## Part 1
### General information

<table>
<thead>
<tr>
<th>Manufacturers details</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Company information</strong></td>
<td></td>
</tr>
<tr>
<td>Name of manufacturer</td>
<td>Aurisco Pharmaceutical Co., Ltd.</td>
</tr>
<tr>
<td>Corporate address of manufacturer</td>
<td>Badu Industrial Park Zone, Tiantai, Zhejiang Province, 317200, P.R. China</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Inspected site</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Address of inspected manufacturing site if different from that given above</td>
<td>Badu Industrial Park Zone, Tiantai, Zhejiang Province, 317200, P.R. China</td>
</tr>
<tr>
<td>GPS: 29.118706 N, 121.055335 E</td>
<td></td>
</tr>
<tr>
<td>DUNS: 545319522</td>
<td></td>
</tr>
<tr>
<td>Unit / block / workshop number</td>
<td>Workshop 805</td>
</tr>
<tr>
<td>Manufacturing license number</td>
<td>ZHE 20050429</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Inspection details</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Dates of inspection</td>
<td>29 January - 1 February 2018</td>
</tr>
<tr>
<td>Type of inspection</td>
<td>Follow up inspection</td>
</tr>
</tbody>
</table>

### Introduction

**Brief summary of the manufacturing activities**

Production and quality control of APIs and intermediates

**General information about the company and site**

Aurisco Pharmaceutical Co. was founded in 2002. The company has three production sites. The site in Zhejiang Tiantai subjected to this inspection is located in Badu Industrial Park Zone. The site is surrounded by light industry. There are no other chemical or pharmaceutical manufacturers in the immediate vicinity. This site produces Tenofovir Disoproxil Fumarate and its intermediate PMPA in workshop 805. It also supplies intermediates to other API synthesis companies. The site also produces several steroidal APIs which are manufactured in a separate workshop.

**History**

This was the second WHO inspection of the Tiantai site. The previous inspection was conducted in April 2017. The site was inspected by USFDA in 2013 and Behörde für Gesundheit und Verbraucherschutz der Freien und Hansestadt Hamburg, Germany in 2016 with positive outcomes, however to note that the product scope and production blocks involved in those inspections were different to the WHO inspection.
### Brief report of inspection activities undertaken

<table>
<thead>
<tr>
<th>Scope and limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Areas inspected</strong></td>
</tr>
<tr>
<td>This was a follow up inspection to the April 2017 inspection which focused on the issues arising from the previous inspection as well as the production and control of Tenofovir Disoproxil Fumarate in Workshop 805. The inspection covered checking the CAPAs implemented following the critical and major deficiencies observed in the aforementioned WHO inspection as well as following sections of the WHO GMP text i.e.</td>
</tr>
<tr>
<td>• Quality management</td>
</tr>
<tr>
<td>• Personnel</td>
</tr>
<tr>
<td>• Buildings and facilities</td>
</tr>
<tr>
<td>• Process equipment</td>
</tr>
<tr>
<td>• Documentation and records</td>
</tr>
<tr>
<td>• Materials management</td>
</tr>
<tr>
<td>• Production and in-process controls</td>
</tr>
<tr>
<td>• Packaging and identification labelling of APIs and intermediates</td>
</tr>
<tr>
<td>• Storage and distribution</td>
</tr>
<tr>
<td>• Laboratory controls</td>
</tr>
<tr>
<td>• Validation</td>
</tr>
<tr>
<td>• Change control</td>
</tr>
<tr>
<td>• Rejection and reuse of materials</td>
</tr>
<tr>
<td>• Complaints and recalls</td>
</tr>
<tr>
<td>• Contract manufacturers (including laboratories)</td>
</tr>
<tr>
<td><strong>Areas visited:</strong></td>
</tr>
<tr>
<td>• Warehouses</td>
</tr>
<tr>
<td>• Workshop 805</td>
</tr>
<tr>
<td>• QC labs</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Restrictions</th>
</tr>
</thead>
<tbody>
<tr>
<td>NA</td>
</tr>
</tbody>
</table>

**Out of scope**

API products other than Tenofovir Disoproxil Fumarate (APIMF320) manufactured on this site were outside the scope of this inspection.

**WHO product numbers covered by the inspection**

Tenofovir Disoproxil Fumarate (APIMF320)
<table>
<thead>
<tr>
<th>Abbreviations</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AHU</td>
<td>air handling unit</td>
</tr>
<tr>
<td>ALCOA</td>
<td>attributable, legible, contemporaneous, original and accurate</td>
</tr>
<tr>
<td>API</td>
<td>active pharmaceutical ingredient</td>
</tr>
<tr>
<td>APQR</td>
<td>annual product quality review</td>
</tr>
<tr>
<td>BDL</td>
<td>below detection limit</td>
</tr>
<tr>
<td>BMR</td>
<td>batch manufacturing record</td>
</tr>
<tr>
<td>BPR</td>
<td>batch packaging record</td>
</tr>
<tr>
<td>CAPA</td>
<td>corrective actions and preventive actions</td>
</tr>
<tr>
<td>CC</td>
<td>change control</td>
</tr>
<tr>
<td>CFU</td>
<td>colony-forming unit</td>
</tr>
<tr>
<td>CoA</td>
<td>certificate of analysis</td>
</tr>
<tr>
<td>CpK</td>
<td>process capability index</td>
</tr>
<tr>
<td>DQ</td>
<td>design qualification</td>
</tr>
<tr>
<td>EM</td>
<td>environmental monitoring</td>
</tr>
<tr>
<td>FAT</td>
<td>factory acceptance test</td>
</tr>
<tr>
<td>FBD</td>
<td>fluid bed dryer</td>
</tr>
<tr>
<td>FMEA</td>
<td>failure modes and effects analysis</td>
</tr>
<tr>
<td>FPP</td>
<td>finished pharmaceutical product</td>
</tr>
<tr>
<td>FTA</td>
<td>fault tree analysis</td>
</tr>
<tr>
<td>FTIR</td>
<td>Fourier transform infrared spectrometer</td>
</tr>
<tr>
<td>GC</td>
<td>gas chromatograph</td>
</tr>
<tr>
<td>GMP</td>
<td>good manufacturing practice</td>
</tr>
<tr>
<td>HACCP</td>
<td>hazard analysis and critical control points</td>
</tr>
<tr>
<td>HPLC</td>
<td>high-performance liquid chromatograph</td>
</tr>
<tr>
<td>HVAC</td>
<td>heating, ventilation and air conditioning</td>
</tr>
<tr>
<td>IR</td>
<td>infrared spectrophotometer</td>
</tr>
<tr>
<td>IQ</td>
<td>installation qualification</td>
</tr>
<tr>
<td>KF</td>
<td>Karl Fisher</td>
</tr>
<tr>
<td>LAF</td>
<td>laminar air flow</td>
</tr>
<tr>
<td>LIMS</td>
<td>laboratory information management system</td>
</tr>
<tr>
<td>LoD</td>
<td>limit of detection</td>
</tr>
<tr>
<td>LOD</td>
<td>loss on drying</td>
</tr>
<tr>
<td>MB</td>
<td>microbiology</td>
</tr>
<tr>
<td>MBL</td>
<td>microbiology laboratory</td>
</tr>
<tr>
<td>MF</td>
<td>master formulae</td>
</tr>
<tr>
<td>MR</td>
<td>management review</td>
</tr>
<tr>
<td>NMR</td>
<td>nuclear magnetic resonance spectroscopy</td>
</tr>
<tr>
<td>NRA</td>
<td>national regulatory agency</td>
</tr>
<tr>
<td>OQ</td>
<td>operational qualification</td>
</tr>
<tr>
<td>PHA</td>
<td>process hazard analysis</td>
</tr>
<tr>
<td>PM</td>
<td>preventive maintenance</td>
</tr>
<tr>
<td>PpK</td>
<td>process performance index</td>
</tr>
<tr>
<td>PQ</td>
<td>performance qualification</td>
</tr>
</tbody>
</table>
Part 2  Brief summary of the findings and comments

1. Quality management

A formal documented system for quality assurance was established, with procedures covering all key quality elements being in place. Operations were specified in a written form and GMP requirements were essentially being met. The procedures that were reviewed and discussed during the inspection were generally of a satisfactory standard. Managerial responsibilities were appropriately specified in written job-descriptions. Product and processes were monitored, and these results considered during batch release; regular monitoring and reviews of the quality of pharmaceutical products were being conducted according to documented schedules and procedures.

The company organization and key staff including General Manager, QA Vice General Manager and QA Director have been changed since the last inspection. The Quality Unit was divided into QA and QC, which was managerially separate from the production department. At the time of the inspection, the post of QA manager was vacant and it was planned for the post to be filled later during February 2018.

The Production VP had overall responsibility for managing production activities and there was a manager for each of the production Workshops. Responsibilities were described in the relevant job descriptions for the key personnel.

Internal audits (self-inspection)
Internal audit was not reviewed in detail during this inspection.
Product quality review (PQR)
PQRs were performed according to an SOP. It was required that PQRs be done annually using data from all batches of APIs produced during the review period. The SOP specified the review of intermediate and API test results, OOS batches, deviations, changes, stability monitoring, returns, complaints and recalls.

The Tenofovir Disoproxil Fumarate (B2) PQR for 2017 was reviewed. There was one OOS batch, no complaints and no returns. There were two batches manufactured in 2016 that had been recalled due to contamination issues discovered in the last inspection. TDF B2 was released in 6 different quality grades all produced by a single process.

PMPA, an intermediate of TDF B2 was supplied to outside API manufacturers as a commercial product. The PMPA 2017 PQR was also reviewed.

Quality Risk Management
A Quality risk management procedure was revised and the FMEA tool for quality risk management had been established. The FMEA model and an associated template had been introduced since the last inspection.

The risk assessment report for cross contamination for Workshop 805 with risks from other workshops was reviewed. The controls in place and monitoring results of steroid residues appeared satisfactory.

Management review
An SOP had been implemented since the last inspection. The procedure requires review and the summarization of separate reviews of CAPA, Audits and Customer Feedback, PQRs, EM, Deviations and OOS.

Deviations
Deviations were handled according to written procedures. Deviations were classified into critical and non-critical as per the SOP. A deviation regarding the B2 OOS bath was reviewed. Non-compliances observed during the inspection that was listed in the full report regarding deviation management, were addressed by the manufacturer to a satisfactory level.

2. Personnel

Personnel qualifications
At the time of the inspection 388 people were employed. There appeared to be a sufficient number of personnel who were qualified through qualifications, experience and training. There was a training programme in place in support of routine GMP training.

Personnel hygiene
Personnel were required to wear protective clothing suitable for the type and stage of manufacturing. Suitable sanitation and change room facilities were provided. Smoking and eating was not permitted in manufacturing areas.
3. Buildings and facilities

Design and construction
The buildings and facilities inspected were designed and constructed to facilitate cleaning, maintenance and operations as appropriate to the type and stage of manufacture. Manufacturing areas were spacious to allow placement of equipment.

The chemical and clean area in Workshop 805 were inspected. Workshop 805 included a general chemical synthesis area and a clean area (classified as Grade D) for crystallization, harvesting and packaging – the latter not dedicated to only B2 API’s.

The design of the rooms, placement of equipment and maintenance thereof appeared suitable for the processes involved with the synthesis of B2.

Since the last inspection, a new API pilot batch, an B2 analogue was manufactured in Workshop 805.

HVAC System
A 100% fresh air HVAC system was used in Workshop 805 clean area. Workshop 805 was stated to have a dedicated AHU equipped with G3 Prefilter, F5 Filter and HEPA final filters.

Water system
Purified water (PW) was not used in the final purification stages of the API manufacturing but for equipment washing. The system was designed using double reverse osmosis to produce purified water. The PW generation system was linked to two distribution loops, one was dedicated for Workshop 805 (B2 line) and the second for all other workshops. This system remains the same as at the last inspection.

Containment
The final synthesis, purification and packaging of B2 API took place in a non-dedicated facility shared with other products. The workshop is well segregated from those producing steroidal APIs.

Lighting
The lighting in all warehouses and production areas, and the QC laboratory was considered to be suitable.

Sanitation and maintenance
All areas inspected were clean and appeared to be well maintained.
4. Process equipment

Design and construction
Equipment used in the manufacture of B2 API appeared to be of appropriate design and size for its intended use, cleaning and maintenance.

Equipment maintenance and cleaning
In general equipment and facilities look well maintained.

The maintenance program for 2017, Workshop 805 was reviewed. There were monthly and quarterly schedules in place. Reactors in chemical area was made with glass lined inner surface and those in clean area from stainless steel. Glass lined reactor integrity tests were performed regularly, as well as being entered via the manway for visual examination.

Calibration
Measuring equipment was required to be labelled with its calibration status and all examples viewed were within date. There was an annual schedule in place and instruments were mainly calibrated in-house but with some work performed under contract with the provincial metrology service.

Computerized systems
Computerized systems were not used for material or production control but used in QC lab for HPLC and GC networking.

5. Documentation and records

Documentation system and specifications
Documents were managed according to an SOP. Activities were documented in SOPs and other appropriate documents such as batch manufacturing records (BMRs) and logs. Those reviewed were seen to be appropriately approved and version controlled. All records and other documentation requested during the inspection were promptly available following request.

Master production instructions (master production and control records)
Approved master production instructions were available. For the production of all grades B2 only one Master Batch Record was used.

Laboratory control records
Laboratory logs were in place for receipt of samples and appropriate testing records were seen to be kept and were available for review.

Batch production record review
Several batches of productions records for B2 were reviewed and discussed. A batch production record, together with the deviation and OOS investigation file were reviewed. Non-compliances observed during the inspection was listed in the full report regarding records and BMR design and use were addressed by the manufacturer to a satisfactory level.
6. Materials management

General controls
Manual systems were in place for the receipt and tracking of inventory. Raw materials and finished goods were stored in a dedicated area of the warehouse. There was a tank farm for the receipt of solvents and other liquid reagents as well as an external drum store. These appeared to be tidy, well managed and appropriately labelled.

Receipt and quarantine
Solid materials were required to be checked on receipt, including for damage and verifying that the supplier was approved. They were placed in quarantine and labelled with the storage location. Bulk liquids were received from either dedicated tankers or tankers accompanied by a cleaning certificate.

Sampling and testing of incoming production materials
Production materials were sampled by QC in a designated sampling area according to a defined sampling plan. After testing by QC, materials were released and an appropriate status label was attached to each container. Records viewed appeared satisfactory. There were two sampling rooms used for raw material sampling, one for steroids and another for other materials.

Storage
The B2 API was stored in 2 to 8°C cold storage. Temperature was controlled and monitored.

7. Production and in-process controls

Production operations
Synthesis and production of B2 with a validated batch size took place in Workshop 805 chemical area. Final purification, crystallization, drying and packaging was performed in the clean area. The intermediate PMPA used in house and for selling were also manufactured in the chemical area. There were 6 different quality grade of B2 manufactured using a single process. There were two crystallizers in the clean area with one dedicated to crystallization of B2.

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

Blending batches of intermediates or APIs
Blending of B2 was permitted with the expiry of the shortest expiring batch retest date allocated to the blended batch. The blending validation protocol and report for B2 were reviewed and acceptable.

Contamination control
B2 API synthesis, purification, crystallization, drying and packaging was performed in non-dedicated facilities. Adequate precautions to minimize the likelihood of contamination, including final stages taking place in a Grade D controlled environment, were in place. Cleaning procedure for equipment had been validated. Final crystallization is performed from non-aqueous media in stainless steel reactors to limit risks of glass and microbial contamination.
8. Packaging and identification labelling of APIs and intermediates
   Packaging materials
   Packaging materials were appropriately stored and subjected to quality control testing before release.

   Packaging and labelling operations
   An area in the warehouse where relabeling was performed was inspected. The corrective action to
   the observations regarding the labelling and records of the labelling operation from the last inspection
   had been put in place.

9. Storage and distribution
   Warehousing procedures
   Finished APIs were stored in a designated warehouse and held in quarantine until released by an
   authorized person.

   Distribution procedures
   APIs and intermediates were released for distribution after release by the Quality Unit. A product
   release SOP was reviewed and discussed. B2 API release specifications for different markets with
   different quality grades, prior to batch release were verified.

10. Laboratory controls
    General controls
    The company had an organized and suitably equipped QC laboratory for API testing.

    Testing of intermediates and APIs
    The sample receiving, and distribution procedure and log books were inspected. Samples for testing
    were kept in a designated area. Non-compliances observed during the inspection that was listed in
    the full report regarding the sample receipt, recording and tracking were addressed by the
    manufacturer to a satisfactory level.

    QC testing was seen to be conducted as specified in the relevant specifications and according to
    documented test methods. Agilent HPLC and GC were used for testing of B2 API. The HPLC and
    GC were networked and OpenLab software installed. The computer access control, authorization of
    the functions and testing method verification were spot checked and appeared to be acceptable.

    Characterization of WRS
    Secondary reference standards were prepared against the primary reference standards according to an
    SOP and were periodically requalified. The characterization record of a WRS batch was reviewed. The
    retesting time of the working reference of B2 API was documented.
Stability monitoring of APIs
Requirements for stability monitoring were described in a documented procedure which included ongoing stability. Chambers for stability monitoring were situated in a dedicated room within the QC Laboratory. Chambers for the applicable temperature/relative humidity requirements for ICH and WHO regions were available. Parameters were measured by recorders for each chamber which were periodically checked. The chambers were provided with UPS.

The stability sample and records for B2 API for the validation batches and ongoing batches appeared satisfactory and reconciled.

Reserve/retention samples
B2 API samples were stored in 2-8°C refrigerator which was located in an access control room. A sample of each batch of API manufactured was kept. Retention samples were stored in containers that were comprised of the same materials as those used for packaging of the final API.

Handling of out of specification (OOS) results
The OOS/OOT handling procedure was reviewed and discussed. Non-compliances observed during the inspection that was listed in the full report regarding the OOS investigation procedure were addressed by the manufacturer to a satisfactory level.

Data management
The company had basic data integrity controls in place. The Waters Chromatographic data system, risk assessment of the archival, back up strategies and associated data life cycle risk were inspected. Data management for the stability monitoring system was inspected. Non-compliances observed during the previous inspection were satisfactory addressed.

11. Validation
Validation policy
Validation policy for B2 was described in VMP with Validation Management described in a written procedure.

Process Validation
Process validation of B2 remains the same as per the previous inspection. Since the previous inspection, additional process validation which include drying, blending and solvent recovery have been performed and was considered acceptable.

Qualification
Equipment qualification requirements were described in the VMP. Equipment performance qualification in Workshop 805 were reviewed together with process validation and considered acceptable.
Cleaning validation
Since the previous inspection, trial batches of a new B2 analogue has been produced in Workshop 805 which shared the B2 equipment in the chemical area. A cleaning validation SOP and cleaning validation report were reviewed and discussed. Non-compliances observed during the inspection that was listed in the full report regarding cleaning validation were satisfactory addressed by the manufacturer.

Validation of analytical methods
A compendial analytical method was used for B2 API testing. Analytical method validation for B2 residue testing was reviewed and considered accepted.

Computerized system validation
Update of the software of the QC HPLC and GC instruments by installation of OpenLab was briefly reviewed. The system was qualified by Agilent with the records signed off by the QA group.

12. Change control
Change control was managed according to an SOP. Changes were classified into critical and non-critical. Several change controls were reviewed and discussed during the inspection. Non-compliances observed during the previous inspection were satisfactory addressed by the manufacturer.

13. Rejection and re-use of materials
Rejection
The register was available and reviewed.

Reprocessing and reworking
Reprocessing and reworking procedure were available and reviewed.

Recovery of materials and solvents
A solvent recovery procedure was reviewed which allowed for the recovered solvents to be used in the same or different processes based on assessment and approved from QA. Recovered solvents are used in the upstream process but not used in the final purification stage.

14. Complaints and recalls
A procedure was in place. No complaints had been received for B2 API since the last inspection. The two contaminated batches identified during the previous inspection was recalled.

15. Contract manufacturers (including laboratories)
No contract manufacturers or contract laboratories were used for routine production and testing. X-ray diffraction testing of B2 polymorph was contracted out during R & D and for validation purposes.
PART 3

Conclusion

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

Aurisco Pharmaceutical Co., Ltd. located at Badu Industrial Park Zone, Tiantai, Zhejiang Province, 317200, P.R. China,

was considered to be operating at an acceptable level of compliance with WHO good manufacturing Practices for pharmaceutical products.

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


   http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_970/en/


   http://whqlibdoc.who.int/trs/WHO_TRS_929_eng.pdf?ua=1


   http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1
   http://whqlibdoc.who.int/trs/WHO_TRS_937_eng.pdf?ua=1


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

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

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

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

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

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

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


http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex03.pdf

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

http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex03.pdf