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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	Aurore Life Sciences Private Limited
Corporate address of manufacturer	Plot # 68,69, 2nd Floor, Jubilee Heights, Beside Shilparamam, Madhapur, Hyderabad, Telangana. Pin Code: 500081 India
Inspected site	
Name & Address of inspected manufacturing site if different from that given above	Plot No. 180/2 & 3, Khazipally (V) Jinnaram (M) Sangareddy District Hyderabad Telangana 502319 India
Synthetic Unit/ Block/ Workshop	MB-I and MB-II
Inspection details	
Dates of inspection	22 to 24 May 2024
Type of inspection	Follow up inspection
Introduction	
Brief description of the manufacturing activities	Manufacturing and quality control of Intermediates and APIs
General information about the company and site	Aurore Life Sciences Private Limited acquired the site in 2019. The old facility was demolished, and a new facility constructed. This new facility was dedicated solely to the production of Intermediates and APIs. The company confirmed that highly sensitive materials (cephalosporin and penicillin), high potent drugs (cytotoxic and steroids) were not manufactured at this site. The production of any materials derived from animals or plants was excluded from the activities of the plant.
History	The initial WHO on-site inspection was performed in June 2023. The site was regularly inspected by CDSCO.

Brief report of inspection activities undertaken – Scope and limitations	
Areas inspected	Document reviewed: • Verified CAPAs implemented in response to the major deficiencies identified in the previous inspection report. Areas visited: • MB-I and MB-II • Warehouses for Finished API products • Quality Control laboratory • Contract Microbiology laboratory • Nitrogen system
Restrictions	The follow-up inspection primarily focused on verifying the CAPAs implemented to address the deficiencies identified in the previous inspection conducted in June 2023.
Out of scope	All other products and production facilities not relevant to the manufacture of Molnupiravir API on the site were outside of the inspection scope and were not visited.
WHO APIs (including WHO API or APIMF numbers) covered by the inspection	WHO API-437, APIMF437 Molnupiravir
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
DUNS	Dats Universal Numbering System
EDI	Electronic deionization
EHS	Environmental Health and Safety
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	Nonconformity
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 (where applicable)**

1. Quality management

A system for managing quality that involved the participation of management and appropriate manufacturing personnel was in place. Quality-related activities were defined and documented. The Quality department was independent of the Production department. Persons authorized to release intermediates and APIs were specified. Quality-related activities were recorded at the time they were performed.

Product quality review (PQR)

The 2023 APQR for Molnupiravir which covered the period from January to December 2023, was checked. The Molnupiravir batch manufactured in 2023, including the stability study and the stability study data, were documented, and the results were within specifications. No OOS was reported. The Change Controls related to the production and

starting materials of Molnupiravir were reviewed. The Change Controls for production were closed.

Management review

Management Review followed an approved SOP. The minutes of the last Management Review meeting were reviewed and discussed.

Quality risk management

The corrective actions taken to address the major deficiency identified in the Quality Risk Assessment were reviewed and found to be generally acceptable.

Deviations

The SOP for Handling of Events in the Quality Control Department was reviewed and discussed.

CAPAs

CAPAs were managed according to an approved SOP. Deficiencies noted in the previous inspection were reviewed and found acceptable.

Batch release

The following SOPs were reviewed and found acceptable:

- SOP for Sampling, Testing and Release of Intermediates and API
- SOP for Batch Release of Intermediate and API

The Molnupiravir PV batches release status in SAP was verified. The CAPAs taken to address the major deficiency identified in Batch Release were generally acceptable.

2. Personnel

An organization chart was available. The organization chart indicated the reporting relationships, including corporate functions. The key personnel in the various departments had pharmaceutical qualifications and were experienced in pharmaceutical manufacturing. At the time of the current inspection, the site employed approximately 218 employees.

3. Buildings and facilities

Production

There were three production blocks on the site. The building MB-I and MB-II were designed for multi-product production. The buildings and chemical area of production blocks MB-I, MB-II and the Clean room-2 in MB-1 were visited. The CAPA implementation with respect to control of contamination and cross-contamination was verified and found to be acceptable generally.

Warehouses

There were separate warehouses dedicated to packaging materials, solid raw materials, liquid raw materials, and final API products. Intermediates were stored separately.

The finished product warehouse was visited. The temperature in the warehouse was controlled. Appropriate areas for rejected, returned, and recalled final products were indicated. The validation batches of Molnupiravir API were kept in the storage room. The

status and quantity of the third validation batch produced after the previous inspection were checked.

Utilities

Air handling units

The Change Control to implement the actions outlined in the proposed CAPA for maintaining airlocks in the Intermediate drying area and the installation of a "Spot Exhaust System" to efficiently extract and remove dust particles, was verified and discussed.

Water system

The PW was used in the manufacture of APIs. The following documentation was reviewed:

- Specification and Test Procedure for Purified Water
- SOP for the Sampling Plan for the Purified Water System
- Daily Chemistry analysis and Microbiology analysis performed on specific sampling points
- Logbook of the Inward Register for Samples sent to Contract Testing Laboratories
- Trend analysis for PW for the period 01/2023 to 12/2023
- SOP for the Sampling of Potable Water, RO Water and Purified Water
- Form which detailed the requirements for Water Samples sent to the Outside Laboratory

Nitrogen system

The nitrogen system was briefly visited. The CAPAs with respect to the filter integrity monitoring were checked, including the updated P & ID of the nitrogen system and the SOP for the Operation and Testing of the Nitrogen Plant.

4. Process equipment

Design and construction

Equipment used in the manufacture of Molnupiravir was, in general, of appropriate design and size for its intended use. The procedures for equipment maintenance and cleaning were available for review.

Calibration

The equipment list and calibration schedule were available. The calibration status of selected equipment in production was checked and found to be valid.

Computerized systems

A computerized system was used in the QC lab for HPLC and GC networking, and SAP was used for material management and release of finished API products. Computerized systems were not used for production control.

5. Documentation and records

Documents related to the manufacture of intermediates or APIs were prepared, reviewed, approved and distributed according to written procedures. The issuance, revision, superseding and withdrawal of documents was manually managed. Master Batch Production Records (MBPR) and Standard Test Procedures of materials and products, and

qualification/validation protocols were prepared by and checked by individual departments and approved by QA.

Batch numbering system

The SOP for the Batch Numbering System was revised to include a procedure for having a unique product-specific batch number identification and the same procedure was integrated for manual batch numbering.

Batch Production Record review

The Molnupiravir Batch Production Record for the third process validation batch, and the associated records for the Intermediates used in this batch, were reviewed. Documents were considered acceptable generally.

Laboratory control records

The testing of starting materials, Intermediate and finished API, and the Analytical Record (AR) number allocation was discussed.

Equipment cleaning and use of record

The SOP for the Operating of Ancillary Manufacturing Equipment was checked and discussed.

6. Materials management

The Intermediate storage warehouse and the sampling room were visited. A CAPA triggered a Change Control, which included several improvement measures, were verified and found acceptable.

7. Production and in-process controls

Production operation

Production of Molnupiravir took place in MB-I and MB-II. The final crystallization, centrifuging, drying and packaging took place in the ISO 8 clean area. Humidity levels were controlled.

Contamination control

The SOP for Prevention of Cross Contamination was checked. The CAPA with respect to the qualification of the magnetic metal detector installed in the Sifting machine and associated documents were checked, including but not limited to:

- SOP for Strength Test of Magnetic Grill
- The qualification document of the Magnetic Grill and its certificate.

Time limits

The holding time for wet crude Molnupiravir was defined.

Blending batches of Intermediates and APIs

The SOP for the Blending Activities was checked. The procedure was established since the previous inspection.

8. Packaging and identification labelling of APIs and Intermediates

Packaging and labelling were not in operation at the time of inspection. The procedures for label issuance and control, and the packaging and labelling operations were checked. The SOP for the Preparation and Maintenance of Product Label was reviewed. The label issuance and reconciliation, and the packaging and labelling operations in a Batch Packaging Record were checked.

9. Storage and distribution

Warehousing procedures

Finished API products were stored in a designated warehouse and held until released by the authorized person. All activities were described in an SOP for the Warehouse Operation.

Distribution procedures

Distribution procedures for APIs and Intermediates were available and checked.

10. Laboratory controls

QC Laboratory

Chemistry laboratory

The QC Chemistry laboratory was briefly visited during the inspection and appeared to be well designed and adequately equipped. The laboratory was divided into the following sections:

- Instrumentation laboratory
- Wet analysis laboratory
- Spectral laboratory
- Stability study laboratory

Microbiology laboratory

A Microbiological laboratory was not available on the site. Microbiological testing for PW and API products were done by a contract laboratory,

Stability studies

The Protocol for Stability Study of Molnupiravir with following storage conditions was checked:

- Accelerated: 40℃ ± 2°C and 75% ± 5% RH
- Long Term: 25℃ ± 2°C and 60% ± 5% RH
- Zone IV B: 30℃ ± 2°C and 75% ± 5% RH
- Cold: 2℃ - 8°C

Stability Study Data Sheet for Molnupiravir accelerated storage condition at Initial, 1 Month and 2 Month was checked, and results were acceptable.

Calibration was performed according to the SOP for the Operation and Calibration of Walk-in Stability Study Chamber. The frequency for calibration was defined.

11. Validation

Validation policy

Validation and qualification policy and requirements were described in the Validation Master Plan.

Process validation (PV)

The following Molnupiravir PV documents were checked and considered acceptable:

- PV Protocol
- PV Report
- API Specification
- Stability study of PV batches

CAPAs taken to address the major deficiency identified in the Process Validation were generally acceptable.

Cleaning validation

SOP for Cleaning Validation was updated since the previous inspection. The Cleaning Validation Report for Molnupiravir and supporting documentation were checked.

12. Change control

Changes were managed according to the SOP for Change Control. Major changes since the previous inspection were checked. These changes were initiated in response to the CAPAs addressing deficiencies identified in the previous inspection and found acceptable.

13. Rejection and re-use of materials

Reprocessing and reworking

Reprocessing and reworking were managed according to a Reprocess Procedure and a Rework Procedure. The SOPs were checked and found generally acceptable.

Recovery of materials and solvents

Solvents and mother liquor were recovered in the various stages of API production. The company declared that no recovered solvents/mother liquor were used in the Molnupiravir production process. An SOP for the Use of Solvent Recovery was in place.

14. Complaints and recalls

Complaints

The procedure has remained the same since the previous inspection. There was no complaint for Molnupiravir as commercial batches have not been supplied to the market.

Recalls

Recalls were handled as per the SOP for Product Recall. The SOP described the sequence of actions to be followed, which included the retrieval of distribution data, notification to customers, receipt/segregation/inspection of returned product, investigation of cause and reporting corrective action. The QA Head was responsible for coordinating product recalls.

15. Contract manufacturers (including laboratories)

The Contract Microbiology Testing laboratory was visited. The Microbiology laboratory has been modified to address the major deficiencies made in the last inspection. The

implementation of the action plan and the updated Quality Agreement for Testing of Samples were verified.

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, ***Aurore Life Sciences Private Limited*** located at ***Plot No. 180/2 & 3, Khazipally (V), Jinnaram(M), Sangareddy (Dist.), Telangana. 502319, India*** was considered to be operating at an acceptable level of compliance with WHO GMP guidelines.

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

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

Part 4	List of GMP guidelines referenced in the inspection report

1. WHO good manufacturing practices for pharmaceutical products: main principles. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Eight Report Geneva, World Health Organization, 2014 (WHO Technical Report Series, No. 986), Annex 2.
   Short name: WHO TRS No. 986, Annex 2

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

3. 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

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

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

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

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

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 3.
   Short name: WHO TRS No. 957, Annex 3

9. WHO good manufacturing practices for sterile pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-Sixth Report Geneva, World Health Organization, 2022 (WHO Technical Report Series, No. 1044), Annex 2.
   Short name: WHO TRS No. 1044, Annex 2

10. WHO guidelines on technology transfer in pharmaceutical manufacturing. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-Sixth Report Geneva, World Health Organization, 2022 (WHO Technical Report Series, No. 1044), Annex 4.
    Short name: WHO TRS No. 1044, Annex 4

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**

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

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

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

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

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

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

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

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

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

21. 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

22. WHO general guidance on variations to multisource pharmaceutical products. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifties Report* Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 10.
Short name: WHO TRS No. 996, Annex 10

23. 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.
Short name: WHO TRS No. 1010, Annex 10

24. 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

25. Points to consider when including Health-Based Exposure Limits in cleaning validation. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-Fifth Report Geneva, World Health Organization, 2021 (WHO Technical Report Series, No. 1033), Annex 2.
Short name: WHO TRS No. 1033, Annex 2

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

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

28. Good chromatography practice. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-Fourth Report. Geneva, World Health Organization, 2020 (WHO Technical Report Series, No. 1025), Annex 4.
Short name: WHO TRS No. 1025, Annex 4

29. WHO good practices for research and development facilities of pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-Sixth Report Geneva, World Health Organization, 2022 (WHO Technical Report Series, No. 1044), Annex 6.
Short name: WHO TRS No. 1044, Annex 6

30. WHO good manufacturing practices for investigational products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-Sixth Report Geneva, World Health Organization, 2022 (WHO Technical Report Series, No. 1044), Annex 7.
Short name: WHO TRS No. 1044, Annex 7

31. WHO good manufacturing practices for excipients used in pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-Fourth Report. Geneva, World Health Organization, 2024 (WHO Technical Report Series, No. 1052), Annex 2.
Short name, WHO TRS No. 1052, Annex 2