## Prequalification Team Inspection services

**WHO PUBLIC INSPECTION REPORT**

(VOPIR)

**Desk Assessment of Active Pharmaceutical Ingredient (API) Manufacturer**

### Part 1

#### General information

<table>
<thead>
<tr>
<th>Company information</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Name of Manufacturer</strong></td>
</tr>
<tr>
<td><strong>Corporate address of manufacturer</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Inspected site</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Name &amp; address of manufacturing site</strong></td>
</tr>
<tr>
<td><strong>Synthetic Unit/Block/Workshop</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Desk assessment details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Date of review</strong></td>
</tr>
<tr>
<td><strong>APIs covered by this desk assessment</strong></td>
</tr>
</tbody>
</table>
- Site Master File, effective 01/12/2018.  
- List of products manufactured on site.  
- Joint GMP certificate from Drugs Control Administration of Telangana and CDSCO.  
- USFDA EIR letter for the inspection conducted 05/07/2018 to 5/11/2018.  
- CAPA to the above-mentioned USFDA inspection.  
- Hungarian inspection report (February 2016) and CAPA (provided on 19 Feb 2019 further to a query).  
- PQR for linezolid (Form III) for 2018.  
- Completed batch manufacturing and packaging records, for linezolid API.  
- Confirmation on the absence of recalls.  
- Confirmation on self-inspection and external audit.  
- Batch manufacturing and packaging records for linezolid.  
- Confirmation on the absence of warning letter or equivalent regulatory action.  
- Confirmation that there were no out-of-stock situations.  
- Response to Query dated 4 April 2019. |
<table>
<thead>
<tr>
<th>Part 2</th>
<th>Summary of SRA/NRA inspection evidence considered (from most recent to last) and comments</th>
</tr>
</thead>
</table>
| National Institute of Pharmacy, Hungary | Dates of inspection: 02/20/2019 to 02/28/2019  
Type of inspection: Routine  
Type of APIs covered: Linezolid Form III and other APIs manufactured by chemical synthesis  
Physical areas inspected: All manufacturing, QC, QA, utilities, warehousing |
| USFDA | Dates of inspection: 7-11 May 2018 (5 days at the facility)  
Type of inspection: Routine re-inspection. Covered APIs manufactured by chemical synthesis (CSN)  
Block/Unit/Workshop: There were 3 blocks on site for production: Blocks A, B and C.  
Type of APIs covered: APIs manufactured by chemical synthesis (CSN), including Linezolid (Form III)  
Physical areas inspected: Not specifically mentioned. |
| National Institute of Pharmacy, Hungary | Dates of inspection: 8-16 February 2016  
Type of inspection: Routine  
Block/Unit/Workshop: Unit II, Blocks A, B, C  
APIs covered: Linezolid Form III and other APIs manufactured by chemical synthesis  
Physical areas inspected: Manufacturing areas  
Warehouses  
Quality control  
Note: Linezolid was inspected in Production Block C, B crystallizer room IV, C crystallizer room IV, clean room III, |

<table>
<thead>
<tr>
<th>Part 3</th>
<th>Summary of the last WHO inspection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date and conclusion of most recent WHO inspection</td>
<td>This site has not been inspected by WHO PQT before.</td>
</tr>
<tr>
<td>Brief description of manufacturing activities</td>
<td>According to the site master file, Symed Labs Limited (Unit-II) manufactures non-sterile active pharmaceutical ingredients. Toxic or hazardous substances are not manufactured at the site. Use of all chemicals inside the plant is governed by specific procedures that include use of personal protective measures to eliminate the effects of chemicals on operators. No veterinary products are manufactured at the site.</td>
</tr>
</tbody>
</table>
**General information about the company and manufacturing site**

According to the site master file, the manufacturing site was audited and approved as an acceptable facility by USFDA, NIP (Hungary), MHLW (Japan), COFEPRIS (Mexico), KFDA and RUSSIAN FDA. Following are the details of the regulatory approvals. The Quality Management System is followed as per ISO 9001:2015, ISO 14001:2015 Schedule-M, ICH Guidelines, EU GMP, EudraLex Volume-4 (Part-II).

<table>
<thead>
<tr>
<th>Abbreviations</th>
<th>Meaning</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMR</td>
<td>Batch manufacturing record</td>
</tr>
<tr>
<td>BPR</td>
<td>Batch production record</td>
</tr>
<tr>
<td>CAPA</td>
<td>Corrective and preventive action</td>
</tr>
<tr>
<td>CC</td>
<td>Change control</td>
</tr>
<tr>
<td>GMP</td>
<td>Good manufacturing practices</td>
</tr>
<tr>
<td>NC</td>
<td>Non-conformity</td>
</tr>
<tr>
<td>NRA</td>
<td>National regulatory agency</td>
</tr>
<tr>
<td>PQR</td>
<td>Product quality review</td>
</tr>
<tr>
<td>PQS</td>
<td>Pharmaceutical quality system</td>
</tr>
<tr>
<td>QA</td>
<td>Quality assurance</td>
</tr>
<tr>
<td>QC</td>
<td>Quality control</td>
</tr>
<tr>
<td>QCL</td>
<td>Quality control laboratory</td>
</tr>
<tr>
<td>QMS</td>
<td>Quality management system</td>
</tr>
<tr>
<td>QRM</td>
<td>Quality risk management</td>
</tr>
<tr>
<td>RA</td>
<td>Risk assessment</td>
</tr>
<tr>
<td>RCA</td>
<td>Root cause analysis</td>
</tr>
<tr>
<td>SOP</td>
<td>Standard operating procedure</td>
</tr>
</tbody>
</table>

**Part 4**

**Summary of the assessment of supporting documentation**

a) **Manufacturing authorization and GMP certificate granted by the local authority:**

The manufacturing authorization from the Government of Telangana (license renewal certificate) was provided and was found acceptable.

b) **Site master file (SMF):**

The site master file was reviewed and was considered acceptable overall.

c) **List of all the APIs or other products (intermediates, dosage forms) manufactured on-site:**

The list of APIs manufactured was provided and was verified not to include beta lactam antibiotics, hormones, steroids, highly potent products or veterinary products. Thalidomide was nevertheless seen to be manufactured on site and queries regarding prevention of cross-contamination of the WHO API were satisfactorily resolved.
d) List of all regulatory inspections performed in the last 3 years and their outcomes:
The site has been inspected by the Russian FDA (6/03/2018-08/03/2018), by the KFDA (17/02/2016-19/02/2016) and found compliant. The USFDA has inspected the site 5 times (2006, 2009, 2013, 2015 and 2018) and was found compliant.

e) Most recent product quality review(s) (PQR)(s) of the concerned WHO API(s):
APQR Linezolid (Form-III), year 2018 was reviewed:
  • It covered API code LIN, which was manufactured at production Block-A, Production Block-B/C, B/C-Crystallizer Room IV and Clean Room-III.
  • A total of 10816.189 Kg (7.10 Kg from the year 2015 batches, 22 94.5 Kg from the year 2017 batches and 8514.589 Kg from the year 2018 batches) of Linezolid (Form-III) material was dispatched from the different batches to various customers during the year 2018.
  • 16 batches from Symed Labs Limited (Unit-I) and 53 batches from Symed Labs Limited (Unit-IV) of RAM-II, 04 batches from Shenyang gold jyouki Technology Co. Ltd & 04 batches from Sulan City Jinma Chemical Co. Ltd of SOTALAL material was procured from approved vendors.
  • There were no failures for yield.
  • No OOT results were obtained in any of the test parameters during the year 2018.
  • Key starting materials were RAM II and Sotalal. Ram II was supplied from Symed Labs Unit I and Unit IV.
  • Stability testing was performed for 36 months.
  • Cleaning validation was conducted in 2016 and 2017 for all equipment and in 2018 only for selected pieces of equipment.
  • Long term and accelerated stability study results were within specifications for all continuing batches.
  • There were 5 OOS reported in 2018. Only one out of 5 was confirmed to be a true OOS and resulted in the rejection of the batch (for an individual unspecified impurity result of 0.24%, against the limit of NMT 0.08% for batch 2LIN(B)119117.
  • Five deviations were reported during the year for linezolid Form III.
  • There were 68 obvious errors. The list was provided.
  • No batches were reprocessed in 2018.
  • Three CAPA were initiated and closed in 2018.
  • One customer complaint was received for the product Linezolid (Form-III) in the year 2018.

f) Batch manufacturing and packaging record(s), including the analytical part, for the most recently released batch of relevant API(s):
A batch record for Batch No. 18070, started on 13/12/2018 was provided and was reviewed.

g) Master batch manufacturing and packaging record(s) of the API(s) of interest:
Blank master batch records dated 30/04/2018 were provided. This is acceptable.

h) Recalls in the past three years related to APIs with quality defects:
The company declared that there were no recalls for any of the APIs from this site. This is acceptable.
i) Confirmation by the senior quality assurance representative that a full self-inspection or external audit dedicated to the API(s) has been performed and all matters dealt with:
A signed statement was provided in this regard. This is acceptable.

j) copy of any warning letter, or equivalent regulatory action, issued by any authority for their market, to which the site provides or has applied to provide the API(s):
The company declared that no Warning Letter or equivalent regulatory action had ever been taken for this site.

k) Out-of-stock situations:
The company provided as signed declaration that they did not experience any out-of-stock situations.

l) Additional documents submitted:
• Revised specifications for the Linezolid API.
• Information on production of thalidomide at the plant and on measures taken to prevent cross-contamination of the WHO API.

### Part 5 Conclusion – Desk assessment outcome

Based on the previous WHO inspections and on the GMP evidence received and reviewed, it is considered that a desk assessment is acceptable in lieu of a WHO onsite inspection. The site Symed Labs Ltd (Unit II), located at Plot-25/B, Phase-III, I.D.A. Jeedimetla, Hyderabad, 500055, Telangana, India, is considered to be operating at an acceptable level of compliance with WHO GMP guidelines for APIs.

This WHOPIR will remain valid for 3 years, provided that the outcome of any inspection conducted during this period is positive.
### Part 6  
**List of guidelines referenced in this inspection report**


[http://whqlibdoc.who.int/trs/WHO_TRS_929_eng.pdf?ua=1](http://whqlibdoc.who.int/trs/WHO_TRS_929_eng.pdf?ua=1)

https://apps.who.int/iris/bitstream/handle/10665/312316/9789241210287-eng.pdf?ua=1

https://apps.who.int/iris/bitstream/handle/10665/312316/9789241210287-eng.pdf?ua=1


http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1
http://whqlibdoc.who.int/trs/WHO_TRS_943_eng.pdf?ua=1

http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_981/en/

http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_981/en/

http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1


http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex05.pdf
