

**Prequalification Team  
WHO PUBLIC INSPECTION REPORT  
(WHOPIR)  
Active Pharmaceutical Ingredient (API) Manufacturer**

**PART 1: GENERAL INFORMATION**

Name of Manufacturer	SYMED LABS LIMITED
Unit	Unit 1
Production blocks	Production Block-A /Clean Room-II
Physical address	Survey No.353, Domadugu, Jinnaram, Medak, Telangana, India-502 313
Postal address	Same as above
GPS	17° 39' 38.26"N, 78° 22' 11.19" E
DUNS	65-053-0301
Date of inspection	19 – 21 October 2015
Type of inspection	Routine GMP inspection (new site)
Active Pharmaceutical Ingredient included in the inspection	Linezolid API
Summary of the activities performed by the manufacturer	Production and quality control of non-sterile intermediates and finished non-sterile APIs. No toxic or hazardous substances were handled or manufactured at the site

***General information about the company and site***

Symed Labs Limited was established in 1998 and it is involved in the manufacture and marketing of intermediates and active pharmaceutical ingredients (APIs). Symed Labs Limited is located at Survey No.353, Domadugu, Jinnaram , Medak, Telangana, approximately 70 kilometres from Hyderabad city. The corporate office of Symed Labs is located at: 8-2-293/174/3, Beside BN Reddy Colony, Road No. 14, Banjara Hills, Hyderabad – 500 034 Telangana, INDIA.

Symed Labs Limited has six (6) Units, located at:

- Unit I - Survey No.353, Domadugu (Village), Jinnaram (Mandal), Medak (Dist) – 502 313. Telangana, India – inspected unit;
- Unit II - Plot-25/B, Phase –III, I.D.A - Jeedimetla, Hyderabad-500055, Telangana, INDIA;
- Unit III - Plot. No: 19&20, Phase-I, I.D.A, Jeedimetla, Hyderabad-500055, Telangana, INDIA;
- Unit IV - Survey.No 163 & 163/A,164/A, Pittampally (Village), Chityal (Mandal), Nalgonda (District)-508114, Telangana, INDIA;
- Unit V Symed research centre - PlotNo-89/A, Phase- I, I.D.A, Jeedimetla, Hyderabad-500055, Telangana, INDIA;
- Unit VI - Survey No: 750, Valigonda Road, Mandollagudem, Chinnakondur (Village), Chowtuppall (Mandal), Nalgonda (District) - 508252,Telangana, INDIA

The inspected Symed Labs Unit I has two production blocs:

- Block A
- Block B

The separate “Clean room” building had five clean rooms and it was commissioned in June 2013.

Linezolid (form II) API manufacturing operations were carried out in Unit I, block A and clean room II.

The number of persons working at Symed Labs was about 126 (including 20 contract workers), of which 42 were involved in production, 18 in quality assurance (QA) and 24 in quality control (QC).

***History of WHO and/or regulatory agency inspections***

The site was not previously inspected by a WHO Prequalification team.

- The site was inspected by US Food and Drugs Administration on 1 – 5 June 2015. Establishment report was sent to the company on 11 September, 2015.
- The site was inspected by INFARMED, Portugal on 12 – 16 October 2015.

### ***Focus of the inspection***

The Inspection focused on the production and quality control operations related to linezolid API.

### ***Inspected Areas***

- Quality Management
- Personnel
- Buildings and facilities
- Process equipment
- Documentation and records
- Materials management
- Production and in-process controls
- Storage and distribution
- Laboratory controls
- Validation
- Change control
- Rejection and reuse of materials
- Complaints and recalls
- Contract manufacturers (including laboratories)

## **PART 3: INSPECTION OUTCOME**

### **3.1 QUALITY MANAGEMENT (QM)**

#### Principles

In general, a system for managing quality was established, documented and implemented. The quality unit was independent of the production department. The person responsible for release of intermediates and APIs was specified. Systems for handling any deviations from established procedures were in place and documented. Materials were released by the quality unit after satisfactory evaluation.

#### Management review (MR)

The SOP “Management review” was checked. The management review group consisted of the following members:

- Managing director (or) representative
- Directors
- Vice presidents
- Managers (all departments)
- Management representative

The following items were discussed during MR meetings:

- Customer feedback
- Customer complaints
- Review of quality policy and objectives
- Process performance, out of specifications (OOS), out of trends (OOT) and deviations

- Status of corrective actions & preventive actions (CAPAs)
- Recommendations for improvement
- Regulatory filings / queries
- Safety health & environment
- Audits by customers /authorities, observations and responses of the company
- Marketing forecasts
- Measurable quality objectives
- Training
- Internal audits reports, non-conformities (NC), responses to NCs and CAPAs
- Details of in house quality control checks
- Updates / amendments to QS

The MR was carried out every three months; meetings summary was prepared as “Minutes”. The last MR meeting was held on 18 July 2015. MR meeting minutes were spot checked.

#### Internal audits (self-inspection)

The SOP “Internal audits” was checked.

The training requirements of internal auditors were defined. The internal audit team leader was a person from the QA department. According to the SOP audit should be performed by a team consisting of personnel from cross-functional areas.

A list of internal auditors was presented to the inspectors. The internal audit team consisted of persons from:

- Quality assurance (QA)
- Quality control (QC)
- Production
- Maintenance

Audits covered the following departments:

- Warehouse
- Production
- QC
- Maintenance
- QA
- Safety health & environment
- Microbiology
- Marketing
- Purchase
- Management representative

Audits were carried out once in three months for warehouse, production, QC, maintenance, microbiology, QA and safety health & environment departments and once in a year for marketing, purchase and management representative.

Internal audits were performed according to the department wise check lists. After the audit, report was written and the deficiencies, observed during the inspections, were listed. Non-conformities were classified as:

- Critical
- Major
- Minor

Root cause analysis and CAPAs proposed by the audited department were evaluated by QA. Audit findings and corrective actions were documented and reported to management.

According to the SOP “Training” internal auditors must undergo 16 hours training by external agency / head of the quality management / senior employee of the company who has undergone external training on internal audits. After training, auditor shall participate in two or three internal audits along with a team. Based on the performance and feedback from the other auditors final conclusion shall be drawn on the qualification of the internal auditor. Internal auditors shall be re-qualified every year. Cice president manufacturing, training certificate “Practical auditing of quality management systems as per ISO 9001:2008 and 19011:2002/2011 was presented to the inspectors. Training was carried out for 5 days.

The internal audit schedule for 2015 was presented to the inspectors.

#### Product quality review (APQR)

The SOP “Annual Review” was reviewed. The time limit for the completion of APQR was set for the first week of February in the subsequent calendar year.

As per the SOP APQRs contained: number of batches manufactured in the respective calendar year, quantities of intermediates and finished products, finished product dispatch review, critical process parameter review, yield, quality trends of intermediates and finished products, trend analysis, validation status, key starting material quality trend, review of rejected materials, retained samples, changes, out of specification (OOS) results, deviations, reprocessing, Status of Drug Master File (DMF), and training.

APQR for linezolid (form II) APQR - 2014 was reviewed.

For each stage the process capability index (cpk) was calculated and evaluated against the acceptance criteria of NLT 1.0. At stages where cpk was less than 1.0, close monitoring of the parameters was recommended. The control of critical parameters has been decided based on development report and process validation.

#### Quality Risk Management (QRM)

The SOP “Quality Risk Management” was checked.

The SOP was applicable to system, design, process and / or services. Scope of the SOP covered the following:

- Major changes to process / system / equipment / new product introduced
- Qualifications and validation
- Repeat OOS / deviations impacting the finished product quality

QRM was carried out by the team representing various functional groups. The SOP specified common risk management tools such as:

- Flow charts check sheets etc.
- Failure mode effect analysis (FMEA)
- Failure mode effect and criticality analysis (FMECA)
- Fault tree analysis (FTA)
- Hazard analysis and critical control points (HACCP)
- Hazard operability analysis (HAZOP)
- Preliminary hazard analysis (PHA)
- Risk ranking and filtering

The most commonly used tool was the risk ranking and filtering.

Risk assessment (identification, evaluation and review) was reviewed for linezolid API for all stages of manufacturing. RA was carried out on October 4, 2015.

### **3.2 PERSONNEL**

#### Personnel qualifications

There was an adequate number of personnel qualified to perform and supervise the manufacture of intermediates and APIs. The responsibilities of personnel engaged in the manufacture of intermediates and APIs were specified in writing. A separate reporting structure was established for production and quality departments.

The current organizational chart was reviewed.

The Managing Director, VP Manufacturing, General Manager Regulatory Affairs and General Manager QA were also responsible for other sites within the Symed group of companies. Assistant Manager QC, Assistant Manager QA, Manager Maintenance, Manager Production and Supervisor Warehouse were dedicated to Unit I. General Manager QA was responsible for 5 manufacturing sites including Unit I. The job description of the QA Assistant Manager has been reviewed and found to be in accordance with QA department responsibilities outlined in the SOP “Quality Assurance Department Responsibilities”. Job descriptions were signed by the person accepting the responsibilities as well as the person empowered to fulfil responsibilities in his/her absence.

Production department responsibilities were outlined in the SOP “Production Department Responsibilities”. Shift in Charge and Block In-Charge position personnel were responsible for the supervision of the shop floor during the 24 hours operation (3 shifts).

The job description of a Shift in Charge was reviewed.

Quality systems and SOPs were specific to the individual departments within Symed Unit I. Facility access of personnel was described in SOP “Access Control” and access levels were defined for: warehouse, production, maintenance, QC, QA and Microbiology Laboratory.

### Personnel hygiene

Good sanitation habits were observed on site. Direct contact with intermediates or APIs was avoided. Personnel were wearing clean clothing suitable for the manufacturing activity that they were performing.

### Training

The SOP “Training”, was checked. The following training modules were provided:

- Induction & orientation training
- cGMP training
- Job training
- Safety, health and environmental training
- Specific training
- Internal auditor training
- External training (only for safety)

The training effectiveness was evaluated by pre-given selective multiple choice questions for unexperienced persons as well as for management.

For the experienced chemists in production, with over two years’ experience, training effectiveness evaluation was carried out verbally. The training records for an unexperienced chemist employed in “clean room” were checked. Mr XXXX joined the company on August 03, 2015. Training was carried out for 64 days.

The SOP “Analyst qualification” was checked. According to the SOP after the completion of the training program, the analyst shall undergo qualification process for all tests/techniques relevant to his/her working area. A new analyst had to perform duplicate tests on a previously approved batch; the acceptance criterion was based on tolerance limits from the original test results within specifications.

The analyst qualification for Mr. XXXX on high performance liquid chromatograph (HPLC) assay test was performed on September 24, 2014. The “Raw data sheet for analyst qualification” was checked. After the qualification Mr. XXXX was certified to perform HPLC tests. Separate qualification was carried out for Mr. XXXX to perform gas chromatography (GC) tests on February 11, 2014, after qualification Mr. XXXX was certified to perform GC tests.

### Consultants

One consultant was used for the filing of the drug master files (DMF) for the US market and submission of the responses to the deficiencies related to the DMF.

## **3.3 BUILDINGS AND FACILITIES**

### Design and construction

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. Buildings and facilities had adequate space for the orderly placement of equipment and materials. The flow of materials and personnel through the

buildings and facilities were designed to prevent mix-ups or contamination. Laboratory areas and operations were separated from production areas.

### Utilities

Utilities were qualified and monitored. Adequate ventilation, air filtration and exhaust systems (HVAC) were provided. HVAC systems were designed to minimize the risks of contamination and cross-contamination. The permanently installed pipework and the direction of flow were identified.

Air Handling Units (AHU) consisted of the following filter cascade:

- 20  $\mu$  - G3
- 10  $\mu$  - G4
- 5  $\mu$  - F5
- H13 - HEPA

The HEPA filters were installed in the plenum. Pressure differentials were monitored between filters; 20 % fresh air was provided for re-circulation.

AHUs were running continuously on “normal” working regime. Filters were changed every year or in case the pressure differentials were out of the specified limits. Filters were cleaned once in 15 days. Filters were cleaned in separate room. AHUs spare filters were stored in the filters cleaning and storage room. HVAC system re-qualification was carried out according to the following program:

- Viable particle counts – every six months
- HEPA integrity, velocity, air changed per hour, non-viable particle counts and recovery study – every year

“Report on performance qualification of clean classified area” was checked. All tests were performed by an external agency. Tests were carried out according to the ISO14644-3 standard.

Calibration certificates were available and provided to the inspectors for the measuring instruments used in the qualification study.

### Water

DMW was used for intermediates washing and equipment cleaning. DM system consisted of:

- City water tank
- Multi gradient filter
- Cation exchange
- Anion exchange
- Degasser
- Mixing bed
- Ultra violet lamp (UV)
- Two 5000 L storage tanks.



Water was in continuous circulation. One storage tank was stand-by. If the stand-by water tank was empty more than 12 hrs, sanitisation using 85 - 90 °C water, was carried out. Loop sanitization was performed once per month using two sanitization cycles.

The DMW was installed in 2009. In 2011 four additional user points were added and three phase validation was carried out. In 2013 fifteen additional user points were added and three phase validation was carried out. In 2014 six additional user points were added and three phase validation was carried out. In 2015 ten additional user points were added and three phase validation was initiated.

DMW action and alert limits were in place.

DMW tanks filters were changed every six months; filter integrity tests were carried out every 3 months.

The DMW quality data for 2014 was spot checked. Results were tabulated and presented graphically. All results were well within alert limits. Till October 4, 2015 DMW routine analysis and analysis validation studies were carried out by a contract laboratory.

The SOP “Sampling program” described the DMW sampling procedure.

#### Containment

Highly sensitizing or highly potent materials were not manufactured on site.

#### Lighting

In general adequate lighting was provided to facilitate cleaning, maintenance and proper operations.

#### Sewage and refuse

Not inspected.

#### Sanitation and maintenance

Buildings used in the manufacture of intermediates and APIs were properly maintained and repaired and kept in a clean condition.

### **3.4 PROCESS EQUIPMENT**

#### Design and construction

Equipment used in the manufacture of intermediates and APIs was of an appropriate design and adequately sized, and suitably located for its intended use. Major equipment such as reactors and centrifuges, and permanently installed processing lines used during the production of an intermediate or API were appropriately identified. Mainly closed systems were used in production. Stainless steel or glass-line reactors were used for production of linezolid API as appropriate to the process stage.

### Equipment maintenance and cleaning

Schedules and procedures were established for the preventive maintenance of equipment. The SOP “Preventive maintenance program (PM)” was spot checked – this was general SOP. PM SOPs were available for all equipment. As example the SOP “Preventive maintenance checks for SS reactors” was checked. PM was done according to the check lists. PM schedules and check lists were cross checked for the reactor XXXX and blender XXXX. Cross checks showed that PM schedules were followed. SS reactors PM was carried out once in six months, some equipment calibration was performed every three months, for example; glass line reactors, centrifuges, tray dryers, blenders, pulverisers micronizers and multi millers every 3 months.

Equipment and utensils cleaning after campaign production was recorded in the relevant batch cleaning records (BCR). Batch to batch cleaning was recorded in the batch production records (BPR).

### Qualification

The SOP “Qualification of equipment” was checked. The SOP was applicable to the equipment being installed at the manufacturing facility. The SOP was applicable for complete re-qualification (installation qualification (IQ), operational qualification (OQ) and performance qualification PQ). According to the SOP all equipment qualification documents should be reviewed once in a six years to assess the need for re-qualification. If needed (in case any changes were made in the equipment, re-location etc.) equipment should be re-qualified. The AHU system should be re-qualified, if there is any change in the design of AHU or facility modification. Equipment re-qualification (re-assessment) schedule for production equipment was spot checked. As an example stainless steel (SS) reactor XXXX initial qualification report was spot checked. Initial qualification covered user requirement specifications (URS), design qualification (DQ), IQ, PQ and OQ. In May, 2013 the reactor was moved to another place and IQ, OQ and PQ were carried out.

### Calibration

Control, weighing, measuring, monitoring and testing of critical equipment that was critical performed according to written procedures and an established schedule. Records of calibrations were maintained. The current calibration status of critical equipment was known and verifiable.

Analytical balance XXXX (range 20 mg – 200 mg) daily and monthly calibration was checked. The calibration certificates of all standard weights were available.

Date and time function on analytical balances was password protected and only IT person had access to this function.

Raw materials dispensing balance was calibrated .The calibration certificates of all standard weights were available and presented to the inspectors.

pH meters were calibrated daily using three standard buffers: 4.00, 7.00 and 9.20.

The SOP “Calibration of equipment” and the calibration schedule were spot checked. This SOP was applicable to all production equipment and QC instruments.

#### Computerized systems

The computerized systems in the laboratory had sufficient controls to prevent unauthorized access or changes to data. The SOP “Electronic data management” was checked. The SOP was applicable for stand-alone instruments (infra-red spectrophotometer (IR), ultraviolet spectrophotometer (UV)) and instruments connected to the Chromeleon 6.8 version software (HPLC and GC). According to the SOP back-up shall be carried out once in a month and stored on external disc. Back-ups from the Chromeleon software were stored on Chromeleon server, located in a separate room. Back-ups from Chromeleon server were taken on CDs/DVDs. Back-ups from the stand alone systems were taken on CDs/DVDs. One copy of stand-alone system CDs/DVDs was stored in QC and one at the Head office. Retrieval of two copies and review of data on CDs/DVDs was carried out every 6 months. The “Electronic analytical data restoration request” for XXXX was spot checked. Data was verified by QA. The “Electronic analytical data storage” log book was also spot checked.

Computerized systems were not used in the warehouse and production.

### **3.5 DOCUMENTATION AND RECORDS**

#### Documentation system and specifications

Documents related to the manufacture of intermediates and APIs were prepared, reviewed, and approved. Specifications were established and documented for raw materials, intermediates, packaging materials and finished API. Acceptance criteria were established and documented for in-process controls.

#### Master production instructions

Master production instructions had been established and appropriately approved.

#### Batch production records and packaging records (BMR/BPR)

BMR/BPR were prepared for each intermediate and API. Issuance of the BMR/BPR was controlled by QA. BMR/BPR were numbered with a unique batch number, dated and signed. Raw material name, batch number, quantity weighed and expiry date were recorded on product labels and with the exception of the expiry date, all information was recorded in the BPR.

Linezolid Batch No XXXX BMR was reviewed.

Weighing slips were attached at each step where material was transferred into drums. Verified data logger printout was also attached to the batch record. Batch production record checklist was verified by production and reviewed by QA. No deviations were recorded.

Packaging record for in process batch No XXXX was reviewed and the documentation related to the subsequent finished batch No XXXX was verified by the inspectors. Packaging material issuance slip was part of the batch record. The packaging operation was described,

weights were recorded, labels were reconciled and packaging material lot numbers were documented.

#### Laboratory control records

Standard tests methods and analytical reports were available. Linezolid API batch No. XXXX analytical print out data (HPLC – assay and impurities) was cross-checked with electronic data. Cross check showed identical data.

#### Out of specification (OOS)

SOP “Resolving out-of-specification” procedure was in place for the investigation and handling OOS results. Phase I included laboratory investigation and Phase II referred to manufacturing process review and additional laboratory testing. Proposal of a hypothesis, and confirmatory test plan had to be approved by QA before testing commenced. Verification of sample validity and approval procedures was also in place.

#### Out of trends (OOT)

The SOP “Trend Analysis” was in place to record, investigate and monitor out of trend results. The quality of the following materials was trended as per the following schedule:

- KSM- half yearly
- Intermediates and finished products (yield and complete specification quality data)- campaign/monthly/yearly
- DM- water Monthly
- Environmental monitoring was not trended in addition to the general annual review.

### **3.6 MATERIALS MANAGEMENT**

#### General controls

Written procedures describing the receipt, identification, quarantine, storage, handling, sampling, testing and approval or rejection of materials were available. In the warehouse, materials were managed according to first in first out (FIFO) principle and using a manual bin card system. First expired first out (FEFO) principle was also applied (for example: the same materials were received from different vendors with different expiry dates). The SOP “Raw materials and packaging materials distribution from warehouse” was checked.

The SOP “Vendor Qualification” was reviewed. The SOP was applicable to the key starting materials (KSM), general raw materials, packaging materials and external analytical laboratories and service providers. According to the SOP manufacturers of key starting materials and primary packaging materials qualification should be carried out every five years. Evaluation of approved manufactures was performed yearly and contained information about previous year consignments supplied.

Qualification of overseas vendors was carried out using questionnaires. Domestic vendors were qualified based on questionnaires and audits. In case of new vendor, purchase department should procure three samples and send questionnaire. Samples and questionnaires were reviewed by the QA department and analysed by the QC. If the samples complied with the specifications, research and development (R&D) department performed user tests. Afterwards user test reports were sent for the QA for review and approval.

“Vendor questionnaire” was presented to the inspectors. XXXX audit was carried out according to the vendor audit check list by QA in charge, executive QA and plant manager. Audit report was presented to the inspectors. Observations were listed; CAPAs were submitted by the audited site and evaluated by the QA in charge.

Primary packaging materials manufacturer XXXX audit was carried out according to the vendor audit check list by head QA and executive QA. Audit report was presented to the inspectors. Observations were listed; CAPAs were submitted by the site and evaluated by the QA in charge.

#### Solvents

Solvents were delivered in dedicated tankers; tankers cleaning certificates were provided. Check list was used to receive solvent deliveries. Samples of the delivered solvents were taken from the tankers. After QC release, solvents were mixed for 30 minutes with existing stock, analysed and a new batch number was assigned. Solvents’ hose pipes (couplings) were solvent dedicated and stored in the maintenance manager’s office.

#### Receipt and quarantine

Materials were held under quarantine until they were sampled, tested and released for use.

#### Sampling and testing of incoming production materials

Containers from which samples were withdrawn were marked to indicate that a sample has been taken.

The SOP “Sampling program” was checked. Liquid raw materials from drums and solid raw materials sampling plan was based on ISO 2859-1.

KSMs samples were withdrawn from all containers; afterwards composite sample was made by composing all samples into one sample.

#### Storage

KSM and other raw materials were stored in raw materials warehouse. Sampling and dispensing was carried out in the separate sampling/dispensing rooms. Separate air handling units (AHU) were used to provide air to the sampling/dispensing rooms. Incoming air was filtered via 5 µ filters. Separate rooms in the warehouse were provided for the storage of hazardous materials and clean containers.

Temperature (T) in the raw material storage room was monitored daily. The T sensor was connected to a data logger that recorded the T every hour.

Separate rooms (entrance from the outside of the building) were provided for the storage of rejected raw materials, charcoal, charcoal mixing, rejected & returned and recalled finished products.

Finished goods (FG) were stored in the FG warehouse. Entrance to the warehouse was via change room. Three “clean rooms”, class ISO 8 were provided in the FG warehouse for the FG sampling, packaging and re-packaging. Entrance to the “clean rooms” was via changing room and air lock. Photos of the dressing procedures were attached to the walls. Pass boxes were provided for the entry of the materials to the clean rooms. Pressure differentials were monitored. Air to the “clean rooms” was supplied via separate AHUs.

FG labelling was carried out in the “clean rooms” by production personnel. The control of labels was the responsibility of QA.

Finished products storage temperature was specified at  $25 \pm 2$  °C in the FG storage room and it was monitored daily. The T sensor was connected to a data logger that recorded the T every hour.

Temperature mapping studies were carried out by an external agency.

### **3.7 PRODUCTION AND IN-PROCESS CONTROLS**

#### Production operations

The manufacturing process of linezolid (form II) was conducted in production block-A and clean room II.

At the time of the inspection the batch being manufactured was the last batch of linezolid (form II) campaign (batch 10 of 10).

In process sampling for TLC testing was performed by production operators using clean sampling tools stored in a dedicated facility. All hoses were dedicated, cleaned, labelled and stored on racks.

Solid materials were added through the manhole and liquid materials such as methanol were charged through identified, fixed transfer lines.

Centrifuge bags were dedicated to each stage of processing; they were cleaned after every batch and changed after being used for 10 consecutive batches.

The finished API was packaged in white LDPE bags (primary packaging) protected by a black LDPE bag and placed in the plastic drums according to customer request.

#### Blending batches of intermediates or APIs

The SOP “Assigning of manufacturing date to in-house batch and blend batch” was checked. The expiry or retest date of the blended batch was based on the manufacturing date of the oldest tailings or batch in the blend. Retest date of the blended batch should be assigned as per manufacturing date and in accordance to the available stability data. Blending operations were part of the BPR. Retest date of the in-house batch (not blended batch) was assigned as per manufacturing date and in accordance to the available long term stability data. Till the date of inspection 24 month stability data was available for linezolid API.

### Contamination control

The environmental monitoring (EM) in clean rooms was carried out every 6 months by settle plate method. The settle plates were exposed for 4 hours. The SOP “Environmental monitoring of clean rooms” was spot checked. Till October 4, 2015 EM was carried out by Symed Labs Unit II. Alert and action limits were set up for total aerobic microbial counts (TAMC). Total yeasts & moulds counts (TYMC) were expected to be 0. EM results were checked for 2014 – all results for TAMC were well within alert limit, TYMC counts were 0.

### Deviations

The SOP “Handling of Deviation” described the procedure of handling critical and non-critical unplanned deviations from an approved instruction or established standard. In addition to the deviation SOP, the SOP “Reporting of Obvious Error” was also in place.

### Corrective Actions and Preventive Actions (CAPA)

SOP “Corrective and preventive actions (CAPA)” was reviewed. CAPA records were kept in one register per year/ product. The register for 2015 was reviewed and XX CAPA records were found.

The progress of implementation and verification of CAPA actions was monitored by Management Reviews quarterly. CAPA XXXX was reviewed and found to be well documented.

## **3.8 PACKAGING AND IDENTIFICATION LABELLING OF APIs AND INTERMEDIATES**

### General

There were written procedures describing the receipt, identification, quarantine, sampling, examination and/or testing and release and handling of packaging and labelling materials.

### Packaging materials

Primary packaging materials were stored in the warehouse in specific storage room.

### Label issuance and control

Finished product labels were partly pre-printed labels. Batch specific information was printed on labels in the warehouse office by the production chemist. Computer connected to the label printer was not password protected.

The SOP “Receipt, inspection, issuance and reconciliation of printed labels” was checked. Labels receipt and inspection was the responsibility of the QA department. Production department’s responsibility was to maintain & update the reconciliation records for the product labels issued to the department. Finished product labels were stored in the FG warehouse in a locked cabinet. The printing of labels was carried out by the production chemist and reviewed by QA. As per procedure FG labels should be inspected in accordance with the approved master labels.

### Packaging and labeling operations

Not performed during the inspection.

### **3.9 STORAGE AND DISTRIBUTION**

#### Warehousing procedures

Facilities were provided for the storage of all materials. Released, rejected and returned materials were stored separately. Quarantine areas were identified.

#### Distribution procedures

The SOP “Quality assurance release for dispatch products” was checked. APIs were released for sale after QA approval. Head of QA or designate was the responsible persons for product release. According to the SOP QA shall check QC records and batch production records (BPR). QC records and BRPs were checked according to the check list. QA should also verify and sign the certificates of analysis (CoA). QA release check list was reviewed for linezolid (form –II), batch No XXXX.

### **3.10 LABORATORY CONTROLS**

#### General controls

Quality department was independent from the production department. Documented procedures describing sampling, testing, approval or rejection of materials and recording and storage of laboratory data were available.

Log books were available for all laboratory instruments.

Four HPLCs and two GCs were connected to the Chromeleon (6.8 version) software. HPLC columns usage was recorded. Upon receipt columns performance tests were carried out and compared with the column CoA.

Linezolid batch No XXXX was placed on stability and the 18 month data was analysed on 28.08.2015. HPLC instrument No XX was used for related substances test. Chromatograms of standard and sample injections (electronic and printed copies) were reviewed in the laboratory during the inspection.

Infrared spectrophotometer and ultra violet spectrophotometer were stand-alone instruments.

In the chemical laboratory only class A volumetric glassware was used. Glassware was received along with calibration certificates; re-calibration was carried on site after three years from the receipt.

Reagents prepared in the laboratory were properly labelled. In case solvents / dry chemicals did not have expiry date the following expiry dates were set up by the QCL:

- Solvents - 1 year from the date of opening
- Dry reagents – 3 years from the date of opening

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The preparation of volumetric solutions was verified in the wet chemistry laboratory. 1 N NaOH solution Lot no. XXXX was prepared and the factor determined using two titrations. Records were verified in LIMS. Volumetric solutions were prepared by a dedicated person once per month and re-standardized weekly.



### Testing of intermediates and APIs

For intermediates and API tests according to the standard tests methods were carried out.

### Validation of analytical procedures

The specification used for the testing and release of linezolid (form II) was XXXX. HPLC and GC instrumentation was used for qualitative and quantitative determination of impurities.

The validation of hydrazine content HPLC method validation report No XXXX was reviewed.

Specificity, system suitability, system and method precision, LOD, LOQ, linearity, range, accuracy, ruggedness and robustness of the method were tested and found acceptable.

### Certificates of analysis (CoA)

The SOP “Preparation & issuance of certificate of analysis” was checked. CoA was generated by the laboratory information management system (LIMS). Data to the LIMS was entered by the analyst(s) who performed the test(s). CoAs were signed by the CoA reviewer, and approved by the QA.

### Batch numbering system

The SOP “Batch numbering system” was checked.

### Stability monitoring of APIs

The SOP “Stability studies” was checked. Samples were stored under the following conditions:

- 40 °C ± 2°C, 75% ± 5%
- 25 °C ± 2°C, 60% ± 5%
- 30 °C ± 2°C, 65% ± 5%
- 30 °C ± 2°C, 75% ± 5%

Window periods between withdrawal of samples and analysis were specified. First batch per year was placed on long term stability monitoring programme. Samples were packed in market simulated conditions. Four stability chambers were provided for the studies. According to the SOP excursions from storage conditions due to power failures / breakdowns may happen. Any deviations for more than 24 hours shall be investigated for the reason and in such cases samples shall be transferred to Symed labs limited, Unit II. It was said that stand-by stability chamber was available at the Symed labs limited, Unit II.

Accelerated and long term stability data was checked for linezolid API batch No:

- XXXX
- YYYY
- ZZZZ

The batches under stability were process validation batches. Accelerated studies were finished in January 2014. Till the date of inspection 24 month stability data was available.

Stability data for accelerated and long term studies were presented as tabulated and as graphical presentations.

T and relative humidity (RH) in the in the chambers were monitored daily. T sensor was connected to the data logger what recorded the T every hour. Print outs were checked daily. Stability chambers were equipped with sound alarm system located in the QC laboratory. Note: QC laboratory was working continuously in 3 shifts.

#### Reserve/retention samples

Reserve samples were retained in representative primary and secondary packaging. T in the storage room was monitored daily. T sensor was connected to the data logger what recorded the T every hour. Print outs were checked daily. Reserve samples were stored for 6 years.

#### Reference standards

If available pharmacopoeia reference standards were used for impurities tests, if not, R & D prepared reference standards were used. Working standards (WS) were qualified against R & D reference standards. WS had an expiry date of 2 years. WS were dispensed in 28 bottles; the maximum validity of each bottle was one month after opening.

#### Microbiological laboratory (MBL)

MBL started operation on October 3, 2015. The following tests were carried out in the MBL:

- DMW
- Total aerobic microbial counts
- Total yeast microbial counts
- Specific pathogen tests

Separate autoclaves were provided for media sterilisation and waste destruction. Double door autoclave was used for media sterilisation. Autoclave validation was carried out by an external agency on September 19, 2015. Media sterilization condition was 15 minutes at 121 °C; pH was checked before and after sterilization.

### **3.11 VALIDATION**

#### Validation policy

The validation policy at Symed Labs was implemented according the SOP “Validation Master Plan”. A validation committee consisting of QA, QC, Production, Safety health environment (SHE), Maintenance and Warehouse was formed to decide on validation activities and agree on the validation matrix for the following year.

Logbooks were used to record process related and analytical methods related validation activities. The logbooks were reviewed quarterly and the validation status was reported at the management review meetings.

#### Qualification

Qualification of critical equipment and utilities was carried out.

The Steam tray dryer XXXX was qualified on 07.05.2013 as per protocol no. XXXX. The qualification was performed by external service provider. The mapping of temperature probes was provided indicating that on each tray (back and front) a temperature probe was placed.

Traceability certificate for the calibration of the probes was included in the qualification report. Probes were positioned alternately on trays and data was collected using data logger. No deviations from the protocol were observed.

The validation certificate of the tray dryer was issued on 09.05.2013 confirming that the equipment is capable to maintain the temperature between 40 °C and 100 °C within a variation of +/- 2.5 °C.

#### Approaches to process validation

SOP “Validation” described the validation approach at Symed Labs.

Prospective validation protocol XXXX was reviewed. The protocol outlined responsibilities, route of synthesis, selection of batches and critical operations. For each stage the following information was provided: raw material requirements, equipment to be used, special instructions. For verification of the drying process individual samples and composite samples were taken from specific trays every 30 minutes. The validation concluded that the yield of all intermediates and finished products were within acceptable limits, testing results of all raw materials and finished products met specifications as per validation Report XXXX.

#### Cleaning validation

The SOP “Cleaning validation” was in place to ensure the effectiveness of the cleaning procedures. Cleaning levels; 2, 1 and 0 were defined as following

- Level 2: changeover of equipment in final step and intermediate/final step of one product to intermediate/ final step of another product.
- Level 1: early step change to intermediates in a product sequence.
- Level 0: in a campaign batch to batch changeover of the same stage.

For Level 2 cleaning: the solubility of product determined the solvents to be used. A protocol was prepared and equipment cleaning record was generated. After execution, samples were sent to QC (rinse and swab as applicable), carryover was checked and the limit was fixed based on maximum allowable carry-over (MACO) calculation. The results were evaluated against the limit; 3 runs were performed.

Reactor XXXX was considered multipurpose equipment and its cleaning validation was performed in March, 2014.

### **3.12 CHANGE CONTROL (CC)**

SOP “Change Control” was in place to evaluate and document the changes.

The classification of changes was according to four categories: major and minor, temporary and permanent .There was a list for guidance regarding the classification of changes into major and minor categories.

### **3.13 REJECTION AND RE-USE OF MATERIALS**

#### Rejection

The SOP “Handling and disposal of rejections and returned goods” was checked. The SOP was applicable for rejections by customers and intermediates and raw material rejections at Symed Labs. Upon receipt of returned goods QA shall log the details of returned good in

“Returned goods register”. Returned goods should be stored in finished goods rejected area. Rejected raw materials shall be sent back to the customer; meanwhile these materials shall be placed in rejected material storage room. The following registers were in place:

- Rejected raw materials log
- Finished goods rejected, returned and recalled inward register
- Rejected intermediates log

#### Reprocessing and reworking

The SOP “Reprocessing” was checked. According to the SOP R&D shall establish the procedure for reprocessing for intermediates and finished products during process development. Reprocessing should be carried out according to the reprocess BPR. Reprocessing should be approved by the QA. Reprocessed batches of the APIs shall be added to stability program. According to the SOP; “As per company’s policy rework is not allowed”.

#### Recovery of materials and solvents

The SOP “Handling of recovery solvents, mother liquors (MLs) and distilled solvents” was checked. Recovery of the solvents from MLs was done according to the recovery BPR. Recovered solvents during distillation could be used as such. Recovered solvents from MLs were mixed with the fresh solvents. According to the SOP recovered solvents should be stored in respective storage tanks, receivers and dedicated drums /containers and should be used in the same stage of the same product or previous stage of the same product. All recovered solvents had to meet solvent specific specifications. As an example recovered methanol (MEOH) and fresh MEOH specifications were checked. Recovered solvents reconciliation registers were maintained.

#### Returns

Returned APIs were identified, quarantined and stored in a dedicated place in the warehouse.

### **3.14 COMPLAINTS AND RECALLS**

Market complaints were recorded and investigated according to the SOP “Complaints”. The SOP was checked. The head of QA had the overall responsibility for dealing with complaints; if the head of QA was not present the designee of QA head was responsible for the investigation. Complaint investigation was carried out by an investigation team. The investigation team shall verify the analytical and process details of the batches produced before and after the occurrence that caused the complaint. QA shall initiate the appropriate follow up action, including recall, if necessary. CAPAs shall be recorded in CAPA report, effectiveness of CAPAs should be evaluated by the QA department.

Complaint registers were product wise.

The SOP “Product recall” was checked. The responsible person for dealing with recalls was the head of QA, if the person was not presented; the designee of the head QA was responsible for recalls. Recalls were classified as:

- Voluntary recall
- Forced recall

Up to the date of inspection there had been no recalls. Recall effectiveness was evaluated by mock recalls. Mock recall was carried out every 5 years. The last mock recall was carried out on 20 March. Mock recall covered the domestic market.

### **3.15 CONTRACT MANUFACTURERS (INCLUDING LABORATORIES)**

Manufacturing operations of the KSM stage XXX was contracted out to Symed Labs Unit III. Contract manufacturing agreement with Symed Labs Unit III was checked.

Quality agreement (QA) with XXXX was also checked.

The above mentioned QA and contract manufacturing agreement specified that contract giver had the right to audit contract acceptors' facilities for compliance with GMP.

### **PART 4: CONCLUSION**

Based on the areas inspected, the people met and the documents reviewed, and considering the findings of the inspection, including the deficiencies listed in the Inspection Report, as well as corrective actions taken and planned, API Linezolid manufactured at SYMED LABS LIMITED Unit I Survey No.353, Domadugu, Jinnaram, Medak, Telangana, India, was considered to be manufactured in compliance with WHO GMP 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.