World Health Organization

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Prequalification Unit Inspection Services
WHO PUBLIC INSPECTION REPORT
(WHOPIR)
Active Pharmaceutical Ingredient Manufacturer

Part 1	**General information**
Manufacturers details	
Name of manufacturer	Optimus Drugs Private Limited
Corporate address of manufacturer	7th Floor, Maximus Towers, 2A Raheja Mindspace IT Park, Madhapur, Hitec city, Hyderabad, Telangana India – 500081
Inspected site	
Name & Address of inspected manufacturing site if different from that given above	Optimus Drugs Private Limited, Unit-I Survey Number: 239 & 240, Dothigudem Village, Pochampally Mandal, Yadadri-Bhuvanagiri District, Telangana, India GPS coordinates: 17°17'18.9"N, 78°51'03.1"E Data Universal Numbering System (D-U-N-S): 86-376-7205
Synthetic Unit /Block/Workshop	Blocks 2, 4 and 5 Note: in comparison to the scope of the last WHO inspection, production block 1 was not covered during this inspection as production operations of WHO prequalified products were no longer performed at that block. The new production block 5 which started operation in 2021 was covered during this inspection as block 5 hosted some production activities of the WHO prequalified products.
Manufacturing license number	License granted from Local Drug Control Administration holding the manufacturing license in Form 25 bearing number: 25/NG/AP/2008/B/R renewed on 10/09/2023 with a valid period up to 08/09/2028. Form 28 bearing number: 28/NG/AP/2012/B/G renewed on 03/08/2022 with a valid period up to 02/08/2027.
Inspection details	
Dates of inspection	9 – 11 October 2024
Type of inspection	Routine inspection
Inspection record number	INSP-API-2019-0154
Introduction	
Brief description of the manufacturing activities	Optimus Drugs Pvt. Ltd, Unit-I was established in 2006 and was engaged in the manufacturing of Active Pharmaceutical Ingredients (drug substances) and Intermediates (drug intermediates).
General information about the company and site	Optimus Drugs Private Limited was founded in 2004 as a small synthetic laboratory to develop intermediates for Active pharmaceutical ingredients. The company is headquartered in the city of Hyderabad. The company had four manufacturing sites: three sites for manufacturing intermediates and APIs and one site for finished dosage forms (formulations). Unit 1 is located about 61.8 Km away from Hyderabad Airport and 775 Km from Mumbai airport. In May 2022, Sekhmet

<table>
<tr><td></td><td>Pharmaventures (the Indian subsidiary of the Asian-based Gamot API) acquired major stake in Optimus Drugs Group of companies.</td></tr>
<tr><td>History</td><td>The site was subject to three earlier WHO PQ inspections in April 2015, August 2016, and February 2019.

Below is the list of major regulatory inspections of Optimus Drugs Private Limited, Unit 1.
<table>
<tr><th>Regulatory / Health Authority</th><th>Year</th></tr>
<tr><td>World Health Organization (WHO), Geneva</td><td>April 2015, Aug 2016, and Feb 2019</td></tr>
<tr><td>US/FDA</td><td>March 2016 and May 2019</td></tr>
<tr><td>EU/GMP by Upper Franconia, Germany</td><td>June 2015 and June 2016</td></tr>
<tr><td>EU/GMP by Hungarian Authority</td><td>Sep 2019</td></tr>
<tr><td>COFEPRIS, Mexico</td><td>Jun 2014</td></tr>
<tr><td>Korean FDA</td><td>Jan 2014</td></tr>
</table></td></tr>
<tr><td colspan="2">Brief report of inspection activities undertaken – Scope and limitations</td></tr>
<tr><td>Areas inspected</td><td>The following GMP subjects were covered during the inspection:
1. Quality management
2. Personnel
3. Buildings and facilities
4. Process equipment
5. Documentation and records
6. Material management
7. Production and in-process controls
8. Packaging and identification labelling of APIs and intermediates
9. Storage and distribution
10. Laboratory controls
11. Validation
12. Change control
13. Rejects and reuse of materials
14. Complaints and recalls
15. Contract manufacturers (including laboratories)</td></tr>
<tr><td>Restrictions</td><td>NA</td></tr>
<tr><td>Out of scope</td><td>Other products and/or processes outside the scope of WHO pre-qualification were not inspected.</td></tr>
<tr><td>WHO APIs (including WHO API or APIMF numbers) covered by the inspection</td><td>• WHOAPI-286: Linezolid, prequalified, TB
• APIMF286: Linezolid, accepted, TB
• WHOAPI-438: Molnupiravir, prequalified, COVID-19
• APIMF438: Molnupiravir, accepted, COVID-19</td></tr>
<tr><td>Major changes since the last WHO inspection</td><td>Several changes were introduced to the site since the last WHO inspection conducted in 2019:
▪ Warehouse
o Expanded finished goods storage area within the same floor.
o Relocation of solvent tank farm area by installing additional capacity of tanks for storage of bulk solvents.
o Additional warehouse-3 was facilitated for storage of liquid materials in drums.</td></tr>
</table>

	▪ **Production** o Production block-5 started its operations with two clean room modules. o Additional two clean room modules were installed and operational from production block-3. o Few equipment's were replaced in PB-1, PB-3, PB-4 and PB-5 with bigger capacities. ▪ **Engineering** o Purified water distribution system-2 was installed and in operation to cater production block-5, production block-4 and production block-3. ▪ **Quality control** o Additional instruments, HPLC and GC were installed. o QC lab expanded and installed new instruments including ICP-MS, PXRD and DSC. o Walk-in stability chambers were installed. o Laboratory Information Management System (LIMS) was implemented for all QC workflow activities. ▪ **Other ongoing and planned changes** o Material management system, SAP was under qualification. o Integration of LIMS and SAP was under development. o EM pro application for digitalization of microbiology department workflows was under qualification. o Digitalization of the QMS was under finalization with vendors. o Building a new warehouse with extended capacity for the storage of raw materials.
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

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
WFI	Water for injection

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

1. Quality management

Principles, quality manual (QM) and quality policy (QP)

Quality Manual was in place. The quality policy included in this manual stated that Optimus was committed to maintaining the highest quality standards in the research, development, and manufacturing of pharmaceutical products. This commitment was sought to be achieved through periodic reviews and continual improvement of the Quality Management System (QMS), striving to enhance customer satisfaction.

The Quality Manual covered all aspects of the product life cycle and management involvement, ensuring that adequate resources were made available. It provided a concise description of all related components of the QMS along with the related roles and responsibilities.

Quality unit (QU)
The QU was involved in core processes such as business development, design and development, production (and service provision), purchasing, and delivery. It also supported processes such as QA, QC, and engineering. SOP on the responsibilities of the QU stated that the QC and QA were individual departments. The responsibilities of QA were comprehensively outlined. In the same document, the responsibilities of QC were also detailed, with no overlapping observed.

Management review (MR)
The SOP for MR was reviewed. The SOP defined the frequency (twice per year), attendance, agenda, and documentation requirements of the MR meetings. A planner was established annually for MR meetings. In 2024, two MR meetings were conducted. Attendance was documented in the form of an attendance sheet. Chief Officers and Directors attended both meetings. MR meeting minutes were available and were signed by the management representative. The meetings started with follow up on actions from the last MR meeting, followed by review and discussion of different quality aspects including deviations, changes, recalls, returns, audits, OOS and others.

Product quality review (PQR)
The periodic product review was governed by SOP for PQRs. As part of the continuous manufacturing verification, a report was prepared every four months to monitor quality trends. The PQR report for Linezolid for the year 2023 for the WHO market was reviewed. The storage conditions for Linezolid were maintained at 30 °C.

The process validation status for each stage was listed, along with the batch numbers in question.

The PQR report for Molnupiravir for the year 2023 for the WHO market was reviewed. The process consisted of two stages, after which the API was produced. The product has two Key Starting Materials (KSM). There were no outstanding CAPAs from previous years, and stability data was available for ongoing stability studies.

Quality risk management (QRM)
The SOP for QRM was checked. A risk register was available.

A draft SOP entitled “data integrity policy” was in the process of establishment and implementation. The SOP was drafted to replace the policy on data integrity. A data integrity risk assessment (DIRA) was recently performed. The DIRA revealed reasonable control over data integrity aspects for activities related to warehouse, production, quality control and quality assurance. The DIRA also recommended some actions for enhancing data integrity controls through introduction of electronic systems for document control, QMS/PQS, and others.

Deviations
The SOP for deviation handling was reviewed. Root cause investigations were to be conducted as per the respective SOP and required closure within 30 days. Deviations were classified as either major or minor. It was confirmed that deviations needed to be reported immediately and documented in the batch record. Annual trending was performed, covering product, human errors, schedule deviations, process deviations, and equipment deviations. A trend was considered for similar deviations occurring up to three

times within two consecutive years. The trending of deviations for the year 2023 was reviewed. Some deviations were spot-checked.

Internal audit (self-inspection)

Internal audits were conducted in accordance with a well-established SOP. Audits for all sections of the factory were performed on a six-months frequency. The internal audit schedule for 2024 was reviewed and included checklists for all departments, ensuring data integrity for laboratories and production areas. The list of qualified internal auditors comprised staff from all departments.

Deficiencies were recorded using a standardized template, and CAPAs were addressed. Deficiencies were classified as critical, major, or minor, with responses due within 7 days. Non-conformances had to be rectified within 30 days, with QA reviewing the effectiveness of all CAPAs prior to the next internal audit.

CAPA management

CAPAs were managed through the respective SOP. All CAPAs raised were manually completed on the CAPA Form. Provision was made for quarterly and half-yearly monitoring on each individual form. The CAPA log indicated the closing date and was monitored by date. A few CAPAs were spot-checked.

2. Personnel

An organogram was well-established at Optimus Drugs Private Limited. The organogram was established as per the SOP for job responsibilities and organogram. The organogram provided for separation between production/operations and quality-related activities. The QA and QC activities at the site were assigned to two different appointed "Site QA Head" and "Site QC Head" reporting functionally to the "Vice President QA" and the "Vice President QC", respectively. However, both heads reported administratively to the "Vice President Site Head". The appraisals of the two mentioned heads were assigned to the respective "functional" supervisor (i.e., Vice President QA and Vice President QC) rather than to the Vice President Site Head to ensure the independence of the quality activities from the production operations.

Personnel qualification

Personnel interviewed during the inspection were adequately qualified based on education, experience and training. The responsibilities of all personnel engaged in the manufacture including production and control were specified in writing in the form of job descriptions. The job descriptions of the Vice President QA, Vice President QC, Vice President Site Head, Site QA Head, and Site QC Head were reviewed and found acceptable.

The site employed 326 staff on a continuous or fixed-term appointment basis. The site did not employ any temporary or seasonal staff.

Training activities were managed as per the SOP for employee training. Training needs were identified by the Heads-QA or designee in consultation with functional Heads. All new employees were given induction training prior to their actual involvement in manufacturing activities. The induction (initial procedural) training included, among others, the concepts and principles of GMP and QMS. If the new personnel belonged to manufacturing, after the initial procedural training, the new personnel took training on equipment and tools handling (practical training) under the supervision of experienced personnel for at least one month. Similarly, on-the-job training took place usually under the guidance of an immediate

supervisor or departmental head. Remedial training was also referenced in the SOP and was provided when evidence showed that the original training was not effective. For specialized trainings, in-house or external courses were organized. Effectiveness of training was assessed in the form of a questionnaire for cGMP-related training activities. For QC analysts' qualification, a dedicated analyst qualification procedure was in place. The latter SOP mandated the performance of a number of mandatory analytical techniques, after the initial procedural training, as part of the analyst qualification, namely analytical balance calibration, pH meter calibration, accuracy of pipetting, description/appearance, and solubility. Additional specified techniques were also assigned to QC analysts as part of their qualification based on their areas of work (e.g., titration, HPLC). The cGMP and QC annual training planners for 2024 were reviewed and examples of such training spot-checked. Records of training and qualification acquired by the employee were documented and maintained by the QA department. Examples of the latter records for one QC analyst were reviewed and found acceptable.

Personal hygiene

In general, as observed during the site tour and witnessing of actual manufacturing activities, personnel followed good sanitation and hygiene practices. An SOP on health and personnel hygiene was in place, which provided for good personal hygiene practices. Another SOP on employee medical checkup provided for pre-employment and regular (annual) medical checkup of the personnel. Proper gowning was observed before access to production and control areas. Personnel engaged in production activities avoided direct contact with the intermediates and APIs.

The SOP for colour coding and cleaning of garments was in place. The procedure provided for regular cleaning of garments used at different departments within the site. Garments used at the cleanrooms were regularly sent for cleaning by an outsourced cleaning service provider.

Consultants

Optimus Drugs Private Limited did not outsource any activities to individual consultants.

3. Buildings and facilities

Design and construction

Out of the five production blocks at Optimus Drugs Private Limited, three blocks were covered by this inspection being relevant to the inspection scope and at which production operations of WHO prequalified products took place. The three inspected blocks were block 2, block 4, and block 5. Within blocks 4 and 5, attention was given to cleanrooms at module 2 and module 1 where Linezolid and Molnupiravir, respectively, were crystallized, purified (centrifuged), dried, milled, sifted and packed.

In comparison to the scope of the last WHO inspection, production block 1 was not covered during this inspection as production operations of WHO prequalified products were not anymore performed at that block. The new production block 5, which started operation in 2021, was covered during this inspection as it hosted some production activities of the WHO prequalified products.

Utilities (e.g. steam, gases, compressed air, and HVAC system)

The utilities were briefly inspected noting that AHU were installed in pharma crystallizer, wet and dry powder processing areas in manufacturing blocks, as well as the sampling and dispensing rooms in the warehouse. Each processing zone (module) was supplied with HEPA-filtered air by dedicated system of AHU, ducts and supply/return air blowers, with no interconnections. Air supplied to the clean zone areas was filtered through pre-filters (20µm, 10µm) fine filters (5µm) and HEPA filters (0.3µm) to prevent

airborne contaminants. These filters were periodically cleaned /replaced. The periodic validation of air handling system was performed twice a year for airborne particle count test, and once a year for air velocity, number of air changes, HEPA filter leakage test, and recovery test.

The nitrogen and compressed air generation systems were inspected and found to be kept in a well maintained, clean, and tidy order. Related measuring equipment was regularly calibrated and tags indicating calibration status and the due date for calibration affixed to the equipment.

Water

The PW system began using municipal water in 2023, with borehole water serving as a backup system. Both borehole and municipal water were tested annually. After pre-treatment and filtration, the water was passed through RO and EDI units, followed by UV irradiation, into two stainless-steel holding tanks. Tank 01 supplied production blocks 1, 2, and 4, while tank 02 supplied production blocks 3 and 5. The second tank and distribution loop were installed in 2019.

Sanitisation of the loops was performed every 15 days by supplying hot water at no less than 80°C for 45 minutes. Qualification was initially performed, and requalification comprising phases 1, 2, and 3 was conducted after the introduction of municipal water. At the time of the inspection, the system was being revalidated, with phase three of the annual revalidation plan underway.

Tests for PQ of WPU included appearance, pH, conductivity, nitrates, heavy metals, TOC, bacterial endotoxins, and microbiological tests for the absence of *Escherichia coli*, *Pseudomonas aeruginosa*, *Salmonella species*, *Burkholderia cepacia*, and bile-tolerant gram-negative bacteria. The limit for TAMC was set at 100 CFU/ml.

The annual report of water quality for the period of January to December 2023 was reviewed. In addition to the annual report, monthly trending was performed.

Daily testing was applied for supply and return loops, and all other user points were tested once a month for purified water. Source water, both borehole and municipal, was tested once a year. Testing was outsourced, and the latest results were comprehensive, including but not limited to microbiological, chemical, and heavy metal analyses, all within the respective regulatory limits.

4. Process equipment

Design and construction

Equipment used for the APIs within the scope of the inspection was generally of good design and suitable for its 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

Preventive maintenance was conducted according to a well-established SOP. The SOP provided for preventive maintenance planning, execution, and documentation. The frequency of preventive maintenance varied from one equipment to another on a monthly, quarterly, semi-annual, or annual basis and the same was defined in the preventive maintenance master planner attached to the mentioned SOP. For example, the preventive maintenance master plan 2024 was reviewed and a few maintenance activities in relation to the rotary cone dryer at block 5 and the purified water system were spot-checked.

In general, equipment cleaning was properly performed as per the respective cleaning validation and well documented. A number of cleaning procedures and records were reviewed as follows:

- The procedure for cleaning of the tray dryer
- The procedure for cleaning of the multi-mill
- The procedure for cleaning of the vibro-sifter
- The product changeover cleaning record of the multi-mill
- The product changeover cleaning record of the vibro-sifter.

The cleaning types included batch-to-batch cleaning, product changeover, stage changeover, and periodical cleaning. The batch-to-batch cleaning was considered between batches of the same product. Product changeover cleaning was considered between batches of different products. Stage changeover cleaning was considered between batches of different stages of the same product. Periodical cleaning was considered in case of extended production campaign, after a specified number of batch-to-batch cleaning. Batch-to-batch cleaning was always considered prior to product changeover cleaning. CEHT and DEHT were defined and justified as per the respective CEHT and DEHT validation studies.

Calibration

The SOP for calibration of measuring, monitoring instruments and master instruments [calibrator] described the requirements for the calibration of all measuring and monitoring instruments. Non-critical equipment was calibrated once a year. Critical equipment, on the other side, was calibrated on a semi-annual or annual basis, as per an annexure attached to the mentioned SOP. Some calibration activities were undertaken internally while others were outsourced. Calibration activities were performed at ranges that encompassed the operating ranges of the respective measuring instruments. The schedule for calibration activities in 2024 was reviewed and a few calibration activities were spot-checked, including calibration of the tray dryer and of the centrifuge at block 4 module 2.

Computerized systems

No computerized systems were used for material or production control of WHO prequalified APIs.

A computerized system Empower 3 was used in the QC laboratory with HPLC and GC equipment being networked. Basic data integrity controls were in place. The computerized system validation (CSV) of the Water Empower® 3 was reviewed and found reasonable. Please refer to the section on validation for further details on CSV.

Autoclave cleaning and usage

The Operation and Cleaning Procedure of the horizontal double-door autoclave was reviewed. Loading pattern schematics were available. Daily vacuum leak tests and chemical indicators were conducted with each load. Bowie-Dick tests were performed monthly, and High-Pressure Vacuum Pump (HPVP) tests were conducted once every three days. Printouts of these tests were available, signed by the responsible personnel, and checked. A Bowie-Dick card/pouch was attached to the printout of each cycle.

5. Documentation and records

Documentation system and specifications

The SOP for document control was checked. The SOP provided for document generation, review, and approval, as well as document distribution and retrieval. The issuance of the batch records was also covered by the same SOP. Batch records issued by QA were stamped as such, along with indication of the batch number on each page of the issued records.

The SOP for preparation, review, approval, distribution, and retrieval of SOPs was in place. The SOPs index was reviewed and indicated the SOPs' effective and review dates. The latter date was spot-checked for a number of SOPs.

Equipment cleaning and use of records

Activities pertinent to equipment use, cleaning, and maintenance were logged in the respective log books. A few log books were spot-checked during the site tour, including the log books of the multi-mill and sifter at block 4 used for the milling and sifting of Linezolid API.

Master production and control records

The master records of production and control of WHO prequalified products were in place. The same was reviewed during the inspection and provided reasonable information on the relevant activities. Master records were stored in the document archiving area under the control of QA.

The master batch production record of Linezolid API was reviewed. The earlier versions of the master records were related to the original process modification for the production of Linezolid (version 00), the optimization of the process and the BPR after the successful completion of the PV (version 01), optimization of the in-process testing parameters (version 02) and finally the update of the BPR to include the information pertinent to the receivers (version 03). No change was introduced to the process of manufacturing Linezolid since the PV completion.

Batch production and control records

The batch production records of the produced API batches were well maintained. The following records were spot-checked:

- The batch packing record of Linezolid
- The batch production record of Linezolid ester
- The batch production record of Linezolid stage 1
- The batch production record of Molnupiravir

Laboratory control records

The laboratory control records of the produced API batches were well maintained. The following records were spot-checked:

- The batch control record of Linezolid
- The batch control record of Linezolid ester
- The batch control record of Linezolid stage 1
- The batch control record of Molnupiravir

For electronic data, a procedure for backup and restoring was in place. Regular backup of data was evidenced as provided within the respective electronic data backup log. Data recovery/restoration was spot-checked and found satisfactory.

Batch release

The procedure for batch release was checked. The release process was well documented for each batch in the form of a batch release checklist. A couple of checklists were used for batch release, namely analytical documents review checklist and batch production record review checklist. One more form

called "dispatch clearance form", as established by SOP for packaging, labelling and dispatch of intermediates and APIs, was used to clear the finished intermediate and API batches for release to the market. The list of persons authorized to perform batch release was established as per a statement made by the Vice President QA. The batch release task was assigned to 4 persons, including Vice President QA, Site QA Head, and a couple of QA officers at the site.

6. Materials management

General controls

All handling of materials and products, such as receipt, quarantine, sampling, storage, labelling, dispensing, processing, packaging, and distribution, was carried out in accordance with written procedures, and records were maintained accordingly. Material Safety Data Sheet (MSDS) were provided for all materials and made available at the warehouses. Four warehouses were available at the site: warehouse 1 for storage of liquid materials in drums, warehouse 2 for storage of intermediates and APIs on the first floor and solid raw materials at the ground floor, warehouse 3 for storage of liquid materials in drums, and warehouse 4 for storage of solvents in tanks.

Receipt and quarantine

Received incoming materials were kept in quarantine status until tested by QC and released by QA. Status labels were attached to the materials in addition to wrapping them with a color-coded ropes to help identify the status (quarantine, released, or rejected). All status labelling was carried out manually with appropriate labels defined in respective SOPs.

Sampling and testing of incoming production materials

Representative samples of the incoming materials were collected at dedicated sampling areas located within the respective warehouse. The sampling procedure included the number of containers to be sampled and amount of material to be taken. Sampling plan was designed based on the nature of the material. Special sampling procedures were written for water, including incoming, RO and PW, to carryout chemical and microbiological analysis. In-process sampling was carried out by the production-chemists and samples were sent to QC for analysis.

Final APIs were sampled by QC personnel after receiving a written test request from Production Department. After QA release, the APIs were transferred to dedicated area for storage of released batches.

Storage

Proper segregation between quarantined, released, returned, and recalled materials was in place. Rejected materials were status-labelled and transferred to a dedicated reject material room in the respective warehouse under lock and key till a decision on its appropriate disposition was made (e.g., return to supplier, reprocessing, destruction).

Supplier evaluation

The procedure for vendor qualification was in place. Supplier evaluation was made primarily through vendor questionnaire. Suppliers of key starting materials were assessed through audit and quality and performance testing of the material.

For Linezolid, three key starting materials (KSMs) were defined, and a sole supplier of each KSM was identified. The records of the vendor qualification of a couple KSM suppliers were spot-checked.

7. Production and in-process controls

Production operations

Production operations for WHO prequalified APIs were carried out in production blocks 2, 4, and 5. It is worth noting that production block 1 was covered during the last WHO inspection as some production operations were performed at block 1 at that time. In 2021, a change was introduced to the production process of Linezolid and, consequently, no more production operation was performed at block 1. On the other side, the newly built production block 5 started operation in 2021 and was used in production of both WHO prequalified products. In general, these production blocks were not dedicated to production of these WHO prequalified APIs and their intermediate. Production blocks 2, 4 and 5 were in operation at the time of inspection and the same was witnessed by the WHO inspection team.

The SOP for assigning manufacturing date for intermediates and API guided the establishment of manufacturing and retest dates. In the case of multiple lots per batch (e.g., multiple lots as output of the centrifuge), the manufacturing date was defined as the date of manufacture of the first lot. The same applied to blended batches where the manufacturing date was defined as the manufacturing date of the oldest batch of the blend. The manufacturing date of a reprocessed batch was defined as the same as the source batch (i.e., no change of date in case of reprocessing).

The handling policy provided a policy for the blending of batches. In general, blending of tailing batches was possible provided the respective validation study supported the same. For WHO prequalified products, as the mentioned validation study had not been performed, the blending of batches was not possible for Linezolid and Molnupiravir.

Final crystallization, purification (centrifugation), drying, milling, sifting, and packaging were performed in Grade D clean areas. The annual requalification of the AHU serving the drying, milling, sifting, and packing areas at block 4 was spot-checked. Additionally, the validation report of the same AHU was reviewed. Both qualification/validation activities were satisfactorily performed according to the respective standards.

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

Actual production operations were witnessed by the WHO inspectors during the inspection visit. Particularly, the following activities were observed:

- The unloading of Linezolid from the centrifuge at block 4.
- The charging of some raw materials and reactants into the reactor for the production of Rifaximin at block 5.
- The loading of Linezolid into the tray dryer at block 4.

8. Packaging and identification labelling of APIs and intermediates

Packaging operations of finished APIs were conducted in grade D cleanrooms of production block 4 (module 2) and 5 (module 1). In addition, a small packing area (grade D cleanroom as well as separate materials and personnel flows) was available for the packaging of small API quantities on the first floor of warehouse 2 (close to the finished API storage rooms).

The packaging and labelling were well documented in the form of batch packaging records. The latter included details on line clearance, materials used for the respective operation, documentation of the activities, as well as supervisor and QA checks.

9. Storage and distribution

APIs were stored in the Finished Goods Warehouse, where temperature was controlled, and humidity monitored for informational purposes only. Temperature records were requested and reviewed, with printouts signed daily by the warehouse manager. No out-of-temperature records were observed in the reviewed printouts.

10. Laboratory controls

The QC department was on the second floor of Building C and operated as an independent entity responsible for the physical, chemical, and microbiological testing (where applicable) of starting materials and packaging materials, in-process controls, stability studies, and (API testing. Process development was situated on the first floor of the same building. All materials received by QC for testing were sampled according to a predefined sampling plan and assigned a unique analytical report number. The samples were manually logged into individual logbooks. Analytical testing tasks were allocated as per a training matrix based on the analyst's skills and training for raw materials, packaging materials, in-process controls, stability studies, and finished products. All analytical data were recorded in analytical worksheets, which were subsequently reviewed by a reviewer and the responsible supervisor.

Receipt, testing, approval, and rejection of samples were managed through the respective SOP. In-process and in-house intermediate samples were provided by the manufacturing department, raw materials by QC, and finished products by QC in the presence of QA. The issuance of report templates was in accordance with the Document Control SOP. QC requested a raw data sheet to be issued by QA, that recorded the batch details and stamped the issued records accordingly.

As part of the review of the test report and data on electronic systems such as Empower, the Analytical Review Checklist included a statement that soft electronic data were reviewed satisfactorily and supported by e-signatures. This was performed in accordance with the Review of Analytical Documents SOP. The SOP had different checklists for each type of instrument, and included a requirement for audit trail checks for HPLCs, GC, UV, FTIR, Polarimeter, Auto Titrators, KF Titrator, etc. Start-up checklists for each type of instrument were also available and signed by both the analyst and the reviewer.

The procedure for preparation, review, and control of specifications and test procedures was discussed. QA issued the latest approved test method for use during the test procedures to QC, as recorded on the Document Distribution record.

During the inspection, it was noted that, in the case of a deviation or non-conformance, only the related test would be repeated, based on the outcomes of the investigation. The process was reviewed to ensure there was no risk of transcription errors or other issues. The test method was used by the analyst, and the reviewer had a checklist to confirm that all steps had been performed correctly, and that the recorded information was accurate.

The SOP for audit trail review of standalone instruments was reviewed. These reviews were conducted once a month by the reviewer or QC manager. Audit trail checklists were created. The audit trail for TOC (total organic carbon) was spot-checked, and no concerns were raised. Controls were in place to

identify any unintended activities on the system. TOC and conductivity testing for water was performed by the microbiology laboratory.

The good chromatographic techniques SOP was reviewed. The SOP indicated that, in the event of a system failure that caused the process to be aborted, the sequence had to be altered, and a proper comment had to be provided. The message center printouts were added to the records. Manual integration was to be performed, in accordance with the manual integration requisition form, which must be finally approved by QA after being signed by the HOD/Designated QC/AD. It also made provisions to reject if required.

Chromatography columns were dedicated for specific products. Upon receipt, the Certificate of Analysis (CoA) for each column was checked in accordance with the respective SOP, and a checklist was completed. Further verification was performed through a suitability run.

All reference materials were stored in a secured and temperature-controlled environment, in accordance with the required storage conditions. The pharmacopeial reference standard for Linezolid (USP) was presented during the inspection. Working standards were prepared from pharmacopeial reference substances (if available) and in accordance with the procedure for management of analytical standards. The preparation and qualification of the Linezolid working standards were reviewed. A total of 24 vials were prepared, one for each month over a period of two years. Identification numbers were assigned to each vial, and registers were utilized for recording the vials and their issuance.

The Certificate of Analysis (CoA) for finished products (FP) was prepared by QC, reviewed, and then approved by QA.

Trending was performed quarterly as part of the APQR process. Trends for Linezolid for 2023 were available. A document existed with criteria for determining OOT results during routine analysis.

The Stability samples management SOP was reviewed. Initial validation batches were placed on stability, along with three batches during re-validation. Subsequently, one batch per year was placed on stability. Samples were withdrawn on the scheduled date, as per protocol, or within four days thereafter.

At the time of inspection, the company utilized both manual and electronic systems. All batches already on stability, including Linezolid, were managed manually, while new batches placed on stability were managed through the Laboratory Information Management System (LIMS). The company had a total of nine stability chambers with the following temperature and humidity ranges:

- 30 °C ± 2 °C / 65 % ± 5 % RH
- 40 °C ± 2 °C / 75 % ± 5 % RH
- 30 °C ± 2 °C / 65 % ± 5 % RH
- 5 °C ± 3 °C
- 25 °C ± 2 °C (Photostability)
- 40 °C ± 2 °C / 75 % ± 5 % RH, 25 °C ± 2 °C / 60 % ± 5 % RH, 30 °C ± 2 °C / 75 % ± 5 % RH, and 30 °C ± 2 °C / 65 % ± 5 % RH
- 30 °C ± 2 °C / 65 % ± 5 % RH
- 25 °C ± 2 °C / 60 % ± 5 % RH
- -20 °C ± 5 °C

The protocol for Linezolid stability under the following conditions was reviewed: 40 °C ± 2 °C / 75 ± 5 % RH for six months, 30 °C ± 2 °C / 75 ± 5 % RH for 12 months, and long-term at 25 °C ± 2 °C / 30 ± 5 % RH, 30 °C ± 2 °C / 60 ± 5 % RH, and 30 °C ± 2 °C / 75 ± 5 % RH, based on the climate zones for WHO products. A full spectrum of stability tests, including microbiological and pathogen tests, was performed for up to 36 months. The stability results for the three validation batches were available and within the required limits. Results for a batch placed on stability in 2023 were reviewed and found to be within the required limits.

The Stability Protocol for Molnupiravir was applied to three validation batches manufactured in 2022. Results up to 24 months were available and found to be within the specified limits.

Expiry and retest dating process was managed according to the respective SOP, which covered the retesting of raw materials, intermediates, and finished products

Raw materials could be retested every year for up to 5 years, with a cut-off if the re-test date was less than 5 years. The stability date would determine the shelf-life extension for finished products (FP).

Handling of OOS was managed as per a dedicated SOP. Investigations consisted of three phases:

- Phase 1: pertained to laboratory errors and was further divided into Phase 1a (obvious laboratory error) and Phase 1b (other than obvious error). Phase 1b could include hypothesis testing, which was comprehensively described in the SOP. It was confirmed that re-sampling could only be performed when justified.
- Phase II: A full-scale investigation.

Trending of OOS for January to June 2024 was reviewed. Errors were categorized into machine, man, method, process, material, and other. Valid versus invalid OOS was recorded and presented on a graph in numbers and percentages.

The SOP for retention samples was in place. Samples were stored in this area for one year after their expiry date, with sufficient quantities retained to ensure the completion of two full tests. All samples were appropriately labelled, and a logbook was maintained to record sample receipt and expiry dates. The temperature was maintained below 25°C, with a sound alarm linked to the temperature monitoring system.

Microbiology laboratory

The microbiology laboratory was separate from the chemistry laboratory. Testing included water analysis, product analysis, and culture handling. Preparation of media, handling of cultures, and other tests were performed in separate areas. Adequate quantity of incubators was available.

The records for *Clostridium sporogenes* were reviewed and compared with the process described in the procedure. No discrepancies were observed. Characterization and purity checks were in place and corresponded with the "record for receipt, revival, seed lot preparation purity check for standard cultures." From the seed lot, slants were prepared as passage 3 and recorded in the culture maintenance record. From this, a culture suspension was prepared (passage 4). No issues were reported.

The report for the holding study of prepared media performed in 2014 for R2A agar was reviewed. *Bacillus subtilis* (ATCC 6633) was chosen due to its spore-forming nature and as a worst-case scenario. For normal growth promotion, each medium's organisms were listed, for example*, Pseudomonas aeruginosa, Staphylococcus aureus, Aspergillus brasiliensis*, and *Candida albicans* for AgarP. Results for all media were reviewed and found to be satisfactory.

The SOP for environmental monitoring in controlled areas of manufacturing and warehouse [sampling and dispensing areas] outlined the process for monthly settle plates and air sampling.

The report for cleanroom area validation of production block-4 (modules I, II, and III) by viable monitoring indicated that all results were below alert limits. Similarly, the report for block 5 for cleanroom area requalification of production block-5 (modules I, II, and crystallizer area) by viable monitoring, showed all results below alert limits.

Release labels (UP)

Product labels were printed using a software system and included the following information: batch number, manufacturing date, retest or expiry date, gross weight, tare weight, net weight, container number, storage conditions, and manufacturing license number. Additionally, the labels featured the name and address of the manufacturer, and a QR code generated by the DataKart software system. QA was responsible for ensuring that reconciliation and record keeping were completed. The in-house release labels also included the grade of material.

The labels of the finished API batches ready for distribution to the market were differentiated from the labels of approved finished API batches awaiting QA release. The same applied for quarantined, rejected and returned finished APIs.

11. Validation

Validation policy

A Validation Master Plan was in place. The policy established an interval of once every 5 years, at the latest, for the revalidation and requalification activities.

Separate documents addressing computer systems validation were in place, namely computerized system validation master plan and computer system validation policy. The latter policy guided CSV in terms of risk assessment, categorization, qualification/validation, periodic review, retirement and revalidation of computerized systems. Both aforementioned documents set the policy for computerized system period review and revalidation at maximum 1 and 5 years, respectively (unless a change was introduced to computerized system sooner than the set interval). The list of computerized systems used in the manufacture of intermediates and APIs at Optimus Drugs Private Limited was available. The CSV report of the Waters Empower® 3.6.0 server and its client systems was spot-checked, including the initial gap assessment, GAMP categorization, IQ, OQ, and PQ.

Validation documentation

Validation activities were well documented in the respective protocol and reports, as provided for in the validation policy.

Qualification

Guidance on equipment qualification was provided in the VMP and equipment qualification SOP. In general, production and control equipment were kept at a satisfactory status of qualification. The equipment qualification status report for 2023 was reviewed and the following was spot-checked.

- The operational qualification of the rotary cone vacuum dryer at module 1 of block 5
- The requalification of the multi-miller at module 2 of block 4
- The operational qualification of the multi-miller at module 1 of block 5
- The operational qualification of the sifter at module 1 of block 5

Process Validation

The SOP for process validation guided activities and controls related to PV, including relevant documentation in the form of PV protocols and PV reports. Process validation involved a series of three stages of activities taking place over the life cycle of the product and process, namely (1) process design, (2) process qualification, and (3) continued process verification. The SOP also guided re-qualification of process (i.e., process revalidation) needed in case of major changes (e.g., manufacturing process, starting materials, production area, critical process equipment). Periodic review of the performance of the process, as evidenced by continued process verification exercise, could result in extension of the PV status even beyond the limit of 5 years. The PV of WHO prequalified product was reviewed as follows:

- Process performance qualification report of Linezolid
- Process performance qualification report of Molnupiravir [final API]
- Process performance qualification report of Molnupiravir [intermediate]

Cleaning Validation

The SOP for cleaning validation (CV) was in place. The limits for cleaning validation activities were calculated based on permitted daily exposure (PDE) limit, therapeutic index (LD50) limit, and general limit of 10 ppm. The lowest limit among these three calculations was considered for CV. The CVs report for Linezolid was reviewed. The toxicological report on the PDE was checked.

The clean equipment holding time study protocol and report, as well as the dirty equipment hold time study protocol and report, were reviewed.

Autoclave qualification

Three runs were performed annually for empty load, minimum load, and maximum load. The empty load cycle was used for heat distribution studies. Heat distribution and penetration studies were conducted with biological and chemical indicators for minimum and maximum loads, as well as three additional loads including accessories.

12. Change control

The SOP for change control was in place and operated on a manual documentation system. A list of changes applicable to the system was maintained, categorized as critical, major, or minor. A few changes were reviewed and spot-checked.

13. Rejection and re-use of materials

Reprocessing and reworking

The SOP for reprocessing and reworking was in place and stated a policy not to perform any rework. APIs and intermediates could be reprocessed, after the approval of QA. Before processing, the concerned intermediate or API should be investigated thoroughly to find and document the root cause for the nonconformance. The reprocessed batch was automatically included in the stability testing and monitoring program. The SOP mandated no reprocessed batches to be supplied to regulated markets (US, EU, Korea, Japan, Canada ,and WHO) unless approval by the respective authority was granted. The SOP also provided for consideration of re-validation for process adjustment and optimization in case of repeated need for reprocessing.

The reprocess log was checked and it was found that no reprocessing was considered for Linezolid or Molnupiravir in 2024.

14. Complaints and recalls

Product complaints were managed in accordance with the respective SOP. Complaints were categorized as critical (to be addressed within 10 days), major (within 20 days), and minor (within 30 days). Complaint trends were analyzed biannually, and the effectiveness of CAPAs was reviewed.

A complaints register was maintained, recording four complaints in 2023, none of which involved WHO APIs. In 2022, one complaint was recorded. A cross-functional team conducted an investigation using the fishbone method. The control sample was tested and found compliant. As a corrective action, the customer was requested to perform a re-analysis, which yielded results within the specified limits.

Product recall was managed according to a well-established SOP. A mock recall was performed once every two years. Recalls were classified based on urgency: Class I recalls were actioned immediately, including out of working hours; Class II recalls within 48 hours; Class III recalls within 5 days; and Class IV recalls were cautions on use. No recall has been recorded since the last WHO inspection.

Records of the mock recall performed in 2022 was reviewed. The concerned product batch was selected by the QA/designee and was widely distributed to various markets. This was a class II simulation, performed during office hours. No variations were observed in the quantity issued, and responses were generally received in less than 30 hours.

15. Contract manufacturers (including laboratories)

The SOP for vendor evaluation for contract services was in place. Testing laboratories were inspected every two years. Only one laboratory was used for testing Epichlorohydrin Content by GC-MS (ppm) for the WHO market. Two QA personnel and one QC person conducted an audit of this laboratory. A report was available on the inspection, and an agreement was in place and was found acceptable.

Part 3	Conclusion – Inspection outcome

Based on the areas inspected, the people met and the documents reviewed, and considering the findings of the inspection, including the observations listed in the Inspection Report, **Optimus Drugs Private Limited** located at **Survey Number: 239 & 240, Dothigudem Village, Pochampally Mandal, Yadadri-Bhuvanagiri District, Telangana, India** was considered to be operating at an acceptable level of compliance with WHO GMP Guidelines for APIs.

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

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

Part 5	List of GMP guidelines referenced in the inspection report

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

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

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

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

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

6. WHO good practices for pharmaceutical quality control laboratories. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth Report. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957, Annex 1.
   Short name: WHO TRS No. 957, Annex 1
   https://www.who.int/publications/m/item/trs957-annex1

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

8. Guidelines on heating, ventilation, and air-conditioning systems for non-sterile pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-second Report Geneva, World Health Organization, 2018 (WHO Technical Report Series, No. 1010), Annex 8.
   Short name: WHO TRS No. 1010, Annex 8
   https://www.who.int/publications/m/item/Annex-8-trs-1010

9. Guidelines on heating, ventilation, and air-conditioning systems for non-sterile pharmaceutical products. Part 2: Interpretation of Guidelines on heating, ventilation, and air-conditioning systems for non-sterile pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-third Report Geneva, World Health Organization, 2018 (WHO Technical Report Series, No. 1019), Annex 2.
   Short name: WHO TRS No. 1019, Annex 2
   https://www.who.int/publications/m/item/trs1019-annex2

10. WHO guidelines on transfer of technology in pharmaceutical manufacturing WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-fifth Report Geneva, World Health Organization, 2022 (WHO Technical Report Series, No. 1044), Annex 4.
    Short name: WHO TRS No. 1044, Annex 4
    https://cdn.who.int/media/docs/default-source/medicines/norms-and-standards/guidelines/production/trs1044-annex4-technology-transfer-in-pharmaceutical-manufacturing.pdf

11. WHO good manufacturing practices for sterile pharmaceutical products. Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-fifth Report Geneva, World Health Organization, 2022 (WHO Technical Report Series, No. 1044), Annex 4.
    Short name: WHO TRS No. 1044, Annex 2
    https://www.who.int/publications/m/item/trs1044-annex2

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***
https://www.who.int/publications/m/item/trs943-annex3

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
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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
https://www.who.int/publications/m/item/trs981-annex2

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
https://www.who.int/publications/m/item/annex-3-trs-981

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
https://www.who.int/publications/m/item/tr961-annex14

17. Good Manufacturing Practices: Guidelines on validation. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-third Report Geneva, World Health Organization, 2019 (WHO Technical Report Series, No. 1019), Annex 3.
Short name: WHO TRS No. 1019, Annex 3
https://www.who.int/publications/m/item/trs1019-annex3

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
https://www.who.int/publications/m/item/trs992-annex4

19. 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**
https://www.who.int/publications/m/item/trs961-annex9-modelguidanceforstoragetransport

20. 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
https://www.who.int/publications/m/item/trs992-annex5

21. WHO Recommendations for quality requirements when plant – derived artemisinin 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
https://www.who.int/publications/m/item/trs-992-annex-6

22. Guideline on data integrity. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-fifth Report Geneva, World Health Organization, 2021 (WHO Technical Report Series, No. 1033), Annex 4.
Short name: WHO TRS No. 1033, Annex 4
https://www.who.int/publications/m/item/annex-4-trs-1033

23. 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 TRS No. 996, Annex 10
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24. Stability testing of active pharmaceutical ingredients and finished 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 10.
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Short name: WHO TRS No. 1033, Annex 2
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26. Points to consider for manufacturers and inspectors: environmental aspects of manufacturing for the prevention of antimicrobial resistance. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-fourth Report Geneva, World Health Organization, 2020 (WHO Technical Report Series, No. 1025), Annex 6.
Short name: WHO TRS No. 1025, Annex 6
https://www.who.int/publications/m/item/trs-1025-annex-6

27. Production of water for injection by means other than distillation. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-fourth Report. Geneva, World Health Organization, 2020 (WHO Technical Report Series, No. 1025), Annex 3.
Short name: WHO TRS No. 1025, Annex 3
https://www.who.int/publications/m/item/trs-1025-annex-3-water-for-injection

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Short name: WHO TRS No. 996, Annex 6
https://www.who.int/publications/m/item/annex-6-trs-996