WHO PUBLIC INSPECTION REPORT (WHOPIR) API Manufacturer

Part 1: General information

Name of Manufacturer	Lonzeal Pharmaceuticals Co., Ltd.
Unit number	NA.
Production Block	No. 1 Work Shop
Physical address	No. 16 West Ring Road, Shenze Shijiazhuang, 052560 China
Contact person and email address.	Dr. Jing Zhang Lonzeal Pharmaceuticals Co., Ltd. Email: jing@lonzeal.com
Date of inspection	8 -11 May 2012
Type of inspection	Routine inspection (new site)
Active Pharmaceutical Ingredient(s) included in the inspection	Lamivudine APIMF 112
Summary of the activities performed by the manufacturer	Production and quality control of APIs

Part 2: Summary

General information about the company and site

Shijiazhuang Lonzeal Pharmaceuticals co., Ltd was established in 2006. It is specialised in the manufacturing of active pharmaceutical ingredients and key intermediates. The company has one manufacturing site manufacturing for one API Lamivudine.

History of WHO and/or regulatory agency inspections

This was the first WHO GMP inspection and the site has been inspected by ANVISA.

Focus of the inspection

The inspection focused on the production and control of Lamivudine API. The inspection covered all the sections of WHO GMP guidelines for active pharmaceutical ingredients, including premises, equipment, documentation, materials, validation, sanitation and hygiene, production, quality control and utilities.

Inspected Areas

Inspection program and the areas inspected

Introductory Meeting
Overview of activities at site
Personnel

- Organization chart
- Job description
- Staff training programme & records

Quality Assurance and Quality Management System

- Product Quality Reviews (PQR)
- Change Control
- Deviations
- Complaints
- Recalls
- Document control
- Self-inspections
- Retention Samples
- Review of batch documents

Inspection of Production Operations & Facilities

- Warehousing and storage
- Production operations
- Packaging and labelling operations

Quality Control

- In-process sampling and controls

- QC Labs (physic-chemical and microbiology)
- Sampling
- Testing of the API and intermediates (IPC)
- Out of Specification investigations
- Reference substance and working standards
- Stability program

Validation

- Validation Master plan, protocols
- Process validation
- Cleaning and cleaning validation

Production facility & equipment management

- Purified Water
- Maintenance program
- Qualification and calibration program
- HAVC

Post inspection summary meeting

2.1 QUALITY MANAGEMENT

General

Quality management systems were established, documented and implemented in general.

The QA/QC department was independent from production.

The production and quality control procedures were satisfactorily defined and were followed in general.

Product Quality Review

The SOP for PQRs and the PQR of Lamivudine (year 2011) was inspected and found to be acceptable in general.

Internal audits

In order to verify compliance with the principles of GMP for APIs, regular internal audits were being conducted in accordance with SMP and an approved schedule. Internal audits were required to be conducted at least once a year, but this could be increased for defined reasons, e.g. a complaint. The last internal audit was conducted in November 2011.

2.2 PERSONNEL

An organization chart was available. The quality assurance and quality control department was independent from the production department. The production activity runs in three shifts.

The total number of personnel working at the site was 210.

Job descriptions

Key personnel responsibilities were specified in job descriptions. The described responsibilities for the following key personnel were reviewed:

- General Manager QA
- Quality Control Manager
- Production Manager

Personnel hygiene

The gowning and changing rules when entering the clean areas were described in standard operating procedures.

The changing rooms for the controlled areas were equipped with hand wash facilities and the procedure was displayed on the wall.

Training

Personnel were qualified by education and training. The training program and the evaluation of the trainings was the shared responsibility of the HR, QA, the concerned departments and the trainers. The training procedure and selected training records were reviewed and found acceptable in general. The training file of an analyst was reviewed.

2.3 BUILDINGS AND FACILITIES

General

The inspected production block and the production equipment were dedicated as only one API product was manufactured at this site. The workshops and the facilities inspected were maintained to be acceptable in general.

Production workshop

The production workshop was in three levels; ground floor, first floor and second floor. The synthesis process was on the first floor. The final recrystallization, drying and packing were performed in the clean area claimed to comply with grade D. The installation of the manufacturing equipment supported the vertical material flow.

Utilities

The pipelines were identified with flow directions indicated.

Purified water

Purified Water was used for cleaning equipment in the controlled area. Demineralized water was used as a solvent in the process of hydrolyzation and extraction but not at the final stages of the production. The specification of the water met the requirements of the Chinese pharmacopeia.

The source water was fed by underground water. After pre-treatment, water went through two ROs and demineralization by mix-bed ion exchange. Water then was transferred to the distribution tank and was circulated continuously through the distribution loop. The loop was equipped with a UV lamp. Conductivity and

resistance of the water were monitored online. It was tested according to a predetermined programme and the system was sanitized by hot water once a month. The qualification of water system was inspected.

Containment

There were no other highly sensitizing materials either produced or handled at this site. Lamivudine was the only API manufactured on the site.

HVAC systems

The environmental conditions in the controlled areas (Crystallization, Centrifugation, drying) were maintained by means of HVAC systems.

The HVAC in the powder generation room was 100% fresh air inlet; the grades of filters were G4, F8 and H13.

2.4 PROCESS EQUIPMENT

General

The equipment used to manufacture of Lamivudine were dedicated.

The process equipment was identified and kept in good condition by means of periodic qualification, calibration, maintenance and cleaning.

Maintenance program

The equipment maintenance was accomplished based on an annual maintenance program and approved maintenance protocols. A SOP on preventive maintenance covered the maintenance policy. The maintenance schedule of 2012 and the records were available. SOP for maintaining glass lined reactors was reviewed.

Cleaning

Cleaning procedures subject to different equipment and records of the cleaning of equipment and facilities were available for inspection.

Calibration

Calibration of devices (e.g. temperature sensor) was conducted according to defined program. The calibration record of the temperature sensor belonging to the water storage tank was available, the relevant SOP was reviewed.

Computerized Systems

Other than for individual pieces of equipment, such as the HPLC and GC equipment, no computerized systems were used in the warehouse, production or QC lab.

2.5 DOCUMENTATION AND RECORDS

Documentation system

The site documentation system was paper based. The procedure for document control was available. GMP documentation included standard operating procedures,

specifications, master batch manufacturing records, etc. The preparation and issuance of specifications, analytical test methods, and submissions for registrations were according to the SMP.

The storage (archive) period of the BMR related documents was one year after the expiry date of the concerned batch. Other GMP related documents were kept permanently.

Batch numbering system

The batch numbers were generated according to the SMP.

2.6 MATERIALS MANAGEMENT

Procedures

There were written procedures describing the receipt, labelling, quarantine, storage, and handling of materials, as well as the procedures for sampling, testing and approval or rejection of materials.

Each raw material was assigned an identification code and the code used to identify the material in documents for all manufacturing and testing processes.

Vendor qualification

Any material used for manufacturing of Lamivudine was required to be purchased from an approved vendor. A list of approved vendors was available.

Vendors were qualified as per written procedure. Materials were classified according to their impact on quality and class A vendors (such as crystallization solvents and primary packaging bags) subjected to on-site audit. Other vendors were qualified based on sample testing and trial production.

The records of vendor approval reviewed, including vendor audits, were satisfactory.

Handling, sampling and identification of materials

The incoming raw materials and packaging materials handling procedure were described by SMPs. The QC was responsible for the sampling.

Weighing, dispensing

Weighing was performed in the production block in the specified area nearby each step of reaction and recorded in the BMR.

The daily check of the balance was recorded and found to be acceptable in general.

2.7 PRODUCTION AND IN-PROCESS CONTROLS

Production process was guided by documented procedures and instructions. Production process including synthesis, purification, crystallization, drying etc. were conducted in dedicated facilities and equipment to manufacture Lamivudine. Clean areas were available for the final steps of the API's manufacture and were maintained at a satisfactory level.

Product blending was handled according to SMP.

In-process controls including PH, water content and impurities were conducted at different stages of the synthesis to monitor performance of the process, quality of the intermediates and recovered solvents. Sampling of the API for release testing was done after drying and before final packing in the clean area.

Production of Lamivudine API was in operation during this inspection. The in-process lab was inspected.

2.8 PACKAGING AND IDENTIFICATION LABELLING OF APIs AND INTERMEDIATES

Packaging and labelling operations were conducted as per standard operating procedures in controlled areas.

The defined package form was two layer PE bags in a fibre drum.

Packaging materials were checked and released according to specifications. The containers and inside PE bags used to pack finished APIs were consistent with the information in dossier.

The labelling operations were designed to prevent mix-ups as only one product was handled in the labelling room at any time.

2.9 STORAGE AND DISTRIBUTION

RM/PM warehouse

The RM/PM warehouse was in a separated area. Different materials were stored in separate storage rooms in terms of solid, liquid RM, as well as packaging materials. There was a solvent tank farm for fresh and recovered solvents.

The solvent used for key intermediate or API manufacturing were stored in the tank farm.

Finished product warehouse

The finished product warehouse (storage) was inspected and found to be acceptable in general.

2.10 LABORATORY CONTROL

General

The QC laboratories were responsible for physical, chemical and microbiological testing of starting materials, packaging materials, products (API's), environmental

monitoring samples, purified water samples. Intermediates testing were performed by IPC lab.

Physical and chemical testing laboratories were in a separate building. The microbiological laboratory was on the second floor of the production block (with separate HVAC).

Sample receiving and testing work allocation were inspected. The product specification was USP plus additional in house requirements. The validation of in house analytical method for impurity was reviewed.

Analytical testing records

The analytical testing was performed according to the written specification/test method.

The selected records of tests were inspected including starting materials of fresh and recovered ethanol, finished API.

Reference materials

For analytical testing purposes working standards prepared in-house were used. The working standards were made from released API batches tested against the standard specification comparing to compendial reference standard.

Stability testing

The QC department was responsible for stability testing of finished APIs.

The stability samples were taken according to the defined program/protocol and stored in a long-term 30°C/65% RH stability chamber. A 40°C/75% RH chamber was available for accelerated stability studies.

One batch from each year was added for long-term on-going stability study as per written procedure.

Retention Samples

The retention samples of finished APIs, raw materials and packaging materials were taken (packed in a container of the same material as used for the commercial products) and stored by the QC according to the SMP.

Retention samples of the Lamivudine API were available in proper amount and packaging.

Handling of out of specification (OOS) results

The SMP describes the handling, investigation and recording of the out of specification results. The procedure covered any non-compliance result of starting material, intermediate and API testing.

The SMP requires that the discovered OOS result should be reported, and recorded in a logbook. Three cases were recorded, investigated and closed in 2011 and one in 2012. All were the OOS of starting materials.

2.11 VALIDATION

Validation Master Plan

The company had policy, procedures, protocols and reports for validation and qualification of processes, procedures, equipment, utilities etc. The Validation Master Plan and Validation Management Procedure regulated all qualification and validation activities.

Manufacturing process validation

The manufacturing process of Lamivudine was revalidated in 2012. It was a concurrent re-validation resulting from capacity expansion and WHO assessment results.

Cleaning validation

Cleaning validation was performed on the final re-crystallization tank and centrifuge according to written procedure and protocol. The acceptance criteria were calculated by MACO approach. The selected cleaning validation report of the recrystallization tank was inspected.

2.12 CHANGE CONTROL

A procedure for change control was according to SMP. The change control register and records were maintained. The change control for the addition of new reactors and the change of the cleaning procedure were reviewed.

2.13 REJECTION AND RE-USE OF MATERIALS

Recovered solvents were used at the site according to the production process. The specifications for recovered solvents were available. Solvent recovery was performed on-site and the company claimed that the recovered solvents were only used in process of origin. Recovered solvents were not used in the final step of the production.

Reprocessing and reworking needed to be approved as per procedure specified in SMP.

2.14 COMPLAINTS AND RECALLS

The standard operating procedures to handle the complaints and recall were available. SOP on handling of market complaints and SOP on handling of product recall were reviewed.

2.14 CONTRACT MANUFACTURERS (INCLUDING LABORATORIES)

According to the company, there were no contracted manufacturing activities.

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, as well as the corrective actions taken and planned, the API manufactured at Lonzeal Pharmaceuticals Co., Ltd. No. 16 West Ring Road, Shenze Shijiazhuang, 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.