initiation of a change. The head of the department/designee was responsible for the initial review, and assessment. The QA department reviewed the change and forwarded to the concerned department. The change was handled through the electronic Quality Assurance Management System (eQAMS) Module. For major changes a risk assessment was mandatory.

Any observations related to this section have been adequately addressed and the implementation of CAPA will be verified at the next inspection

13. Rejection and re-use of materials

There was a procedure in place for reprocessing, reworking and recovery of materials. Definitions for reprocessing, reworking and recovery were included in the procedure.

A batch could only be reprocessed once for the same process step. A different batch number from the original was assigned to a reprocessed batch. The first reprocessed batch for a specific manufacturing step was placed in stability studies.

A batch could be reworked on a case-by-case basis and a protocol would be initiated to define the process steps, testing and stability study and a report would be generated. If more than one batch with the same profile were reworked with the same method, the company would initiate a validation study including placing two batches in stability.

Recovery of solvents and other materials was allowed. Upon recovery they were tested according to established STPs and had to meet predefined specifications. Based on experimental data, recovered solvents could present different specifications from fresh solvents provided they did not affect the process step they were used in. Approved recovered solvents could only be used for the same or previous stages from which they were recovered of the same product, according to the relevant SOP. Recovered solvents originating from other Laurus Units had the same specifications as the ones established at Unit 4 and full testing was performed before use.

Any observations related to this section have been adequately addressed and the implementation of CAPA will be verified at the next inspection

14. Complaints and recalls

There was a procedure in place for handling market complaints. Business Development was usually the recipient of customers' complaints which were forwarded to QA and were documented within one day of receipt. Complaints were categorized into three classes (critical, major, or minor). Risk assessments were carried out for critical complaints while for the other two categories it was on a case-by-case basis. For critical and major complaints investigations were extended to other products/batches depending on the nature of the complaint. Complaints were also logged electronically. The Business Development department was responsible for communicating to the customer the outcome of the investigations and the CAPA, if appropriate. Examples of complaint handling were reviewed.

The procedure for recalls was presented. The QA department was responsible for coordinating the recall operations. The Business Development department was responsible for identifying the quantities distributed and for communicating the recall to customers. The warehouse was responsible for the inventory of the product/batch recalled. Timelines for conducting investigations and for taking the recall decision were established. A mock recall was carried out every 3 years unless a recall was carried out in the previous year.

Any observations related to this section have been adequately addressed and the implementation of CAPA will be verified at the next inspection

15. Contract manufacturers (including laboratories)

An approved vendor list for key starting materials for each intermediate and API was established. The Tenofovir approved vendor list was reviewed.
The Contract Testing Laboratory Quality Agreement between Laurus Unit 4 and Unit 3was also reviewed.

Any observations related to this section have been adequately addressed and the implementation of CAPA will be verified at the next inspection

Part 3	Conclusion – Inspection outcome

Based on the areas inspected, the people met and the documents reviewed, and considering the findings of the inspection, including the observations listed in the Inspection Report, ***Laurus Labs Limited Unit 4***, located at ***Plot No.25, 25A to 25K, APSEZ De-Notified Area, Lalamkoduru Village, Rambilli Mandal Anakapalli, Andhra Pradesh 531011 India*** was considered to be operating at an acceptable level of compliance with WHO GMP Guidelines for APIs.

All the non-compliances observed during the inspection that were listed in the full report as well as those reflected in the WHOPIR, were addressed by the manufacturer, to a satisfactory level, prior to the publication of the WHOPIR

This WHOPIR will remain valid for 3 years, provided that the outcome of any inspection conducted during this period is positive.

Part 4	List of WHO Guidelines referenced in the inspection report

1. WHO good manufacturing practices for pharmaceutical products: main principles. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-eight Report Geneva, World Health Organization, 2014 (WHO Technical Report Series, No. 986), Annex 2.
   Short name: WHO TRS No. 986, Annex 2
   https://www.who.int/publications/m/item/trs986-annex2

2. WHO good manufacturing practices for active pharmaceutical ingredients. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth Report. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957), Annex 2.
   Short name: WHO TRS No. 957, Annex 2
   https://www.who.int/publications/m/item/annex-2-trs-957

3. WHO guidance on good practices for desk assessment of compliance with good manufacturing practices, good laboratory practices and good clinical practices for medical products regulatory decisions. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-second Report. Geneva, World Health Organization, 2018 (WHO Technical Report Series, No. 1010), Annex 9.
   Short name: WHO TRS 1010, Annex 9
   https://www.who.int/publications/m/item/trs1010-annex9

4. WHO Good Manufacturing Practices: water for pharmaceutical use. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-fifth Report. Geneva, World Health Organization, 2021 (WHO Technical Report Series, No. 1033), Annex 3.
   Short name: WHO TRS No. 1033, Annex 3
   https://www.who.int/publications/m/item/annex-3-trs-1033

5. WHO guidelines for sampling of pharmaceutical products and related materials. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-ninth Report. Geneva, World Health Organization, 2005 (WHO Technical Report Series, No. 929), Annex 4.
Short name: WHO TRS No. 929, Annex 4
https://www.who.int/publications/m/item/annex-4-trs-929

6. WHO good practices for pharmaceutical quality control laboratories. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-seventh Report. Geneva, World Health Organization, 2024 (WHO Technical Report Series, No. 1052), Annex 4.
Short name: WHO TRS No. 1052, Annex 4
https://www.who.int/publications/i/item/9789240091030

7. WHO Good Practices for Pharmaceutical Products Containing Hazardous Substances. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth Report. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957), Annex 3.
Short name: WHO TRS No. 957, Annex 3
https://www.who.int/publications/m/item/trs957-annex3

8. Guidelines on heating, ventilation and air-conditioning systems for non-sterile pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty Second Report Geneva, World Health Organization, 2018 (WHO Technical Report Series, No. 1010), Annex 8.
Short name: WHO TRS No. 1010, Annex 8
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