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Prequalification Team Inspection services
WHO PUBLIC INSPECTION REPORT
of the Active Pharmaceutical Ingredient (API) Manufacturer

Part 1	**General information**
Manufacturers Details	
Company information	
Name of manufacturer and address	**Laurus Labs Limited Unit 3** Plot No. 18, Jawaharlal Nehru Pharma City, Parawada, Visakhapatnam- 531021 Andhra Pradesh, India Tel: +91 891 668 2500 Fax: +91 891 668 2501 E-mail: info@lauruslabs.com Latitude N 17° 39' 42.7176" Longitude E 83° 5' 33.36'' DUNS No: 65-075-1774 **Laurus Labs Limited Unit 1** Plot No. 21, Jawaharlal Nehru Pharma City, Parawada, Visakhapatnam-531021, Andhra Pradesh, India. Tel: +91 891 306 1222 & +91 891 306 1441 Fax: +91 891 306 1270 E-mail: info@lauruslabs.com Latitude N 17° 42' 00.04" Longitude E 83° 15' 00.01' DUNS No : 91-507-5687

Corporate address of manufacturer	2nd Floor, Serene Chambers, Road No.: 7, Banjara Hills, Hyderabad-500034, Telangana, India. Tel: +91 40 2342 0500 & +91 40 2342 0501, Fax: +91 40 3980 4320 Website: www.lauruslabs.com
Inspected site	
Address of inspected manufacturing site if different from that given above	As above
Manufacturing license number	**Unit 3** License number: 27/VP/AP/2014/B/CC Type of licence: Form-25 (Manufacturing license for sale or distribution of drugs) **Unit 1** License number: 05/VP/AP/2008/B/CC Type of license: Form-25 (Manufacturing license for sale or distribution of drugs)
Inspection details	
Dates of inspection	4 – 7 September 2017
Type of inspection	Routine inspection
Introduction	
Brief summary of the manufacturing activities	The manufacturer was involved in the manufacturing, packaging, labeling, testing and storage of the APIs at these two sites. .
General information about the company and site	Laurus Labs is a research-driven and customer-focussed pharmaceutical services organization head-quartered in Hyderabad, India offering a broad and integrated portfolio of research and manufacturing services spanning the entire drug development continuum to the global pharmaceutical Industry. Laurus Labs has a unique combination of the highest quality standards, cost effectiveness and has a strong focus on intellectual property management. The firm offers medicinal chemistry services, Drug Product Development & Manufacturing, Discovery Research, Analytical services, Process technologies for drug substances and Drug substance manufacturing. Laurus Labs Research & Development centre is located at Plot No: DS1, IKP Knowledge Park, Shameerpet, Turkapally, Hyderabad-500078, Rangareddy (Dt.), Telangana, India. The R&D center comprises of process chemistry labs, Analytical Laboratories with state of the art equipment/ instruments and Formulation Development Laboratories and a small scale cGMP drug product manufacturing facility for solid oral

dosage forms. In addition to this, a well-equipped Kilo lab facility is located in the same premises to take up scale up from laboratory scale to pilot- scale under cGMP conditions.

One of the Laurus Labs Limited drug substance manufacturing facility (Unit-3) is situated at Plot No: 18, Jawaharlal Nehru Pharma City, Parawada, Visakhapatnam-531021, Andhra Pradesh, India. Vishakhapatnam is a city situated in south east coastal area of India. This facility has been designed and constructed to comply with the current regulatory guidelines. This facility commenced operations in the last quarter of 2014. This site is engaged in the manufacturing of Drug Intermediates, Dietary ingredients and Active Pharmaceutical Ingredients (APIs).

Unit 3 is licensed to manufacture wide range of APIs and Intermediates to cater to various therapeutic segments. The products manufactured are licensed by Local Drug Control Authorities. No Penicillin, beta lactam antibiotics, pesticides or insecticides are manufactured at this site.

Unit 1 is located at Plot No: 21, Jawaharlal Nehru Pharma City, Parwarda, Visakhapatam-531021, Andhra Pradesh, India. This unit is licensed to manufacture wide range of APIs and Intermediates to cater to various therapeutic segments. The products manufactured are licensed by Local Drug Control Authorities.
Oncology and non-oncology drugs substances are manufactured at this site in dedicated blocks. There are separate manufacturing facilities for oncology and non-oncology API manufacturing. No Penicillin, beta lactam antibiotics, pesticides or insecticides are manufactured at this site.

History

The site was inspected by WHO in April 2015.

The **Unit 1** was inspected by the following authorities:

Authority	**Scope of Inspection**	**Dates of Inspection**
USFDA	Initial Inspection	26-29 October 2009
	cGMP Inspection	19-27 November 2012
		20-24 April 2015
		14-18 August 2017
WHO	Initial Inspection	18-21 July 2011
	cGMP Inspection	09-12 April 2013
WHO & NIP - Hungary	cGMP Inspection	25-28 August 2014
WHO & NIP - Hungary	cGMP Inspection	13-15 April 2015

<table>
<tr><td></td><td>The Unit 3 was inspected by the following authorities:

<table>
<tr><th>Authority</th><th>Scope of inspection</th><th>Dates of Inspection</th></tr>
<tr><td rowspan="2">USFDA</td><td>Initial Inspection</td><td>20-24 April 2015</td></tr>
<tr><td>cGMP Inspection</td><td>14-18 August 2017</td></tr>
<tr><td>WHO & NIP - Hungary</td><td>Initial Inspection</td><td>13-17 April 2015</td></tr>
</table></td></tr>
<tr><td>Brief report of inspection activities undertaken</td><td></td></tr>
<tr><td>Scope and limitations</td><td></td></tr>
<tr><td>Areas inspected</td><td>• Pharmaceutical Quality System
• Documentation system
• Production System
• Facilities and Equipment System
• Laboratory Control System
• Packaging/labelling system</td></tr>
<tr><td>Restrictions</td><td>N/A</td></tr>
<tr><td>WHO product numbers covered by the inspection</td><td>• APIMF 090 Efavirenz (Unit 1)
• APIMF 141 Nevirapine anhydrous (Unit 1)
• APIMF 152 Lamivudine anhydrous (Unit 1&3)
• APIMF 193 Abacavir hemisulfate (Unit 1)
• APIMF 139 Emtricitabine (Unit 1&3)
• APIMF 195 Tenofovir disoproxil fumarate (Unit 1&3)
• APIMF 319 Sofosbuvir (Unit 1) - under assessment
• APIMF 325 Dolutegravir Sodium (Unit 1) - under assessment
• APIMF 335 Daclatasvir Dihydrochloride (Unit 1) - under assessment</td></tr>
<tr><td>Abbreviations</td><td>
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<tr><td>AHU</td><td>air handling unit</td></tr>
<tr><td>ALCOA</td><td>attributable, legible, contemporaneous, original and accurate</td></tr>
<tr><td>AQL</td><td>Acceptance quality limit</td></tr>
<tr><td>API</td><td>active pharmaceutical ingredient</td></tr>
<tr><td>APQR</td><td>annual product quality review</td></tr>
<tr><td>BDL</td><td>below detection limit</td></tr>
<tr><td>BMR</td><td>batch manufacturing record</td></tr>
<tr><td>BPR</td><td>batch packaging record</td></tr>
<tr><td>CAPA</td><td>corrective actions and preventive actions</td></tr>
<tr><td>CC</td><td>change control</td></tr>
<tr><td>CFU</td><td>colony-forming unit</td></tr>
<tr><td>CoA</td><td>certificate of analysis</td></tr>
</table></td></tr>
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CpK	process capability index
DQ	design qualification
EM	environmental monitoring
FAT	factory acceptance test
FBD	fluid bed dryer
FG	finished goods
FMEA	failure modes and effects analysis
FPP	finished pharmaceutical product
FTA	fault tree analysis
FTIR	Fourier transform infrared spectrometer
GC	gas chromatograph
GMP	good manufacturing practice
HACCP	hazard analysis and critical control points
HPLC	high-performance liquid chromatograph
HVAC	heating, ventilation and air conditioning
ID	identity
IR	infrared spectrophotometer
IPC	In process control
IQ	installation qualification
KF	Karl Fisher
LAF	laminar air flow
LIMS	laboratory information management system
LoD	limit of detection
LOD	loss on drying
MB	Microbiology
MBL	microbiology laboratory
MF	master formulae
MR	management review
NIR	near-infrared spectroscopy
NMR	nuclear magnetic resonance spectroscopy
NRA	national regulatory agency
OQ	operational qualification
PHA	preliminary hazard analysis
PM	preventive maintenance
PpK	process performance index
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
RH	relative humidity
RM	raw materials
RS	reference standard
SAP	system applications products for data processing
SFG	semi-finished goods
SOP	standard operating procedure
STP	standard test procedure
T	Temperature
TAMC	total aerobic microbial count
TFC	total fungal count
TLC	thin layer chromatography
TMC	total microbial count
TOC	Total organic carbon
URS	user requirements specifications
UV	ultraviolet-visible spectrophotometer
VMP	Validation Master Plan
WFI	water for injection
WS	working standard

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

Brief summary of the findings and comments

1. Pharmaceutical Quality System

In general the system for managing quality encompassed the organizational structure, procedures and processes. There were QA and QC departments that were independent of production. In general deviations from established procedures were documented and explained. Procedure was in place for notifying responsible management of regulatory inspections, serious cGMP deficiencies, product defects and related actions.

The traceability of records and documentation system were satisfactory.

Product Quality Review (PQR)

The SOP "Preparation of product quality review" was discussed. The PQR covered but was not limited to:

- Number of batches manufactured
- Key starting materials (KSM) yield and material balance for intermediates and finished product
- In-process controls and quality data
- Critical process parameters and data
- Quality of intermediate
- Quality of API
- Yield details

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- Deviations, change controls, rejected materials
- Complaints
- Recalls, reprocessed and reworked batches
- Returned batches
- Environmental monitoring (EM) trend analysis in clean rooms
- Nitrogen system, purified water system, HVAC system
- CAPAs
- Stability and trends
- Vendors change summary
- OOS/OOT
- Intermediates
- Purified water (PW)
- Validation summary

PQR was performed annually and according to the SOP should be completed by the end of March of the following year or on rolling basis

Process capability was evaluated by ± 3 sigma.

PQR of Emtricitabine, for year 2015 and year 2016 and PQR for Daclatasvir Dihydrochloride for year 2016, were discussed.

Quality risk management (QRM)

The SOP "Procedure for quality risk management" and register were discussed. The SOP was applicable for:

- New product
- Major changes in existing process
- Change in KSM
- Change in excipient
- Major changes to facilities, utilities, equipment and process
- Customer and regulatory audit compliance responses
- Environmental monitoring (EM) trends and purified water (PW) trends
- Introduction of new equipment or system
- Stability and retest period assignment
- Packaging and labelling
- Intermediates/drug substances/drug product manufactures under customer projects

Tool specified in the SOP for RA was:
- Failure modes and effects analysis (FMEA)

The SOP "Failure modes and effects analysis" and SOP "Hazard analysis and critical control points" were discussed. Scoring from 1 to 5 was used for RPN calculations.

RAs for manufacturing of Emtricitabine API and for collection of purified water from PW3 sampling point XX were discussed.

Deviations
The SOP "Deviation handling procedure" its flow chart and register were discussed. SOP was applicable to planned and unplanned deviations. Unplanned deviations were classified as:
- Critical
- Non-critical

Deviations were reviewed, approved and closed by QA. QA also performed CAPA effectiveness evaluation and implementation. Deviation number and short explanation of deviation was recorded in related batch processing record.

According to the SOP deviations should be closed within 30 working days.

A number of deviations related to the Daclatasvir Dihydrochloride were discussed.

Root cause analysis (RCA)
The SOP "Procedure for investigation to identify the root cause of the failures" was discussed. The SOP was applicable to all kind of failures initiating through deviations, OOS, complaints and rejections. According to the SOP Ishikawa diagram was used for RCA. RCA related to the unplanned deviation XX was discussed.

Corrective actions and preventive actions (CAPA)
The SOP "Corrective and preventive actions" and register were discussed. The SOP was applicable but not limited to:
- Deviations
- Change controls
- OOS
- Rejects
- Complaints
- Self-inspection/external inspection

According to the SOP, CAPAs were proposed by concerned departments and evaluated by QA.

CAPA related to the unplanned deviation XX was discussed.

Change control (CC)

The SOP "Procedure for change control system" its flow chart and register were discussed. CCs were classified by QA department as:

- Minor
- Major

It was discussed with the company that classification should be included in the register to facilitate easy review of CC

Changes were initiated by concerned departments and approved by Unit QA. The SOP was applicable for cGMP and development related activities.

A number of minor CC related to the Daclatasvir Dihydrochloride were discussed:

Management review (MR)

The SOP "Management review" was discussed. Management review was performed twice per year for well-established units and Quarterly basis (four times /year) for new units. According to the SOP the following items should be covered by MR:

- Follow-up actions from previous MR meeting
- Major changes
- Deviations
- OOS
- Internal audits/customer audits
- Recalls
- Status of CAPAs
- Progress on infrastructural plans
- Learning points from annual product reviews
- Review of process performance
- Measurable quality objectives
- Recommendation for improvements

Last Unit I MR was discussed.

Self-inspection

The SOP "Internal audits (Self-inspection)" was discussed. Self-inspections were performed by cross functional team, every four months. Internal audit schedule and internal audit log for 2017 were presented to the inspectors.

Self-inspection team members' qualification files were available.

Audits were performed following departments wise check lists. Observations were recorded. CAPAs were submitted by the audited department and evaluated by QA. Follow-up was performed by QA.

Complaints

The SOP "Procedure for handling of customer complaints" and register for 2016 (Unit 1 and Unit 3) were discussed. Complaints were classified by head QA based on risk assessment as:

- Critical
- Major
- Minor

Complaints were trended annually.

A number of complaint investigation records were discussed.

Recalls

The SOP "Recall procedure for drug substance/drug intermediate" and its flow chart were discussed. There were no product recalls in Company history. Three types of recalls were specified in the SOP:

- Voluntary recall
- Forced recall
- Mock recall

Last mock recall was initiated for three overseas customers and three domestic customers.

Supplier qualification

The SOP "Identification, qualification and requalification of vendors" and its flow chart were discussed. The SOP was applicable for key starting materials (KSM), all raw, packaging materials vendors and catalysts vendors. KSM and primary packaging materials vendor's requalification audits were performed every 3 years.

Approved suppliers list was presented to the inspectors. Approved suppliers list was reviewed every three months. Vendor audit schedule for 2017 was presented to inspectors; spot checks showed that schedule was followed.

Supplier of KSM for Emtricitabine and Abacavir and supplier of KSMs for Sofosbuvir audit reports were discussed.

Validation Master Plan (VMP)

The SOP "Procedure for preparation of validation master plan" and VMP for Unit 3 were discussed. The VMP was applicable for:

- Validation of process/equipment/system
- Process validation
- Cleaning process validation
- Equipment/system qualification and validation

According to the VMP if there were no changes process re-validation should be performed every 4 years.

The following documents for Empower 3 software retrospective validation were discussed:

- URS
- IQ
- PQ

The draft data integrity policy document was discussed.

Contracts

The company had contracted out some intermediates manufacturing activities, however all manufacturing activities related to the PQ products and products under WHO assessment were carried out on site.

The SOP "Vendor appraisal for contract testing laboratory" and list of approved contract testing laboratories were discussed. Contract testing laboratories were requalified every 3 years.
Quality agreement for contract testing with XX labs, used for elemental analysis was discussed.

Personnel

The current organization chart of the company was available. The company had sufficient number of personnel with responsibilities according to their respective unit and department.

Both units employed and number of contract workers.

Personnel were wearing clothing suitable for the manufacturing activities.

Training

The SOP "Employee training" and its flow charts were discussed. The following types of training were described:

- Induction
- cGMP/GLP/data integrity general training programs
- Job specific – on job training
- Training on changed systems/procedures
- Unscheduled training

The SOP "Contract workmen training" was discussed. Mr XX training evaluation form for the SOPs "Cleaning of dispensing areas", "Cleaning of manufacturing areas" and ¨do and don't" was checked.

The SOP "Procedure for evaluation of analytical/microbiology lab personnel" was discussed. The following training modules were specified:

- Basic tests (common for all analysts)
- Tests for wet chemistry analysts
- Test for solid state analysts
- Tests for HPLC analysts
- Tests for GC & GC-HS analysts
- Test for Microbiologists
- Tests for dissolution analysts

Analysts were requalified every 3 years. Mr XX, HPLC analyst, initial qualification reports were checked.

The following training modules were checked:

- Data integrity
- cGMP
- General guidelines for contract workmen (English and local language)
- Training programme of contract workmen on manufacturing activities under supervision of manufacturing personnel (English and local language)

The SOP "Procedure for medical check-up of employees" was discussed. According to the SOP all personnel working in the company shall undergo medical examination annually.

2. Documentation system

Documents related to the manufacture of intermediates and APIs were prepared, reviewed, approved and distributed according to written procedures.

Production, control and distribution records were retained for one year after the expiry date of the batch. Validation documents, PQRs, SMFs, VMPs, stability reports, process development reports, transfer of technology documents, DMFs, vendor qualification documents, instrument/equipment qualification documents and SOPs were retained forever. Specifications were established for raw materials, intermediates and APIs. The issuance, revision, superseding and withdrawal of documents were controlled with maintenance of revision histories. The Company had a policy to retain registers and logbooks for six years.

The following documents were discussed:

- SOP "Retention and destruction of documents"
- SOP "Procedure for batch release" – BPCRs were reviewed by QA, analytical reports and calculations were reviewed by QCL review team and final review was done by QA. Certificate of Analysis (CoA) was reviewed by QCL and approved by QA
- SOP "General instructions to reviewers and procedure for equalisation of reviewers of analytical laboratory"
- SOP "Procedure blending process validation/blending homogeneity" and
- SOP "Procedure for reprocess, rework and recovered material usage policy"
- SOP "Handling and usage of recovered solvent and recovered raw material". According to the SOP recovered solvents can be used in the same stage of the same product or in earlier stages of the same product
- SOP "Operation of dryers"
- SOP " In process sampling"
- SOP "Procedure on breakdown maintenance"
- SOP "Preventive maintenance of reactors"
- SOP "Procedure for cleaning of sampling and dispensing tools"
- Quality technical agreement with XX (contractor for solvent recovery)
- SOP Procedure for handling of returned goods" and returned goods register
- SOP "Procedure for batch numbering system"
- SOP "Procedure for issuance and retrieved of batch production control record and cleaning record" and register. BPCRs and cleaning records were issued and controlled by QA. Starting from 2017 these documents were issued and controlled by DIMS software
- SOP "Procedure for document archival, retrieval and assigning file numbering system"
- SOP Cleaning validation was reviewed and discussed. Four types of different cleanings are carried out on equipment
- Preventive maintenance record and general cleaning done after maintenance of stainless steel reactor XX was checked.

If there were no changes, documents review period was three years. Documents were stored in QA archive and QC archive in mobile compactors.

3. Production system

In general, production operations followed defined procedures. Process flows (with IPCs) and routes of synthesis were available. Deviations from procedures were recorded; major deviations were investigated. Access to production premises was restricted to authorized personnel. Weighing and measuring devices were of suitable accuracy for the intended use. The processing status of major units of equipment was indicated.

A number of batch production records were reviewed and the process steps compared with the process described in the last version of the APIMF submitted to WHO. No discrepancies were identified between the process described in the APIMF and assessed by WHO and the actual process.

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A number of reprocessing BPRs were also reviewed.

4. Facilities and equipment system

Buildings and facilities used in the manufacture of intermediates and APIs were located, designed, and constructed to facilitate cleaning, maintenance and operations as appropriate to the type and stage of manufacture. Facilities were designed to minimize potential contamination. Adequate space was provided for orderly placement of equipment and materials to prevent mix-ups and contamination. Generally the permanently installed pipework was appropriately identified.

Chemical and instrumental laboratories were designed to suit the operations to be carried out. Sufficient space was given to avoid mix ups and cross- contamination. Adequate suitable storagespace was provided for storage of samples, reference standards, solvents, reagents and records.

QCL premises were separated from manufacturing facilities. Stability chambers were located at Unit 1, microbiological laboratory was located at Unit 3.

Utilities

Purified water (PW)

There were five (5) PW systems installed in Unit 1, supplying purified water to production blocks via seven (7) loops. There were one (1) PW systems installed in Unit 3 , supplying water to production blocks via four (4) loops. Samples from return loops were collected and analysed daily, from other sampling points monthly on rotational basis. Total aerobic microbial count trends for all loops for 2016 were checked. PW storage tanks and loops were sanitized every 15 days using hot water 80 °C – 85 °C for 45 minutes.

For Unit-3 PW system loop No XX qualification the following documents were checked:

- URS
- DQ
- IQ
- OQ
- PQ

The SOP “Procedure for monitoring of quality parameters of purified water system” was discussed. PW trends were reviewed monthly and annually. Action and alert limits were specified.

HVAC system

Re-circulated air was supplied to clean rooms. As an example: Unit-3 , MBI, Module 2 AHU No 101 was discussed. Filter cascade was following G4 → F5 → F9. Terminal HEPA filters H13 were installed in the rooms. G4, F5 and F9 filters were cleaned weekly. Pressure differentials between G4, F5 and F9 filters were checked daily. HEPA filters integrity tests were contracted out and performed annually.

Environmental monitoring (EM)
The SOP "Environmental monitoring of clean rooms/areas" was discussed. Clean rooms EM was done quarterly – settle plates and active air sampling. Alert and action limits were established.

EM trends for 2016 for WS XX clean rooms were discussed Action and alert limits were set up.

Nitrogen
Nitrogen was used for some finished API purging during packaging operations. N_2 was generated on sites from air. N_2 quality was checked annually by contracted laboratory. N_2 tests certificate from XX was checked. N_2 concentration was 99.8 %, oxygen concentration was 0.2%. N_2 was filtered via 1 micron and 0.1 micron filters. At the user points N_2 was filtered via 0.5 micron filter.

5. Laboratory control system

Laboratory areas were separated from production areas. Laboratory was operating on 3 shifts continuously. There were two teams in the lab:

- IPC/intermediates team
- Finished API and stability team

In both Units (1 and 3) all HPLCs and GCs were connected to the Empower 3 software. IRs and UVs were stand-alone instruments. Audit trails were activated for stand-alone instruments.

The SOP "Procedure for creating projects, privileges of users and system policies in empower" was discussed.

The SOP "Procedure for back-up, archival, restoration and disaster recovery of Empower data" was discussed. Hot back-up was performed daily and cold weekly automatically to the Empower server; project back-up was performed monthly on tapes. Disaster server was located at the corporate office in Hyderabad. Back-up tapes were stored in two different locations. Monthly projects back-ups log book for 2017 was presented to the inspectors.

The SOP "Data backup and restoration from standalone computers connected to analytical instruments" was discussed. Daily back-up was automatically performed to the stand alone server. Tapes were used for weekly back up; tapes were stored in two different locations. Data backup log book for stand-alone instruments for 2017 was presented to the inspectors.

The SOP "Sampling procedure for raw materials, packaging materials, intermediates, recovery solvents, APIs and handling of in-process samples and Process Development lab samples" was discussed. Sampling plan $\sqrt{n+1}$ was applied for raw materials sampling. NIR was used for 100 % identity tests of raw materials. Samples from intermediates and APIs were taken from each container.

The SOP "Procedure for handling of out of specification" and its flow chart were discussed. This version of the SOP was effective from 01/06/2017 and was written following MHRA guideline. OOS register was presented to the inspectors. OOS were trended and graphical presentations of trends for 2016 and 2017 (Jan –Aug) were checked.

A number of OOS investigation reports were discussed

The SOP "Qualification, handling and storage of standards" was discussed. Working standards were qualified against pharmacopoeia standards. In case pharmacopoeia reference standard had been changed, WS was verified against the new lot of RS. Standards were store in refrigerator. Temperature was recorded every hour, printouts were reviewed daily. Refrigerator was equipped with audible alarm system and connected to the UPS.

The SOP "General stability program" and stability schedule were discussed. One batch per year was placed for on-going stability studies. Spot cross checks showed that stability schedule was followed.

The SOP "Procedure for integrating chromatographic peaks using Empower software" was discussed. Manual integration (MI) was allowed only for impurities, related substances and residual solvents. MI should be approved by head of QC, following SOP on incidents. The SOP QC/042, version 00 "Procedure for handling of quality control incidents" and incidents log for 2017 were discussed.

The SOP "Procedure for reserve/retention samples management for drug substances, intermediates and KSMs" was discussed. Retention period of APIs was specified expiry date plus one year.

Specimen signature log was presented to the inspectors.

During laboratory inspection as an example Tenofovir disoproxil fumarate analytical raw data was cross checked with instrument log books.

Analytical balances were verified, daily using 3 standard weights and calibrated quarterly.

A number of contract laboratories were used.

6. Packaging/labelling system

Packaging / labelling operations were not seen during inspection.

The SOP was discussed. According to the SOP APIs were packed in double PE bags. Two identical labels were placed on the outer PE bag and LDPE container.

The SOP "Procedure for operation and printing of labels" was discussed. Product labels were printed in QA, using dedicated two computers and two printers. Labels were printed using commercial software. Access to these computers/printers was by using software key only.

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PART 3
CONCLUSION

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, as well as corrective actions taken:

- APIMF 090 Efavirenz (Unit 1)
- APIMF 141 Nevirapine anhydrous (Unit 1)
- APIMF 152 Lamivudine anhydrous (Unit 1&3)
- APIMF 193 Abacavir hemisulfate (Unit 1)
- APIMF 139 Emtricitabine (Unit 1&3)
- APIMF 195 Tenofovir disoproxil fumarate (Unit 1&3)
- APIMF 319 Sofosbuvir (Unit 1)
- APIMF 325 Dolutegravir Sodium (Unit 1)
- APIMF 335 Daclatasvir Dihydrochloride (Unit 1)

Manufactured at Laurus Labs Limited Unit 1, located at Plot No. 21, Jawaharlal Nehru Pharma City, Parawada, Visakhapatnam-531021 Andhra Pradesh, India and Unit 3, located at Plot No. 18, Jawaharlal Nehru Pharma City, Parawada, Visakhapatnam - 531021 Andhra Pradesh, India, was considered to be manufactured in compliance with applicable sections of WHO cGMP for Active Pharmaceutical Ingredients.

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 GMP guidelines used for assessing compliance

1. 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
   http://www.who.int/medicines/publications/44threport/en/

2. 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.
   http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_986/en/
   Short name: WHO TRS No. 986, Annex 2

3. WHO good manufacturing practices for sterile pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 6
   Short name: WHO TRS No. 961, Annex 6
   http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

4. WHO Good Manufacturing Practices: water for pharmaceutical use. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fourth-six Report. Geneva, World Health Organization, 2012 (WHO Technical Report Series, No. 970), Annex 2
   Short name: WHO TRS No. 970, Annex 2
   http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_970/en/

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
   http://whqlibdoc.who.int/trs/WHO_TRS_929_eng.pdf?ua=1

6. WHO guidelines on good manufacturing practices for heating, ventilation and air-conditioning systems for non-sterile pharmaceutical dosage forms. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 5
   Short name: WHO TRS No. 961, Annex 5
   http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

7. Supplementary guidelines on good manufacturing practices: validation. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fortieth Report. Geneva, World Health Organization, 2006 (WHO Technical Report Series, No. 937), Annex 4
   Short name: WHO TRS No. 937, Annex 4
   http://whqlibdoc.who.int/trs/WHO_TRS_937_eng.pdf?ua=1

8. WHO Good Practices for Pharmaceutical Control Laboratories. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth Report. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957, Annex 1
   Short name: WHO TRS No. 957, Annex 1
   http://www.who.int/medicines/publications/44threport/en/

9. 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 2
   Short name: WHO TRS No. 957, Annex 3
   http://www.who.int/medicines/publications/44threport/en/

10. WHO guidelines on transfer of technology in pharmaceutical manufacturing WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 7
    Short name: WHO TRS No. 961, Annex 7
    http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

11. Model guidance for the storage and transport of time-and temperature-sensitive pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 9
    ***Short name: WHO TRS No. 961, Annex* 9**
    http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

12. General guidelines for the establishment maintenance and distribution of chemical reference substances. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-First Report Geneva, World Health Organization 2007 (WHO Technical Report Series, No.943) Annex 3
    Short name: WHO TRS No. 943, Annex 3
    http://whqlibdoc.who.int/trs/WHO_TRS_943_eng.pdf?ua=1

13. WHO good practices for pharmaceutical microbiology laboratories. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 2
    Short name: WHO TRS No. 961, Annex 2
    http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

14. WHO guidelines on quality risk management. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Seventh Report Geneva, World Health Organization, 2013 (WHO Technical Report Series, No. 981), Annex 2
Short name: WHO TRS No. 981, Annex 2
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_981/en/

15. WHO guidelines on variation to a prequalified product. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Seventh Report Geneva, World Health Organization, 2013 (WHO Technical Report Series, No. 981), Annex 3
Short name: WHO TRS No. 981, Annex 3
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_981/en/

16. WHO guidelines for drafting a site master file. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 14
Short name: WHO TRS No. 961, Annex 14
http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

17. WHO Guidelines on good manufacturing practices: validation, Appendix 7: non-sterile process validation. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Ninth Report Geneva, World Health Organization, 2015 (WHO Technical Report Series, No. 992), Annex 3
Short name: WHO TRS No. 992, Annex 3
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf

18. WHO General guidance on hold-time studies WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Ninth Report Geneva, World Health Organization, 2015 (WHO Technical Report Series, No. 992), Annex 4
Short name: WHO TRS No. 992, Annex 4
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf

19. WHO Technical supplements to Model Guidance for storage and transport of time – and temperature – sensitive pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Ninth Report Geneva, World Health Organization, 2015 (WHO Technical Report Series, No. 992), Annex 5
Short name: WHO TRS No. 992, Annex 5
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf

20. WHO Recommendations for quality requirements when plant – derived artemisin is used as a starting material in the prosecution of antimalarial active pharmaceutical ingredients. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Ninth Report Geneva, World Health Organization, 2015 (WHO Technical Report Series, No. 992), Annex 6
Short name: WHO TRS No. 992, Annex 6
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf

21. WHO good manufacturing practices for biological products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifties Report Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 3
Short name: WHO TRS No. 996, Annex 3
http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex03.pdf

22. Guidance on good data and record management practices. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifties Report Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 5
Short name: WHO TRS No. 996, Annex 5
http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex05.pdf

23. WHO general guidance on variations to multisource pharmaceutical products. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifties Report* Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 10
Short name: WHO TRS No. 996, Annex 10
http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex10.pdf