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Prequalification Team Inspection services

WHO PUBLIC INSPECTION REPORT (WHOPIR)

Active Pharmaceutical Ingredient Manufacturer

Part 1	General information
Manufacturers details	
Name of manufacturer	Optimus Drugs Private Ltd
Corporate address of manufacturer	Plot No. 6P, 2nd Floor, Signature Towers, Kothaguda, Kondapur, Hyderabad 500084, Telangana, India
Inspected site	
Name & Address of inspected manufacturing site if different from that given above	Survey No. 239 and 240, Dothigudem (V), Pochampally (M), Yadari – Bhuvanagiri (D) 508284, Telangana, India DUNS: 86-376-7205 Latitude: $17^0$30.191, Longitude: $78^0$84.782
Synthetic Unit /Block/ Workshop	Block 1, Block 2 and Block 4
Manufacturing license number	License 25/NG/AP/2008/B/R, valid until 09/09/2023
Inspection details	
Dates of inspection	25-28 February 2019
Type of inspection	Routine re-inspection
Introduction	
Brief description of the manufacturing activities	Production and quality control of APIs and intermediates.
General information about the company and site	The company was founded in 2004 and the current facility was acquired in 2006. During 2009-2010, the current multipurpose API facility was constructed, manufacturing products for the local market. From 2014-2015, materials were being supplied to the markets with DMF filings to WHO, EU and US FDA. 282 people were employed by the company at the time of inspection. Penicillins, cephalosporins and high potent APIs were not manufactured on the site.
History	This was the third WHO GMP inspection. The API facilities have previously been inspected by WHO in April 2015 and August 2016. The site had been inspected by USFDA and the EU (State Upper Franconia Germany) in 2016 with positive outcomes.

Brief report of inspection activities undertaken – Scope and limitations	
Areas inspected	• Quality Management System • Document System • Warehousing, (Liquids, Raw Materials, Packaging Materials, APIs) • Production Blocks 1,2 and 4. • QC Laboratories, • Water system
Restrictions	Other products and/or processes outside of WHO pre-qualification were not inspected.
Out of scope	Activities not related to the manufacture of Linezolid Form 2 and micronised Linezolid APIMF-286. Linezolid APIMF-255 had been withdrawn from WHO PQ programme in 2018.
WHO APIs	Linezolid APIMF-286

Abbreviations	**Meaning**
AHU	Air handling unit
ALCOA	Attributable, legible, contemporaneous, original and accurate
API	Active pharmaceutical ingredient
APR	Annual product review
BMR	Batch manufacturing record
BPR	Batch production record
CC	Change control
CIP	Cleaning in place
CoA	Certificate of analysis
CpK	Process capability
DQ	Design qualification
EDI	Electronic deionization
EM	Environmental monitoring
FMEA	Failure modes and effects analysis
FPP	Finished pharmaceutical product
FTA	Fault tree analysis
GMP	Good manufacturing practices
HEPA	High efficiency particulate air
HPLC	High performance liquid chromatography (or high performance liquid chromatography equipment)
HVAC	Heating, ventilation and air conditioning
IQ	Installation qualification
KF	Karl Fisher
LAF	Laminar air flow
LIMS	Laboratory information management system
MB	Microbiology
MBL	Microbiology laboratory
MR	Management review

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

Part 2	**Summary of the findings and comments**

1. Quality management

A formal documented system for quality assurance was established, with procedures covering key quality elements being in place. Operations were specified in written procedures and critical GMP requirements were essentially being met. Regular monitoring and reviews of the quality of pharmaceutical API and intermediates were being conducted according to documented procedures. The procedures that were reviewed and discussed during the inspection were generally of an acceptable standard.

Product quality review

PQRs were conducted according to an SOP. Interim PQRs were prepared as a trending of critical parameters every four months. The review of batches covered the period from January to December of calendar year and were completed within 30 working days after the end of calendar year. The PQR reviewed each route of synthesis of the same product.

There were four different manufacturing processes (product codes) Linezolid API in the previous inspection. On 12 November 2018 the APIMF255 application was withdrawn from WHO PQ programme. Only OP-LIZ (Route 2) - APIMF 286 is valid in WHO PQ Programme.

There were three quality grades of Linezolid API: WHO and EU, USP

The PQR of Linezolid (Polymorph 2) in 2018 and 2017 were reviewed. Each stage of the process was reviewed in a separate document. Non-compliances observed during the inspection that was listed in the full report regarding PQRs were addressed by the manufacturer to a satisfactory level.

Deviation and CAPA management

Deviations were managed according to an SOP. Deviations were classified as critical, major and minor. The procedure was reviewed. Non-compliances observed during the inspection that was listed in the full report regarding deviation were addressed by the manufacturer to a satisfactory level.

CAPAs were managed according to an SOP. A log book for CAPAs was maintained.

Quality risk management

The QRM procedure was described in an SOP. Non-compliances observed during the inspection that was listed in the full report regarding risk management were addressed by the manufacturer to a satisfactory level.

Internal audits

Internal audits were conducted according to an SOP. All sections of the factory were included within a six-month cycle. Non-conformances were rectified within 30 days with QA reviewing the effectiveness of all CAPAs.

2. Personnel

Personnel met during the inspection were adequately qualified based on education, experience and training. vA company organization chart was in place. Quality and production departments were separate and independent. The job description of Senior General Manager - Production and Head of QA were reviewed and were acceptable.

Personnel Hygiene

Protective clothing was provided, as appropriate, for activities being conducted. Smoking, drinking and eating were only permitted in designated areas.

Training

Employee training was conducted according to an SOP. Non-compliances observed during the inspection that was listed in the full report regarding training were addressed by the manufacturer to a satisfactory level.

3. Buildings and facilities

Buildings were constructed of painted, rendered masonry with internal and external finishes appropriate to the activities being conducted. Manufacturing areas were generally designed, and constructed to facilitate cleaning, maintenance and operations as appropriate to the type and stage of API manufacture.

Water
A purified water system used raw borehole water accessed from outside the factory perimeter. After pre-treatment and filtration, the water was passed through RO and EDI units, UV irradiation to a stainless-steel holding tank. From this, the purified water was fed through a loop system. Logbooks and SOPs were available. Sanitisation of the loop was performed by heating the jacket of the storage tank with steam. At the time of the inspection, the system was being revalidated and phase three of the annual revalidation plan was underway.

Containment
Overall, procedures for containment were adequate but some deficiencies were observed, particularly in the intermediates drying area in Production Block 4 that was listed in the full report regarding the area for equipment cleaning were addressed by the manufacturer to an acceptable level.

Lighting
Lighting was adequate in all areas inspected.

4. Process equipment

Design and construction
Equipment used for the APIs within the scope of the inspection was generally of an acceptable standard and suitable for intended use. Process equipment was of satisfactory construction material. Reactor systems were configured for heating, cooling, distillation and reflux at reduced or atmospheric pressure.

Equipment maintenance and cleaning
Preventative maintenance was conducted according to an SOP. This was an "umbrella" document with additional SOPs for specific types of equipment e.g. an SOP addressed preventative maintenance checks for stainless steel reactors. Details for a reactor were checked and were in accordance with the SOPs.

Equipment cleaning area in the intermediate drying area was inspected. The procedure for cleaning of tray dryers was reviewed. The cleaning type included batch-to-batch, periodic cleaning and product change-over cleaning. For product change-over cleaning, it was required to move the trays from the tray dryers to the cleaning area. Non-compliances observed during the inspection that was listed in the full report regarding equipment cleaning and cleaning validation were addressed by the manufacturer to a satisfactory level.

Calibration
An SOP "calibration philosophy of measuring, monitoring instruments and master instruments" described the requirements for calibration check of all measuring instruments. A comprehensive list of gauges was available with references to a certificated master gauges. The schedule at the time of the inspection was checked. Details were satisfactory.

Computerised Systems

Computerized systems were not used for material management or production control of Linezolid API.

A computerized system was used in QC lab with HPLC and GC equipment being networked. Basic data integrity controls were in place.

5. Documentation and records

Documents were controlled according to an SOP. An associated SOP was concerned with distribution of documents and retrieval of superseded/obsolete versions. In addition, there was an SOP "documentation requirements and retention Policy". Retention period of each document was stated. Details were acceptable.

Batch production records and batch testing records were reviewed during the inspection and found acceptable.

6. Materials management

Materials were received in warehouses according to an SOP. In the solids warehouse, the receiving area was equipped with a balance with standard weights for calibration check available. A copy of the current version of approved suppliers list was available. At the time of the inspection, the locked "Reject" area was empty. Details were acceptable.

A warehouse for liquids was visited. At the time of the inspection, the locked "Reject" area was empty. Details checked were acceptable.

Materials were sourced and purchased according to an SOP. For key starting materials, the approval of a supplier included a site audit. Details were acceptable, and the requirements of the SOP met.

Materials were sampled by QC according to an SOP. The QC laboratory was notified of a delivery by an intimation slip sent from the warehouse. Quantities required were stated in the relevant STPs. Receipt and handling of samples at the laboratory was in accordance with an SOP.

7. Production and in-process controls

Production operations for Linezolid APIs were carried out in three production blocks 1, 2 &4. Production blocks were not dedicated for production of Linezolid and its intermediate. Production blocks 1, 2 & 4 were in operation at the time of inspection.

Final purification, crystallization, drying and packaging was performed in a Grade D clean area. Different grade and different polymorphs of Linezolid API were manufactured by using different processes.

In-process sampling was performed at defined and documented stages during processing. In-process samples were tested in the QC laboratory.

8. Packaging and identification labelling of APIs and intermediates

Packaging areas for intermediates and finished APIs were inspected. Line clearance and room usage records were checked. Non-compliances observed during the inspection that was listed in the full report regarding line clearance and cleaning of the secondary packaging materials were addressed by the manufacturer to a satisfactory level.

9. Storage and distribution

APIs were stored in a finished goods warehouse. The area was temperature controlled with a daily printout available. RH was recorded "for information" only.

A procedure on batch release was reviewed and found acceptable.

API distribution procedures were described in an SOP "procedure for evaluation of outside parties for transportation and laundry services".

10. Laboratory controls

Usage logs were available for instruments. The logs for IR spectrometer was checked and was found acceptable. The operation of the IR spectrometer was described in an SOP. A polystyrene reference standard was verified and was found satisfactory. Non-compliances observed during the inspection that was listed in the full report regarding handling of KBr were addressed by the manufacturer to a satisfactory level.

Preventative maintenance of all analytical instruments was described in an SOP. The maintenance schedule was verified and found acceptable.

Primary and working standards were stored in a chamber at 2-8^{0}C. At the time of the inspection, the working standard for Linezolid was checked. Deficiencies were noted in the records for the reference standards. Non-compliances observed during the inspection that was listed in the full report regarding the record control were addressed by the manufacturer to a satisfactory level.

Retained samples were kept in a dedicated, temperature-mapped room. Humidity is recorded for reference only.

Stability chambers were located at specified area. Chambers were available for stability studies at 25±2^{0}C/60±5% RH, 30±2^{0}C/65±5% RH, 30±2^{0}C/75±5% RH (two chambers) and 40±2^{0}C/75±5% RH. A standby chamber was available as well as a chamber operating at 5±3^0 C and one at 25±2^0 C for photostability. The 2018 stability batch of Linezolid was in a chamber operating at 30±2^{0}C/75±5% RH. Details were acceptable.

OOS investigations were handled according to an SOP. OOS logbook was maintained.

The Microbiological laboratory was not functional at the time of inspection. The change control regarding microbiological laboratory was delayed and deficient. Non-compliances observed during the inspection that was listed in the full report regarding microbiological laboratory were addressed by the manufacturer to a satisfactory level. It needs to be verified in next inspection.

11. Validation

Validation master plan
A validation master plan was written by QA according to an SOP. A separate procedure addressing computer systems, "computer system validation policy" was available.

Revalidation is conducted on a risk-based approach and/or the outcome of a PQR with the maximum time line identified as five years. These documents were found acceptable.

Process validation
The process for Linezolid Form 2 was revalidated in 2017. The process validation protocol and report were available. Batches used during the study were documented. Details in the protocol and report were comprehensive and included critical parameters, equipment, gauges and personnel. Included was reference to a change control regarding the introduction of the use of reactors.

Water system
At the time of the inspection, the water system was being revalidated (Phase III) with a planned completion. IQ, OQ and PQ documents were available for requalification with the PQ describing the three-phase requirement. The sampling plan was according to an SOP. The TAMC specification had a specification alert limit, action limit and maximum 100cfu/ml.

Cleaning validation
Cleaning validation was managed according to an SOP. The record for cleaning validation of product changeover was checked. Non-compliances observed during the inspection that was listed in the full report regarding cleaning validation were addressed by the manufacturer to a satisfactory level.

12. Change control

Changes were controlled according to an SOP. Several changes relating to the facility and Linezolid in the inspection scope have been made since last inspection and were reviewed. Non-compliances observed during the inspection that was listed in the full report regarding change control were addressed by the manufacturer to a satisfactory level.

13. Rejection and re-use of materials

Reprocessing and reworking
Reprocessing and Reworking procedure was described in an SOP which stated that reprocessing was not to be conducted and reworked batches were never to be dispatched to regulated markets, including WHO markets, unless pre-approval was obtained. Reworked batches were assigned new batch numbers with details recorded in a logbook. Traceability was vis the OOS procedure.

Returns

Handling returned goods was described in an SOP. QA were responsible for primary investigation to check that seals were intact and that the transport was correct. It was stated no returned batch would be sent to the regulated markets without addressing the WHO markets.

Recovery of materials and solvents

There was no recovered solvent used for the WHO product as per the commitment made in the DMF.

14. Complaints and recalls

Product complaints were handled according to an SOP. Complaints were classified into critical, major and minor. A complaints register was maintained. No complaints for Linezolid API were recorded in 2017 and 2018.

Product recall was managed according to an SOP. A mock recall was performed once every two years. No recall was recorded since the last WHO inspection.

15. Contract manufacturers (including laboratories)

Contract laboratories were evaluated according to an SOP "vendor evaluation for contract testing laboratories". QA conduct an audit of the laboratory and an agreement was drawn up. An agreement with the laboratory contracted for XRD analysis and a report were reviewed. Details were acceptable.

PART 3

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. *Linezolid APIMF-286* manufactured at ***Optimus Drugs Private Limited*** located at ***Survey No. 239 and 240, Dothigudem (V), Pochampally (M), Yadari – Bhuvanagiri (D) 508284, Telangana, India*** was 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.

PART 4 Guidelines and Standards

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 GMP for APIs or WHO TRS No. 957, Annex 2***
   http://apps.who.int/medicinedocs/documents/s20119en/s20119en.pdf

2. WHO good manufacturing practices for pharmaceutical products: main principles. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-eighth Report Geneva, World Health Organization, 2014 (WHO Technical Report Series, No. 986), Annex 2. ***Short name: WHO TRS No. 986, Annex 2***
   http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_986/en/

3. WHO good manufacturing practices: water for pharmaceutical use. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fourth-sixth 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/

4. 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

5. Guidelines on heating, ventilation and air-conditioning systems for non-sterile pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-second Report Geneva, World Health Organization, 2018 (WHO Technical Report Series, No. 1010), Annex 8. **Short name: WHO TRS No. 1010, Annex 8**
   http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_1010/en/

6. 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

7. WHO Good Practices for Pharmaceutical Quality 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. 961, 957), Annex 1
   http://www.who.int/medicines/publications/44threport/en/

8. 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 2
http://www.who.int/medicines/publications/44threport/en/

9. 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

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

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