



Prequalification Team Inspection Services
WHO Public Inspection Report of the
Finished Product Manufacturer (FPP)

Part 1: General information

Name of Manufacturer	Shanghai Desano Bio-Pharmaceutical Co., Ltd
Unit number	N/A
Production Block	N/A
Physical address	1479 Zhangheng Road, Zhangjiang, High-Tech Park, Shanghai 201203, Peoples Republic of China
Date of inspection	7 – 9 January 2015
Type of inspection	Follow-up inspection
Summary of activities of manufacturer (e.g. manufacturing, packing).	Coated tablets and capsules
Dosage forms(s) included in the inspection	Film coated tablets
WHO product numbers covered by the inspection	Prequalified products: HA286 Lamivudine / Zidovudine 150 mg /300 mg Film coated Tablets HA323 Lamivudine / Nevirapine / Zidovudine 150 mg/ 200 mg/ 300 mg Film coated Tablets
Summary of the activities performed by the manufacturer	Manufacturing, packaging, quality control, stability testing

Part 2: Summary

General information about the company and site

Shanghai Desano Bio-pharmaceutical Co., LTD is a solid pharmaceutical products manufacturing company which was established in July 2000. The plant inspected was built in 2011.

No hormones, steroids, cephalosporins, beta-lactams or cytotoxic were manufactured at the site.

History of WHO and/or regulatory agency inspections

The site was previously inspected by the WHO team in June 2014. This was follow-up inspection to evaluate implementation of corrective and preventive actions (CAPA) and evaluate transfer of technology from Ranbaxy, India.

The site had a valid Pharmaceutical Manufacturing License and GMP certificate issued by the Chinese Regulatory Authorities in 2012.

Focus of the inspection

The inspection focused on evaluation of implementation of corrective and preventive actions (CAPA) and evaluation of transfer of technology from Ranbaxy, India, relevant to the Ranbaxy prequalified products:

- HA286 Lamivudine / Zidovudine 150 mg /300 mg Tablets
- HA323 Lamivudine / Nevirapine / Zidovudine 150 mg/ 200 mg/ 300 mg Tablets

Inspected Areas

Elements of various systems were inspected, and included:

Quality Assurance

Sanitization and hygiene

Qualification and validation

Complaints

Recalls

- Supplier qualification
- Personnel
- Training
- Personal hygiene
- Premises
- Equipment
- Materials
- Documentation
- Production
- Quality control

2.1 PHARMACEUTICAL QUALITY SYSTEM (PQS)

In general a PQS was implemented. Production and control operations were specified in written form and GMP requirements were generally followed. Managerial responsibilities were specified in job descriptions.

The Quality manual was available and presented to the inspectors. The document was spot checked and generally acceptable.

Management review:

The SOP “Quality information notification” was reviewed. The Plant Quality Council (PQC) was responsible, but not limited to, the review and assessment of problems reported, CAPAs and CAPA plans. PQC meetings were held periodically - usually every month. If required, an emergency meeting was held. Meeting minutes were drafted and approved within 5 days by the QA and sent to the members of the PQC. Emphasis of the meetings was on QA for ensuring quality management

Product Quality Review (PQR)

The SOP for “Product Quality Review (PQR)” was reviewed .

Products manufactured for Ranbaxy (HA286 Lamivudine / Zidovudine 150 mg / 300 mg Tablets and HA323 Lamivudine / Nevirapine / Zidovudine 150 mg / 200 mg / 300 mg Tablets) – were not commercialized as of the date of the inspection.

However PQRs were available and reviewed. Although there was no manufacturing in 2014, the PQR covered all aspects of the QA including complaints, water quality, and source of raw materials etc.

Quality Risk Management

The SOP “Risk assessment procedure (RA)” was reviewed. The RA report “Multiple product line in solid dosage form manufacture” was also reviewed. RA was carried out by the team which consisted of:

- Three persons from Quality Assurance (QA)One person from Quality Control (QC)
- One person from production
- One person from engineering
- Associated General Manager

Change controls (CC)

The SOP “Change control procedure”, flow chart, change application form and CC registers for 2013 and 2014 were reviewed. The SOP was applicable, but not limited to:

- Materials
- Manufacturing process
- Equipment
- Instruments
- Cleaning validation
- Documents
- Computerized systems

CCs were classified as:

- Major
- Minor

The changes made during 2014 were discussed. There were no issues noted and the changes were successfully made according to the SOP.

Deviation management

The SOP “Deviation investigation and handling procedure”, flow chart, deviation notification form and register were reviewed. This SOP was applicable for unplanned deviations. Deviations were classified as:

- Non-critical
- Critical

Deviations were trended every 6 months and annually.

2.2 GOOD MANUFACTURING PRACTICES (GMPs) FOR PHARMACEUTICAL PRODUCTS

In general good manufacturing practices were implemented. The necessary resources were generally provided. Manufacturing steps were recorded in batch manufacturing and packaging records. Instructions and procedures were generally written in clear and unambiguous language. Qualifications and validations were performed, adequate premises and equipment were available for production, in-process controls and storage, and operators were trained.

2.3 SANITATION AND HYGIENE

Premises and equipment were maintained at a high and acceptable level of cleanliness. The company had a standard operating procedure as the basis for its approach to personal hygiene and sanitation in its production facility.

2.4 QUALIFICATION AND VALIDATION

Validation master plan (VMP)

The validation master plan approved on 30 April, 2014 was checked.

Process validation

The process validation protocol, report and analytical raw data for HA323 Lamivudine / Nevirapine / Zidovudine 150 mg/ 200 mg/ 300 mg Tablets were spot checked. Three batches were included in the validation.

Critical process parameters were defined based on information supplied from Ranbaxy, Paonta transferring unit.

Cleaning validation

Cleaning validation of equipment after the production of Lamivudine / Nevirapine / Zidovudine 150 mg/ 200 mg/ 300 mg tablets was inspected. A protocol, report and analytical raw data were reviewed. Samples were taken by swab and rinse methodology. Swab recovery studies were carried out for Stainless Steel surfaces for APIs and cleaning agent residue. The analytical method used for validation studies was HPLC method.

Purified water (PW) system qualification

The PW system was installed in 2011. Till the date of inspection there were no changes to the PW system. A 3 phase approach was used for PW system qualification. Phase 1 and 2 lasted for 1 month each; phase 3 lasted for 1 year. The following tests were done on-line:

- Total organic carbons
- Conductivity
- Velocity
- pH

AHU qualification

AHU 6208 re-qualification protocol and report were reviewed. The following tests were carried out:

- Viable particle counts
- Non-viable particle counts
- Air exchanges per hour
- HEPA filter integrity
- Microbial counts
- Air velocity
- Pressure differential

2.5 COMPLAINTS

The SOP “Customer complaints procedure”, flow chart and customer complaint form were reviewed. Till the date of inspection there were no complaints received. Operations at the site started in October 2012. According with the SOP complaints should be closed within 30 days. Three levels of complaints were specified:

- Critical
- Major
- Minor

A complaints summary report and trends should be prepared in January-February for the previous year.

2.6 PRODUCT RECALLS

The SOP “Product recall procedure” and flow chart were reviewed. Recalls were classified as:

- I level (critical) should be handled within 24 h
- II level (major) should be handled within 48 h
- III level (minor) should be handled within 72 h

Till the date of the inspection there were no recalls registered. The Qualified Person was responsible for handling the recalls. Evaluation of recall procedure (mock recall) was done every year. Up to the date of inspection two mock recalls had been carried out.

2.7 CONTRACT PRODUCTION AND ANALYSIS

The Technical Agreement with Ranbaxy was reviewed. Responsibilities of contract giver and contract acceptor were specified.

2.8 SELF INSPECTION AND QUALITY AUDIT

Self-inspection

The SOP “Internal audit procedure” and schedule for 2014 were reviewed. Self-inspection was carried out by an audit team according with audit plan. Check lists were used for self- inspection. Afterwards, the inspection report was written and approved by the QA manager.

CAPAs were proposed by the inspected departments and evaluated by the audit team. Implementation of CAPAs was reviewed by the delegated person from the QA department

Self- inspection was carried out once per year for each department.

Supplier’s audits and approval

The SOP “Suppliers management” and flow chart were reviewed. The SOP was applicable for evaluation of API, excipients and packaging material manufacturers and suppliers. Critical suppliers and manufacturers of APIs, excipients, packaging materials were audited – every 3 years or approval was based on questionnaires. Non critical material manufacturer’s audits were carried out every 5 years. The audit plan for 2014 was presented to the inspectors.

2.9 PERSONNEL

In general the manufacturer had an adequate number of personnel with the necessary qualifications and practical experience. Responsible personnel’s specific duties were recorded in written job descriptions. Personnel were aware of the principles of GMP and received initial and continuing training.

2.10 TRAINING

Training was provided for all workers. The “SOP Training management” was reviewed.

- Introduction training
- Ongoing training
- Job transfer training

An annual training master plan was available. Training effectiveness was mainly evaluated by multiple choice questions.

Analyst’s qualification was carried out. The sample what had been already analyzed was given for analysis. Obtained results were compared and RSD was specified.

2.11 PERSONAL HYGIENE

The SOP “Personal hygiene management” was spot checked. Direct contact was avoided between the operator’s hands and starting materials, primary packaging materials and intermediate or bulk product. Smoking, eating, drinking, chewing, and keeping plants, food, drinks, smoking material and personal medicines was not permitted in production, laboratory and storage areas. Wrist-watches, cosmetics and jewelry were not being worn in clean areas.

2.12 PREMISES

In general the buildings and facilities used for manufacture and quality control were located, designed, and constructed to facilitate proper cleaning, maintenance and production operations. Premises were designed to ensure the logical flow of materials and personnel. An in-process quality

control laboratory was located in the production block. Quality control laboratories were separated from production areas. Sufficient space was given to avoid mix-ups and cross-contamination. Premises were protected from entry by insects, birds and animals. Premises were clean and well maintained.

Storage areas

Receiving and dispatch bays protected materials and products from the weather. Segregation was provided for the storage of rejected, recalled, or returned materials or products. Temperature mapping in warehouses was carried out. The temperature was monitored by an environmental monitoring system. Further mapping studies were carried out in 2014 (post the WHO inspection). The temperature mapping was found to give satisfactory control of temperatures and relative humidity in critical areas.

Production areas

In general, the production area was laid out to allow the production steps to take place in a logical order. The surfaces were smooth and free from cracks. Equipment and materials were orderly positioned to minimize the risk of confusion between different pharmaceutical products or their components. Temperature, relative humidity and pressure differentials were continuously monitored by Environment Management system (EMS) and controlled by Building Management System (BMS).

Quality control areas

Quality control areas were separated from production areas. Sufficient space was provided for storage of samples, reference standards, solvents and reagents.

2.13 EQUIPMENT

Balances and other measuring equipment with appropriate range and precision were available for production and control operations and were calibrated on a scheduled basis. Calibration due-date labels were attached to the equipment.

Calibrated standard weights used for in-house verification of balances were available. The calibration certificate for the set of standard weights was presented to the inspectors.

2.14 MATERIALS

Materials were obtained from approved suppliers. There was no electronic system for material management. Materials were controlled by means of bin cards.

Sampling was carried out in 4 sampling rooms. One sampling room was dedicated for capsule sampling. Entrance to the sampling rooms was via change rooms for personnel and separate entries for materials.

Dispensing was carried out in 2 dispensing rooms. Entrance to the Dispensing rooms was via change rooms for personnel and separate entries for materials. Dispensing was done under Reverse Laminar Airflow Bench.

The SOP "Product reprocessing and reworking procedure" was spot checked.

2.15 DOCUMENTATION

In general documents were designed, prepared, reviewed and distributed with care. In general, documents were approved, signed and dated by the appropriate responsible persons. Documents were laid out in an orderly fashion and were easy to check. Reproduced documents were clear and legible. Documents were regularly reviewed and kept up to date.

2.16 GOOD PRACTICES IN PRODUCTION

In general the surfaces were smooth and free from cracks (clean room design approach). Equipment and materials were orderly positioned to minimize the risk of confusion between different pharmaceutical products or their components.

Entrance to the different production rooms was via airlocks.

Temperature, relative humidity and pressure differentials were continuously monitored through the EMS.

2.17 GOOD PRACTICES IN QUALITY CONTROL (QC)

The QC function was independent from other departments. Samples of starting materials, packaging materials, intermediate products, bulk products and finished products were taken by approved methods. Sufficient samples of starting materials and products were retained to permit future examination of the product. A brief inspection of the quality control laboratory was done. Some documents including SOPs, log books/registers, reports and analytical reports were reviewed. In general the laboratory was well equipped and organized.

Out of specifications (OOS)

The SOP “Out of specification investigation procedure” and flow chart were reviewed. The updated SOP included “Out of Trend” (OOT) and “Out of expectations” (OOE).

Stability testing

The SOP “Stability study procedure” and the protocol, and tabulated results for Lamivudine/Zidovudine tablets were reviewed. Results checked were within specification limits. The results were presented in tabular form and were also presented graphically. A trend line was calculated using regression analysis.

Reference standards

Pharmacopoeia reference standards (RS) and working standards (WS) were kept in desiccators at room temperature, in a fridge at 2 - 8 °C and in freezer at -20 °C. RS and WS usage was recorded. The temperature in the freezer and fridge was recorded manually twice per day.

Retention samples

Finished product retention samples were stored for a period of 1 year after expiry date. API retention samples were stored for at least 5 years from the date when the sample was received at the retention sample storage room. (The maximum expiry date for the FPP was 2 years). The temperature was controlled and monitored.

Microbiology laboratory (MBL)

The microbiological quality control laboratory was fully inspected including media preparation, autoclave validation and microbiological testing of raw materials, water, environment and finished

product. The laboratory is modern and very well equipped. Some documents including SOPs, log books/registers, reports and analytical reports were reviewed. In general the MBL was well equipped and organized.

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, a decision on the compliance of Shanghai Desano Bio-Pharmaceutical Co., Ltd, located at 1479 Zhangheng Road, Zhangjiang, High-Tech Park, Shanghai 201203, Peoples Republic of China 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.