<table>
<thead>
<tr>
<th>Part 1</th>
<th>General information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manufacturers details</td>
<td></td>
</tr>
<tr>
<td>Name of manufacturer</td>
<td>Jiangsu Puxin Pharmaceuticals Co. Ltd</td>
</tr>
<tr>
<td>1 Chenli Rd., Chemical Park, Binhai Economic Development Zone, Jiangsu 224555, China</td>
<td></td>
</tr>
<tr>
<td>Latitude (N): 34.29139, Longitude (E): 120.07583. D-U-N-S: 527539103</td>
<td></td>
</tr>
<tr>
<td>Corporate address of manufacturer</td>
<td>As above</td>
</tr>
<tr>
<td>Name &amp; address of inspected manufacturing site if different from that given above</td>
<td>As above</td>
</tr>
<tr>
<td>Phase I, buildings</td>
<td>A03-3, A03-4, A03-5, B03-6, B03-8, B04-1, B04-4, B05, B06, B07, B08 and A03</td>
</tr>
<tr>
<td>Phase II, building</td>
<td>E05</td>
</tr>
<tr>
<td>Inspection details</td>
<td></td>
</tr>
<tr>
<td>Dates of inspection</td>
<td>14 - 17 May 2019</td>
</tr>
<tr>
<td>Type of inspection</td>
<td>Routine</td>
</tr>
<tr>
<td>Introduction</td>
<td></td>
</tr>
<tr>
<td>Brief description of the manufacturing activities</td>
<td>Main manufacturing activities at Puxin site are:</td>
</tr>
<tr>
<td>• Starting materials and intermediates related to Zidovudine, Lamivudine, Emtricitabine and Tenofovir</td>
<td></td>
</tr>
<tr>
<td>• APIs</td>
<td></td>
</tr>
<tr>
<td>General information about the company and site</td>
<td>Puxin site was founded in 2006 and is a wholly owned subsidiary of Shanghai Desano Pharmaceuticals Investment Co., Ltd., located at 1 Chenli Rd., Chemical Park, Binhai Economic Development Zone, Jiangsu with a total area of approximately 287,000 square meters. The main products were starting materials and intermediates of anti-retroviral drugs.</td>
</tr>
<tr>
<td>History</td>
<td></td>
</tr>
<tr>
<td>Authority</td>
<td>Dates of inspection</td>
</tr>
<tr>
<td>US FDA</td>
<td>March 2014</td>
</tr>
<tr>
<td>WHO</td>
<td>April 2014</td>
</tr>
<tr>
<td>WHO</td>
<td>January 2017</td>
</tr>
<tr>
<td>ANVISA</td>
<td>February 2018</td>
</tr>
</tbody>
</table>
| Areas inspected | Warehouses Phase I and Phase II  
| | Phase I: B04-1, B04-4, B05, B06, B07, B08  
| | Phase II: E05, tank farm  
| Restrictions | N/A  
| Out of scope | Products which are not under WHO prequalification  
| WHO products related to this the inspection |  
| | • Emtricitabine Intermediate FCME  
| | • Tenofovir disoproxil fumarate Intermediate PMPA  
| | • Lamivudine Intermediate CME  
| | • Zidovudine Intermediate  
| Abbreviations | Meaning  
| ADE | Acceptable daily exposure  
| ADR | Adverse drug reaction  
| AHU | Air handling unit  
| ALCOA | Attributable, legible, contemporaneous, original and accurate  
| API | Active pharmaceutical ingredient  
| APQR | Annual product quality review  
| APS | Aseptic process simulation  
| AQL | Acceptance quality limit  
| BMR | Batch manufacturing record  
| BPR | Batch production record  
| CAPA | Corrective and preventive action  
| CC | Change control  
| CCEA | Complete, consistent, enduring, available  
| CFU | Colony-forming unit  
| CIP | Cleaning in place  
| CoA | Certificate of analysis  
| Cpk | Process capability index  
| DQ | Design qualification  
| EDI | Electronic deionization  
| EHS | Environment, health and safety  
| EM | Environmental monitoring  
| FMEA | Failure modes and effects analysis  
| FPP | Finished pharmaceutical product  
| FTA | Fault tree analysis  
| GMP | Good manufacturing practices  
| GPT | Growth promotion test  
| HACCP | Hazard analysis critical control point  
| HAZOP | Hazard and operability study  
| 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  

Jiangsu Puxin Pharmaceuticals Co. Ltd, China-API  
14-17 May 2019  
This inspection report is the property of the WHO  
Contact: prequalinspection@who.int  
Page 2 of 13
<table>
<thead>
<tr>
<th>Acronym</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>KPI</td>
<td>Key performance indicators</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>MACO</td>
<td>Maximum allowable carry over</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>NC</td>
<td>Non-conformity</td>
</tr>
<tr>
<td>NCA</td>
<td>National control authority</td>
</tr>
<tr>
<td>NCL</td>
<td>National control laboratory</td>
</tr>
<tr>
<td>NRA</td>
<td>National regulatory agency</td>
</tr>
<tr>
<td>OOS</td>
<td>Out of specification</td>
</tr>
<tr>
<td>OOT</td>
<td>Out of trend</td>
</tr>
<tr>
<td>OQ</td>
<td>Operational qualification</td>
</tr>
<tr>
<td>PDE</td>
<td>Permitted daily exposure</td>
</tr>
<tr>
<td>PHA</td>
<td>Process hazard analysis</td>
</tr>
<tr>
<td>PLC</td>
<td>Programmable logic controller</td>
</tr>
<tr>
<td>PM</td>
<td>Preventive maintenance</td>
</tr>
<tr>
<td>PQ</td>
<td>Performance qualification</td>
</tr>
<tr>
<td>PQR</td>
<td>Product quality review</td>
</tr>
<tr>
<td>PQS</td>
<td>Pharmaceutical quality system</td>
</tr>
<tr>
<td>PW</td>
<td>Purified water</td>
</tr>
<tr>
<td>QA</td>
<td>Quality assurance</td>
</tr>
<tr>
<td>QC</td>
<td>Quality control</td>
</tr>
<tr>
<td>QCL</td>
<td>Quality control laboratory</td>
</tr>
<tr>
<td>QMS</td>
<td>Quality management system</td>
</tr>
<tr>
<td>QRM</td>
<td>Quality risk management</td>
</tr>
<tr>
<td>RA</td>
<td>Risk assessment</td>
</tr>
<tr>
<td>RCA</td>
<td>Root cause analysis</td>
</tr>
<tr>
<td>RO</td>
<td>Reverse osmosis</td>
</tr>
<tr>
<td>RPN</td>
<td>Risk priority number</td>
</tr>
<tr>
<td>SMF</td>
<td>Site master file</td>
</tr>
<tr>
<td>SOP</td>
<td>Standard operating procedure</td>
</tr>
<tr>
<td>URS</td>
<td>User requirements specifications</td>
</tr>
<tr>
<td>UV</td>
<td>Ultraviolet-visible spectrophotometer</td>
</tr>
</tbody>
</table>
Part 2  
Summary of the findings and comments

1. Quality system
   Principle
Production and control operations were specified in written form and GMP requirements were essentially being met. Managerial responsibilities were specified in written job descriptions. Product and processes were monitored, and the results were reviewed as part of the approval process of batch release. Regular monitoring and reviews of the quality of pharmaceutical products were being conducted according to specified procedure.

Data integrity policy
The following documents were briefly discussed:
- “Good data and record management practices”. The SOP was applicable to all paper based and electronic data and was based on ALCOA principles.
- “Administration of user classification and privileges”. The SOP explained general approach to all software e.g. Attachment No. X listed users by name.
- “Operation of empower chromatography data software”. Attachment No. X defined users and privileges.
- “Save and back up of the electronic data in QC lab”. SOP also very briefly explained electronic data restoration.
- Empower 3 computerized system validation report XX.

Management review (MR)
SOP “Management review”, MR plan for 2018 and MR report for 2018 were briefly discussed. MR was performed to ensure that continuous improvement actions were suitable, effective and implemented. According to the SOP, MR should be performed at least once per year. Standard agenda was specified, and the MR report followed.

Quality Risk Management
SOP “Management procedure of quality risk” was briefly discussed. Tools used for RA were FMEA, HACCP and HAZOP.

RA “Change of location and process of Zidovudine production” was briefly discussed.

Product Quality Review (PQR)
SOP “Result of product quality review” was briefly discussed. According to the SOP, PQRs should be prepared covering calendar year and finalized within the first quarter of the following year. The statistical method was used for trend analysis.

A number of PQRs were briefly discussed for the 2018 period.
Deviations/corrective actions and preventive actions (CAPA)
SOP “Deviation investigation” and its flow chart were briefly discussed. SOP was applicable for materials purchase, intermediates, APIs, recovered materials, including QC deviations. Deviations were classified as:
- Critical
- Major
- Other

Ishikawa diagram was used for RCA. Deviations related to production operations were recorded in the BMRs.
SOP “Corrective and preventive action management procedure” and its flow chart were briefly discussed.

A number of deviations and related CAPAs were briefly discussed.

Change control (CC)
SOP “Change control program” and its flow chart were briefly discussed.
Changes were classified by QA change controller as:
- Critical
- Major
- Other

Changes were approved by QA Manager. A number of CCs were briefly discussed.

Complaints
SOP “Complaints management procedure”, its flow chart and complaints registers for 2018 were briefly discussed. No complaints were registered in 2019. Dealing with complaints was QA responsibility. Complaints were classified as:
- Quality related
- Non-quality related

A number of complaint investigation reports were briefly discussed.

Recalls
SOP “Management procedure for recall of products” and its flow chart were briefly discussed. According to the SOP, the QP was responsible for taking decision with regards product recall. Recalls were classified as:
- Class I - Notification within 24 hours, to authority within 1 working day.
- Class II - Notification within 48 hours to clients/agents, to authority within 3 working days.
- Class III - Notification within 72 hours to clients/agents, to authority within 7 working days.

Effectiveness of the recall procedure was checked by performing a mock recall every two year. According to the company there were no actual recalls.
Self-inspection
SOP “Self-inspection procedure” and its flow chart were briefly discussed. Two types of self-inspection were specified:
• Periodic - At least every year
• Non-periodic
Lead auditor was Qualified Person or person from QA.

Supplier management
Supplier qualification was performed by Shanghai Desano.

Documentation
SOP “Document management program” was briefly discussed. Document review period was specified as 3 years.
Documents levels were as follows:
• General system documents
• QA documents
• QC documents
• Materials management documents
• Production/packaging/labelling documents
• Facility/engineering documents
• Metrology documents
• HR and training documents

Lot numbering system
SOP “Lot number assignment” was briefly discussed.
• For blended batches, letter “b” was added.

Personnel
Job descriptions
A number of Job descriptions were briefly discussed; responsibilities were detailed.

Training
SOP “Training Program” was briefly discussed. Training effectiveness assessments were performed as on the job evaluation, oral (question and answer) or written (pass mark was 80 %). HR was responsible for the retention of training records.

A number of training records were briefly discussed.

2. Production system
Production operations followed defined procedures. Significant deviations from the initial protocol were recorded and investigated, root causes were determined and CAPAs were implemented where necessary. Checks on yields and reconciliation of quantities were carried out. Access to production premises was restricted to authorized personnel.
Batch Production Record (BPR)
A number of BPR’s were briefly discussed.

Rejection and re-use of materials
SOP “Reprocessing and reworking management procedure” was briefly discussed and covered intermediates and APIs failing to meet established specifications.

SOP “Management of blending batches” was briefly discussed. Expiry date/retest date was based on the manufacturing date of the oldest tailings or batch in the blend.

Cleaning validation
SOPs “Cleaning principles” and “Procedure for cleaning validation verification” were briefly discussed. Three levels of cleaning were explained.

Hold time studies
Zidovudine crude hold time studies were briefly discussed.

Contract manufacturing
The Technical Agreement for contract manufacturing with XX was briefly discussed. Contract givers and contract acceptors responsibilities were clearly specified.

3. Facilities and equipment system
Production premises were located, designed, constructed, adapted and maintained to suit the operations to be carried out. Premises were cleaned according to written procedures, records were maintained. Production buildings were seen to be clean and in good order. Labels attached to the equipment clearly indicated equipment identification numbers, qualification status and due date. Production rooms visited were clean and well maintained. All equipment was made of stainless steel.

Calibration
SOP “General principle for in-house calibration” and calibration plan was briefly discussed.

Laboratory premises
Laboratory facilities were of a suitable size, construction and location and were designed to suit the functions and operations to be conducted. Chemical/physical/ instrumental laboratories were separated from microbiological laboratory. Laboratories were seen to be clean and well maintained.

Laboratory equipment
Laboratories were equipped with necessary instruments and equipment. HPLCs and GCs were connected to the Empower 3 software, IR and UV to Lab solution. Balances of appropriate range were available. Balances verification was performed daily by two standard weights. Monthly calibration was performed according to the USP Chapters 41 and 1251.
4. Laboratory control system

The following SOPs were briefly discussed:

- **SOP “Administration principle of Chromatogram integrate”**: According to the SOP manual integration was applied only for impurities and should be approved by QC Manager, and supervisor (leader).
- **SOP “Review of laboratory electronic data”**: Each batch electronic meta data was reviewed by QC and monthly for selected batches by QA.
- **SOP “Sampling management procedure”**: SOP was applicable to sampling of all materials including intermediates made on site.
- **SOP “Evaluation and release of manufacturing products”**: SOP explained BMRs/BPRs and analytical worksheets review procedure. BMRs/BPRs were reviewed by responsible person from production and QA. Analytical worksheets were reviewed by QC and QA. CoA was signed QA person authorized by QP.

Inspectors requested company to export to Excel sheets system and project audit trails for WHO products. Presented audit trials were reviewed and no data integrity issues noted for reviewed audit trails.

Inspectors cross-checked Lamivudine crude, lot No. XX analytical raw data with electronic meta data, equipment ID numbers, usage logs for the following analyses according to the STP No. XX. The following data was cross checked. No discrepancies were noted.

**QC Microbiology**

The Microbiology laboratory was separated from the Chemistry laboratory. Access was restricted to authorized personnel only. The laboratory activities, such as media, equipment preparation, testing and enumeration of microorganisms was segregated. There were appropriate entry and exit procedures, including gowning procedures.

Media was prepared in-house as stipulated in SOP “Administration of culture media”. Growth promotion testing was done on all media on every batch. The performance of the media was checked with regard recovery of the target organisms.

Reference cultures were used for establishing acceptable performance of all media.

**Out of specification**

SOP “Investigation of out of specification” was briefly discussed.

**Stability monitoring**

SOP “Stability study program” was briefly discussed. If an out of compliance result or adverse trend was encountered, a deviation was required to be initiated and then investigated. If an OOS was noted, the impact on other related batches was to be investigated. It was confirmed that the stability study samples were stored in containers that simulated the market packaging.
5. Materials system

Warehouses for storage of self-made intermediates and APIs and for storage of purchased materials were visited during inspection. Places for storage of products under quarantine were clearly marked. Both warehouses had separate sampling and dispensing (weighing) rooms provided with exhaust ventilation. Both warehouses had separate rejected and returned materials storage rooms. Materials in the warehouses visited were stored under appropriate conditions and in orderly fashion to permit batch segregation and stock rotation. Stock control was performed manually. Warehouses inspected were clean and in good order.

Solvents in large quantities were stored in 30 tanks (carbon stainless steel, stainless steel and glass lined) located at the tank farm. Upon arrival, solvent delivery tankers were quarantined, samples withdrawn and analysed. After release, solvents were transferred to the respective tanks. Another sample was withdrawn and analysed after mixing existing solvents with newly delivered.

Solvents in drums were stored in hazardous materials warehouse.

Company explained that reserve samples were retained for 3 years after the batch has been completely distributed by the manufacturer and that reserve sample were stored in the same packaging system in which the intermediates were stored.

The following documents were briefly discussed:
- SOP “Handling and control of rejected material” and returned products registers for FCME and CME.
- SOP “Management of recycled/recovered material”. According to the SOP recycling (re-use) was applicable to solvents, mother liquors and process aids. Recovery was applicable to solvents, and products. During inspection, Zidovudine crude recovery process was under validation.
- SOP “Reprocessing and reworking management procedure” and reprocess products registers.
- SOP “Administration of chemical reference standards”. Working standards (WS) were standardized against official standards and dispensed in amber colour vials.
- SOP “Disposition of returned goods”.
- Specification “Mother liquor from X purification”.
- Specifications “Toluene”, “Recovered Toluene Y”, “Recovered Toluene X”, “Methanol” and “Recovered methanol”.
- Approved supplier list.
- DMF, toluene and methanol manufacturers declarations: Dedicated tankers and dedicated transfer hoses used for supply and well as delivery trucks plate numbers.

6. Packaging and labelling system

No packaging/labelling operations were carried out during inspection. According to the company procedure, packaging of intermediates and Zidovudine crude was carried out in production buildings. Labels issuance and printing was responsibility of warehouse staff. Labels for packaging were released by QA.
## Part 3  
### Initial 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, **Jiangsu Puxin Pharmaceuticals Co. Ltd**, located at **1 Chenli Rd., Chemical Park, Binhai Economic Development Zone, Jiangsu 224555, China** was considered to be operating at an acceptable level of compliance with WHO good manufacturing practices for active pharmaceutical ingredients 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


   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://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_1010/en/

https://apps.who.int/iris/bitstream/handle/10665/312316/9789241210287-eng.pdf?ua=1

https://apps.who.int/iris/bitstream/handle/10665/312316/9789241210287-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

19. WHO Technical supplements to Model Guidance for storage and transport of time – and
temperature – sensitive pharmaceutical products. WHO Expert Committee on Specifications for
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_T
RS_992_web.pdf

20. WHO Recommendations for quality requirements when plant – derived artemisin is used as a
starting material in the production of antimalarial active pharmaceutical ingredients. WHO
Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Ninth Report
Short name: WHO TRS No. 992, Annex 6
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_T
RS_992_web.pdf

21. Guidance on good data and record management practices. WHO Expert Committee on
Short name: WHO GDRMP guidance or WHO TRS No. 996, Annex 5
http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex05.pdf

22. WHO general guidance on variations to multisource pharmaceutical products. WHO Expert
Committee on Specifications for Pharmaceutical Preparations. Fiftieth Report Geneva, World
Short name: WHO Multisource guidance or WHO TRS No. 996, Annex 10

23. WHO guidance on Stability testing of active pharmaceutical ingredients and
finished pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical
Report Series, No. 1010), Annex 10. Short name: WHO guidance on Stability testing or
WHO TRS No 1010, Annex 10