### PART 1: GENERAL INFORMATION

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<th>Name of Manufacturer</th>
<th>Shanghai Shyndec Pharmaceutical (Haimen) Co Ltd</th>
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<tr>
<td>Building</td>
<td>E1</td>
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<tr>
<td>Workshop</td>
<td>No 4 (dedicated for Zidovudine API)</td>
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<tr>
<td>Physical address</td>
<td>No.1 Linjiang Avenue, Linjiang Town, Haimen, Jingsu, Peoples Republic of China</td>
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<tr>
<td>Date of inspection</td>
<td>24 – 27 August 2015</td>
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<td>Type of inspection</td>
<td>First inspection (new site)</td>
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<td>Active Pharmaceutical Ingredient included in the inspection</td>
<td>APIMF267 Zidovudine</td>
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<td>Production Lines</td>
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PART 2: SUMMARY

General information about the company and site

The Shanghai Shyndec Pharmaceutical (Haimen) Co., Ltd. (hereinafter refer to as "Shyndec Haimen") was founded in January 2010, as a wholly owned subsidiary of the Shanghai Shyndec Pharmaceutical Co., Ltd. The Shyndec Haimen started the trial production in August 2013 after the Government issued the trial production approval. The main products of Shanghai Shyndec Pharmaceutical were anti-HIV, macrolide antibiotics and cardiovascular APIs.

The site is located at No.1 Xiandai RD. Linjiang Industrial Park, Linjiang New Area, Haimen, Jiangsu, China. There were seven production workshops, one hydrogenation workshop, one building for QC laboratory and administration office, one utility centre, and warehouses for starting and finished substances. The workshop 4 was divided into 2 parts: The general production area and “clean area”.

The API products under the Chinese Food and Drugs Administration (CFDA) license were:
- Zidovudine API
- Azithromycin API
- Nebivolol HCL
- Nevirapine

According to the Site Master File (SMF) 13 staff members were involved in the Quality assurance (QA) activities, 32 in the Quality control (QC) and 239 in the production activities. Total number of the employees was 428.

History of WHO and/or regulatory agency inspections

This was first WHO inspection. The site has been inspected by CFDA in July 2012.

The site has been inspected by United States Food and Drugs Administration (USFDA) for the Zidovudine API in April 2014 (letter 483 was issued). The final letter was dated 07 July 2014 and stated that the facility is classified as acceptable.

Focus of the inspection

The inspection focused on the production and quality control operations related to the Zidovudine API (APIMF267).

The inspection covered all the sections of the WHO good manufacturing practices for active pharmaceutical ingredients, including premises, equipment, documentation, materials, validation, sanitation and hygiene, production, quality control and utilities.

Inspected Areas
- Quality Management
- Personnel
- Buildings and facilities
- Process equipment
- Documentation and records
World Health Organization

PART 3: INSPECTION OUTCOME

3.1 QUALITY MANAGEMENT

Principles
In general, a system for managing quality was established, documented and implemented. The quality unit was independent of the production department. The person responsible for release of intermediates and APIs was specified. The systems for handling any deviations from established procedures were in place and documented. The materials were released by the quality unit after satisfactory evaluation.

Responsibilities of the quality unit(s) and production unit
The “Responsibilities of Quality Assurance (QA) Department”, the SOP “Responsibilities of the production department” and the SOP “Batch records review and product release SMP” were checked.

The quality director job description was checked. The quality director was also the site Qualified Person (QP). In the absence of the Quality director the QA manager was assigned as his deputy. This was specified in the document “Authorization letter of second QP”. The authorization letter was similar to the job description.

Finished product release was responsibility of QP. QC manager was responsible for release of starting materials, packaging materials and intermediates.

Internal audits (self-inspection)
The SOP “Self inspection” was reviewed. The QA unit was responsible for preparing the self-inspection plan/report and implementation of the corrective actions and preventive actions (CAPAs). The main components of the self-inspection were:

- Personnel
- Premises
- Equipment
- Documentation
- Production
- QC
- Distribution
The self-inspection team members consisted of the heads of the departments. The lead inspector was the Quality director. The self-inspection team member’s qualification requirements were specified. The self-inspection was carried out in accordance to the protocol. After inspection the report was written and CAPAs proposed by the inspected department. The self-inspection was carried out at least once per year.

Product quality review (PQR)
The SOP “Product Quality review” was reviewed. According to the SOP PQR should be finished by the end of February next year.

The PQR for the Zidovudine API, 2014 was reviewed. The following items were covered by the PQR:
- Starting material and primary packaging material quality data and statistical analysis
- Critical process parameter implementation status assessment
- Intermediate quality data statistical analysis
- Finished API Microorganism limit review
- Finished product quality data statistical analysis
- Deviation review
- Non-conforming product
- Out of specification (OOS) review
- Change control (CC) review
- Stability
- Validation and qualification review
- Complaints
- Returned goods
- Recalls
- Corrective actions and preventive actions (CAPA)
- Marketing authorisation (MA) variations review
- Technical agreement (TA) review
- Unresolved issued from previous PQR
- Conclusions and recommendations.

Quality Risk Management (QRM)
The SMP “Quality Risk management” was reviewed. The QRM management SMP was applicable for product life time, R&D, production, distribution, inspection and marketing authorization applications. According to the SMP the following tools should be used for the QRM:
- Failure Mode Effect Analysis (FMEA)
- Failure Mode Effect and Criticality Analysis (FMECA)
- Fault Tree Analysis (FTA)
• Hazard Analysis and Criticality Control Points (HACCP)
• Hazard Operability Analysis (HOA)
• Preliminary Hazard Analysis (PHA)

The FMEA was specified as the main tool used for the QRM. The SMP “QRM tools SMP” was checked. For the FMEA risk priority numbers range was specified from 1 to 10.

According to the QRM register till the date of the inspection 16 Risk Assessments (RA) were carried out.

The RA “Zidovudine quality risk assessment” was reviewed. The RA performed was detailed and 24 CAPAs were proposed. RA team consisted of:
• QA Manager
• Production Manager
• R&D Manager
• Engineering department Manager
• Purchasing department Manager
• Logistic department Manager
• Human Recourses department Manager
• Marketing department Manager
The RA report was approved by the Quality Director.

The RA “Quality Risk Assessment of Zidovudine critical technologic parameters” was checked.

3.2 PERSONNEL
Personnel qualifications
There were an adequate number of personnel qualified to perform and supervise the manufacture of intermediates and APIs. The responsibilities of personnel engaged in the manufacture of intermediates and APIs were specified in writing.

Personnel hygiene
Good sanitation habits were observed on site. The direct contact with the intermediates or APIs was avoided. The personnel were wearing clean clothing suitable for the manufacturing activity they were involved. Smoking, eating, drinking, chewing and the storage of food was restricted to certain designated areas separate from the manufacturing areas.

Training
The SMP “Personnel training” was reviewed. According to the SMP there were the following training modules:
• New staff induction training
• On-job training
• “Switch off” job training
• Contract workers training
• GMP training
The training effectiveness was evaluated by the several ways:

- Written open questions
- Multiple choice pre-given answers
- “Yes” or “no”
- Verbal questions

The training records, common for all specific training participants, were maintained by the Human Resources Department.

The list of qualified analysts was presented to the inspectors.

Consultants
Outside consultants were not used,

3.3 BUILDINGS AND FACILITIES
Design and construction
The buildings and facilities used in the manufacture of intermediates and APIs were located, designed, and constructed to facilitate cleaning, maintenance and operations as appropriate to the type and stage of manufacture. The buildings and facilities had adequate space for the orderly placement of equipment and materials. The flow of materials and personnel through the buildings and facilities were designed to prevent mix-ups or contamination. The laboratory areas and operations were separated from the production areas.

Utilities
The utilities were qualified and monitored. The drawings for these utility systems were available. An adequate ventilation, air filtration and exhaust systems (HVAC) were provided. HVAC systems were designed to minimize the risks of contamination and cross-contamination. The permanently installed pipework’s were appropriately identified.

One air handling unit (AHU) was serving air to the all “clean rooms”. The SOP “HVAC SOP” was checked. The AHU unit was equipped with the alarm system for Temperature (T) and Relative Humidity (RH) and power failure.

Water
The purified water system (PW) was installed in July 2013. The design qualification (DQ), installation qualification (IQ), operation qualification (OQ) and PQ protocols / reports were checked. The welder’s certificates and welding reports (boroscopic photos) were available and presented to the inspectors.

3 phase approach was used for the PW qualification. Totally there were 14 sampling points. The phase I and phase II lasted for 2 weeks each (samples were collected from all sampling points). The Phase III lasted for one year. The action and alert limits were set up.
Nitrogen
Nitrogen was generated at the site. The drawing of the system was presented to the inspectors. The IQ, OQ and PQ reports / protocols were available, but not checked during the inspection. Nitrogen was filtered via 0.45µ and 0.22µ filters. The document “Standard test procedure for gases in direct contact with API” was checked. Nitrogen analysis was carried out every 3 months.

Containment
Highly sensitizing materials were not manufactured on site.

Lighting
An adequate lighting was provided to facilitate cleaning, maintenance and proper operations.

Sewage and refuse
Sewage, refuse and other waste (e.g. solids, liquids, or gaseous by-products from manufacturing) were disposed of in a safe, timely and sanitary manner.

Sanitation and maintenance
The buildings used in the manufacture of the intermediates and the APIs were properly maintained and repaired and kept in a clean conditions.

3.4 PROCESS EQUIPMENT
Design and construction
The equipment used in the manufacture of intermediates and APIs was of an appropriate design and adequately sized, and suitably located for its intended use. The major equipment such as reactors and centrifuges, and permanently installed processing lines used during the production of an intermediate or API were appropriately identified. Mainly closed systems were used in production. Stainless steel or glass-line reactors were used for production of the Zidovudine API as appropriate to the process stage.

Equipment maintenance and cleaning
The schedules and procedures were established for the preventive maintenance of equipment. Equipment and utensils were cleaned according to the written procedures.

Calibration
The control, weighing, measuring, monitoring and test equipment that was critical were calibrated according to the written procedures and an established schedules. The records of calibrations were maintained. The current calibration status of critical equipment was known and verifiable.

The SOP “Calibration criteria of measuring equipment” was checked. The SOP was applicable for the instruments which calibration was done by the external agencies. The calibration certificates were presented for PW flow meter and High Performance Liquid Chromatograph (HPLC). The calibration schedules were prepared monthly.
The HPLC internal calibration record “Calibration record for HPLC” was checked. The traceability to the standards used for the calibration was ensured.

**Computerized systems**

In the quality control laboratory computerized system was used only for HPLC and Gas Chromatographs. The Empower 3 software was validated by the supplier (Waters). The validation reports were not checked during the inspection.

The computerized systems were not used in production.

**3.5 DOCUMENTATION AND RECORDS**

**Documentation system and specifications**

Documents related to the manufacture of intermediates and APIs were prepared, reviewed, and approved. The specifications were established and documented for the starting material, intermediates, packaging materials and finished API. The acceptance criteria were established and documented for the in-process controls.

**Equipment cleaning and use record**

Records of the major equipment use, cleaning, sanitization and maintenance showed the date, time, product and batch number of each batch processed in the equipment, and the person who performed the cleaning and maintenance.

The SOP “Equipment maintenance” was checked. This SOP was applicable for the production equipment.

The maintenance and cleaning records were checked for the AHU and PW storage tank and PW distribution loop.

**Records of raw materials, intermediates, API labeling and packaging materials**

Some records were spot-checked.

**Master production instructions**

The master production instructions had been established and appropriately approved.

**Batch production records**

Several in-process batch records were inspected during the visits to the workshops and all were up to date and had been properly filled in.

**Laboratory control records**

The standard tests methods and analytical reports were available. Some laboratory records were spot checked.
3.6 MATERIALS MANAGEMENT

General controls
Written procedures describing the receipt, identification, quarantine, storage, handling, sampling, testing and approval or rejection of materials were available. In the warehouse, materials were managed manually.

Batch numbering system
The SOP “Batch numbering SMP” was checked. The reprocessed / reworked and blended batches were indicated using letters R for the reprocessed batches; W for the reworked batches and digits 20 for the blended batches.

Receipt and quarantine
Materials were held under the quarantine until they were sampled, tested and released for the use. The SOP “Materials releasing SMP” was reviewed. According to the SOP starting materials, packaging materials and intermediates release was responsibility of the quality control department (QC). Finished product release was responsibility of the QP.

Sampling and testing of incoming production materials
Containers, from which the samples were withdrawn, were marked to indicate that a sample has been taken.

The SOP’s “Raw materials sampling plan” and the SOP “Packaging materials sampling” were checked.

Supplier’s management
The SOP “Classification of materials and management of suppliers” was reviewed. According to the SOP suppliers were classified as:
- Class “A” (impact of product quality and safety, including key starting materials, solvents and primary packaging materials) suppliers
- Class “B” suppliers

Storage
The solvents used in Zidovudine API manufacturing process were stored in the “Solvent farm”. The solvents were delivered in dedicated tankers. The supplier’s certificate of analysis (CoA) were delivered together with solvents and stored in the QC laboratory. Solvents were sampled from the tankers and after release transferred to the storage tanks.

All warehouses, except packaging materials warehouse, had separate sampling rooms, equipped with dust extraction system.

The temperature (T) mapping protocol/report “Temperature Uniformity validation of finished product warehouse 15 – 30 ºC” was reviewed. The T mapping studies were carried out from 28th July 2014 - 4th August, 2014. Valid calibration certificates for each of the data loggers used in the studies were available and presented to the inspector.
3.7 PRODUCTION AND IN-PROCESS CONTROLS

Production operations
Production of Zidovudine API was carried out in five steps. There were two production lines in the production block 4 used for Zidovudine API manufacturing. The raw materials for manufacturing of intermediates and APIs were dispensed under appropriate conditions in dedicated rooms. The weighing and measuring devices were of suitable accuracy for the intended use. The deviations were documented in the Batch Records (BR). The processing status of major equipment was indicated.

Time limits
Time limits specified in the master production instructions were met. Spot checks showed that records to the BR were made at the time of actions.

In-process sampling and controls
In-process sampling was carried out. In-process sampling and some tests at the production workshops e.g. Thin Layer Chromatography and pH were done by the operators.

Blending batches of intermediates or APIs
The SOP “Handling of product tailings” was reviewed. The expiry/ retest date of the blended batch was based on the manufacturing date of the oldest tailings or batch in the blend.

Contamination control
The SOP “Prevent contamination & cross contamination” was checked.

Deviations
The “Handling of deviations” and register were reviewed. The deviations were classified as:
- Critical
- Major
- Minor

According to the SOP cross functional team should be set up for investigation of the critical and major deviations. In case of the critical and major deviations investigation should be initiated to find out the root cause, conduct impact analysis and propose corrective actions (CA) and preventive actions (PA). The follow-up actions should be carried out by the QA to ensure that actions recommended are completed effectively and on time. The deviation investigation reports should be completed and approved within two months from the first notification to the QA. The deviation registers were product based.

The deviations were recorded in related BR’s.
3.8 PACKAGING AND IDENTIFICATION LABELLING OF APIs AND INTERMEDIATES

General
There were written procedures describing the receipt, identification, quarantine, sampling, examination and/or testing and release and handling of packaging and labelling materials.

Packaging materials
The primary packaging materials were stored in a separated room in the finished product warehouse in carton bags.

Label issuance and control
Finished product labels were printed in the QA using two label printers. The SOP “Label management SMP” was reviewed. Printing, issuance and reconciliation of the labels were the QA department responsibility.

Packaging and labeling operations
During the inspection labelling operations were not carried out. According to the SOP finished API labeling was carried out by warehouse personnel and supervised by the QA personnel.

3.9 STORAGE AND DISTRIBUTION

Warehousing procedures
The inspectors visited all warehouses and solvent farm. The facilities were provided for the storage of all materials. The released and rejected materials were stored separately. The quarantine areas were identified.

Distribution procedures
APIs were released for sale after the QA approval. According to the company, records for dispatch of batches (linked to the release of batches, as well as issuing of the BRs) were kept by the QA.

3.10 LABORATORY CONTROLS

General controls
The SOP “Finished product sampling” was checked.

HPLCs and Gas Chromatographs (GC) were connected to the Empower 3 software. The SOP “Empower system” used for HPLC and GC was spot checked. “Off line” back up was carried out every week to the separated server.

The SOP “The security of GMP computer system” was checked. According to the SOP passwords should be changed once per month.

The SOP “OOS and atypical results investigation” and OOS register were reviewed. The SOP was applicable for all starting materials, intermediates and finished APIs. Investigations were carried out according to the Check list.
Testing of intermediates and APIs
The intermediates and APIs were tested to determine conformance to the specifications. The Zidovudine (United States Pharmacopoeia (USP) specifications) Batch control record (analytical report) was reviewed and cross checked with related equipment log books and standards.

The balances used in the QC laboratory were regularly calibrated; daily, monthly and yearly. The standard weights calibration certificates were presented to the inspectors.

The class “A” glassware was used in the QC laboratory. The glassware was re-calibrated every 3 years.

Validation (verification) of analytical procedures
The verification protocol and report of assay & relative substance testing method of Zidovudine was reviewed.

Certificates of analysis (CoA)
The SOP “Batch records review and product release SMP” was reviewed. According to the SOP, BR’s were pre-reviewed by the production department relevant staff and reviewed by the QA.

The SOP “Certificate of analysis” was reviewed. Data from the analytical reports were transferred to the CoA’s by the quality control (QC) document control staff. The CoA’s were reviewed and signed by the QC manager and reviewed and released by the QA Manager. According to the SOP, the QP was responsible for approval of the CoA and release of the product. This responsibility according to the “Authorization letter” was delegated to the QA Manager.

Stability monitoring of APIs
The SOP “Stability studies SMP” was reviewed.
Samples for stability tests were stored in the following conditions:
- 40 ºC ± 2ºC, 75% ± 5%
- 30 ºC ± 2ºC, 65% ± 5%
- 30 ºC ± 2ºC, 75% ± 5%
- 25 ºC ± 2ºC, 60% ± 5%

The window period for accelerated and long term stability studies was defined. At least one batch per year was placed for on-going stability studies. The stability schedule was cross reference with the date of analysis.

The temperature (T) and relative humidity (RH) in the stability chambers were controlled: T and RH records were printed out every 4 minutes and checked once per day.

Expiry and retest dating
The SOP “Retest date of materials” and the SOP “Manufacturing date and retest date or expiry date determination” were checked.
Reserve/retention samples
The SOP “QC retention samples” was checked. According to the SOP retention samples should be stored in the packaging system simulating marketing packaging. Sufficient quantities were retained to conduct three full compendia analyses.

The retention samples were store in the separate room. The room T limits were 10 – 30 ºC what simulated finished APIs storage T.

Reference standards (RS)
The SOP “Reference standards” was reviewed. The working standards (WS) preparation procedure was explained in the SOP. The Pharmacopeia RS were used for impurities tests, WS’s were used for assay tests. WS were qualified against Pharmacopeia RS.

The SOP “Zidovudine USP assay WS calibration” was checked. The WS standards were dispensed in vials for single use.

3.11 VALIDATION
Validation policy
The validation policy was explained in the Validation Mater Plan (VMP).

The document “Facility, utilities, equipment qualification SMP” was checked. The document was applicable to the:
- Facilities
- Utilities
- Equipment/system which are considered critical and for which validation has been deemed necessary

The operation qualification (OQ) protocol/report for the Air Handling Unit (AHU) was checked. The calibration certificates used for the OQ were available and presented to the inspectors.

Qualification
The document “Validation and qualification SOP” was checked. User’s requirement specifications (URS) were available for review.

Process validation programme
The initial Zidovudine process validation protocol / report were reviewed.

Cleaning validation
There were two types of the equipment cleaning:
- Batch to batch cleaning
- Monthly thorough cleaning

The clean equipment hold time studies were performed. Swab and rinse samples were collected for the analysis. The HPLC method used was validated.
Microbiological laboratory
The microbiological laboratory was briefly visited. The media preparation procedure and log
book were reviewed. The testing procedure for PW was reviewed.

3.12 CHANGE CONTROL (CC)
A formal CC system was established. The SOP “Change control” was reviewed. The SOP
was applicable to the CCs in:
- Product
- Raw materials
- Specifications
- Testing methods
- Processes
- Equipment or instruments
- Environment
- Maintenance systems and tools
- Labelling and packaging
- Computer systems
- Any changes impacting product quality, safety, efficacy and compliance

According to the SOP the QA was responsible to establish, oversee and monitor the CC
system and ensure that the CC meets regulatory requirements and is being consistently
followed, approve the CC request, participate in the change impact evaluation and approval of
the action plan and implementation.

Changes were specified as:
- Temporary change
- Permanent change
- Emergency change

and classified as:
- Critical
- Major
- Minor

In case of the major or critical changes marketing authorisation (MA) holders and customers
should be informed and approval from MA requested. The CC registers were product based.

The CC application form “Adding air milling equipment” was reviewed.
3.13 REJECTION AND RE-USE OF MATERIALS

Rejection
The SOP “Handling of Nonconforming products” was checked.

Reprocessing reworking
The SOP “Reprocessing SMP” was checked.

Reworking
The “Reworking SMP” was checked. The SOP specified that in general reworking of finished product was not allowed, but in case the batch would be reworked, batch should be subject of the stability studies.

Recovery of materials and solvents
The SOP “Solvents recovery” was checked. According to the SOP recovered solvents should be used for the same process, the same product.

Returns
The SOP “Product returns” was checked.

3.14 COMPLAINTS AND RECALLS

The SOP “Customer complaint SMP” was reviewed. According to the SOP the QA department was responsible for investigation and coordination of the complaints. Records of the complaints should be retained in order to evaluate the trends. It was said that till the date of inspection no complaints were received.

The SOP “Product recalls SMP” was reviewed. The Quality Director was responsible for recalls. It was said that till the date of inspection no recalls were carried out. According to the SOP mock recall should be carried out every two years. The last mock recall was carried out in May 2015 for local market.

The common register formats were maintained for complaints / recalls / returns.

3.15 CONTRACT MANUFACTURERS (INCLUDING LABORATORIES)
Production / laboratory control activities were not contracted out.

PART 4: CONCLUSION
Based on the areas inspected, the people met and the documents reviewed, and considering the findings of the inspection, including the deficiencies listed in the Inspection Report, as well as corrective actions taken and planned, Zidovudine (APIMF267)API manufactured at Shanghai Shyndec Pharmaceutical (Haimen) Co Ltd, located at No.1 Xiandai RD. Linjiang Industrial Park, Linjiang New Area, Haimen, Jiangsu 226133, Peoples Republic of China, was considered to be manufactured in compliance with WHO GMP for Active Pharmaceutical Ingredients.
All the non-compliances observed during the inspection that were listed in the full report as well as those reflected in the WHOPIR, were addressed by the manufacturer, to a satisfactory level, prior to the publication of the WHOPIR.

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