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20, avenue Appia – CH-1211 Geneva 27 – Switzerland – Tel central +41 22 791 2111 – Fax central +41 22 791 3111 – www.w

WHO PUBLIC INSPECTION REPORT (WHOPIR) of the API manufacturer

Part 1: General information

Name of Manufacturer	Hainan Poly Pharma Co. Ltd
Unit number	N/A
Production Building	Building No 4
Physical address	Guilinyang Economic Development Area Haikou City, Hainan Province. People's Republic of China
Summary of activities of manufacturer (e.g. manufacturing, packing)	Production and quality control of injections, tablets, capsules, granules, dry suspensions, ointments and APIs
Type of inspection	Routine GMP inspection
Active Pharmaceutical Ingredient included in the inspection	Ganciclovir sodium API
Date of inspection	20 June 2014

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Part 2: Summary

General information about the company and site

Hainan POLY Pharm. Co., Ltd. (hereinafter referred to as POLY) was founded in 1992. The site is specialized for production of pellets, injections, and lyophilized powders for injection, taste masking & oral dispersible dosage forms. Marketing & sales operations and manufacture for local market were carried out by the subsidiary - Zhejiang POLY Pharm. Co., Ltd. (6F, Jintai Commercial Building, 571 Qingtai Street, Hangzhou City, Zhejiang Province, China). Research and development was carried out by Hangzhou SHARPLY Pharmaceutical Research Institute Co., Ltd. (4F, West Building 2, 1180 Binan Street, Binjiang District, Hangzhou City, Zhejiang Province, China)

No hormones, steroids, cephalosporin's, beta-lactams or cytotoxins were produced and no poisonous /or hazardous materials were manufactured or handled at the POLY site.

At the time of the inspection the site employed approximately 248 full time employees, 56 of whom worked in the Quality Department.

History of WHO and/or regulatory agency inspections

The site was previously inspected by a WHO inspection team on 14-18 November 2011; on 14 to 16 May 2012 for manufacture and control of FFPs; and on 21 - 23 November 2011 for manufacture and control of APIs.

The site was inspected by the following authorities:

- State Food and Drug Administration in 2002 and 2013
- Dutch inspectorate in 2012
- US Food and Drug Administration in 2014

Based on the Dutch inspectorate inspection the site was approved by the German authorities and a GMP certificate for manufacture of powder for injection was issued.

Focus of the inspection

This inspection focused on the production and control of Ganciclovir Sodium API.

Inspected Areas

- Pharmaceutical quality system
- Qualification and validation
- Complaints
- Recalls
- Personnel
- Premises
- Documentation

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- Production
- Quality control

2.1 PHARMACEUTICAL QUALITY SYSTEM (PQS)

In general 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.

Quality risk management

The SOP "Quality risk management" was checked. The SOP was applicable for:

- Deviations
- Out-of-specification/Out-of-trend (OOS/OOT)
- Quality complaints
- Product recall
- Change control (CC)
- Returns
- Abnormal tendency of process performance and product quality
- External GMP audits
- Reprocessing & reworking

Risk assessment (RA) team was defined in the SOP. Tools for RA were defined in the SOP "Quality risk management tools". The SOP "Risk assessment using FMEA" was checked. 10 score system was used for RA. Tools for risk assessment were specified in the separate SOP "Recommended tools for risk assessment". The SOP specified FMEA, HACCP, FTA, FMECP, HAZOP and Fish bone as tools to be used for RA. The lists of performed RA in 2013 and 2014 were presented to the inspectors.

Management review

Management meetings were carried out monthly. On spot checks meeting minutes were available.

Change controls

The SOP "Changes control (CC)", flow chart and change registers for 2013 and 2014 were checked:

Changes were classified

- Critical (III) should be closed within 6 months
- Major (II) should be closed within 3 months
- Minor (I) should be closed within 1 month

Progress of CC implementation was reviewed and monitored by QA every month. If the CC could not be implemented within the target date - QA and responsible department evaluated whether the target date should be postponed or CC should be cancelled.

Change request form for new addition of air compressor and auxiliary machine in the compression plant was spot checked.

Observations are listed in the section 5.

Deviation management
The SOP "Deviation management" and log book for 2014 were checked. The SOP was applicable to all deviations or observed abnormal trends in manufacture and quality management.

According to the SOP definition of deviation is: deflection from the approved procedures instructions or established standard or abnormal trend.
Deviations were classified as:

- Minor
- Major
- Critical

According to the SOP there were planned and unplanned deviations. Deviations were to be reviewed quarterly and annually for whole year. Deviations were to be closed within 30 days.

Product Quality Review
The SOP "Annual Product review (APR)" was checked. According to the SOP, a APR should be carried till January 31st following year. Software programme "Minidata" was used for the process capability calculations (CpK). The SOP reflected only the parameters recommended as a minimum in the GMP guidelines.

2.2 GOOD MANUFACTURING PRACTICES (GMPs) FOR PHARMACEUTICAL PRODUCTS

Good manufacturing practices were generally implemented. The necessary resources were provided. Manufacturing processes were defined and systematically reviewed. Qualification and validation were generally performed. Operators were trained to carry out procedures correctly, and records were made during manufacture.

2.3 SANITATION AND HYGIENE

In general, premises and equipment were maintained at an acceptable level of cleanliness. Special attention was not paid on sanitation and hygiene during this inspection.

2.4 QUALIFICATION AND VALIDATION

API cleaning validation

Cleaning validation for APIs was done in 2010. No new products were introduced on site after 2010. There was no policy for revalidation unless there was a specific change; however the cleaning validation plan for 2014 was presented to the inspectors.

2.5 COMPLAINTS

The SOP "Handling of complaints", flow chart and registers were spot checked. Complaints and other information concerning potentially defective products were reviewed according to written procedure and the corrective actions were taken. Till the date of inspection complaints regarding product quality were not received.

2.5 PRODUCT RECALLS

Till the date of inspection there were no recalls. SOP product recall, flow chart and last mock recall, performed September 2013 were spot checked. Mock recall was done for local market. Recalls were classified as:

- Class I
- Class II
- Class III

2.6 CONTRACT PRODUCTION AND ANALYSIS

Neither production nor quality control operations were contracted out.

2.7 SELF INSPECTION AND QUALITY AUDIT

Not covered during this inspection.

2.8 PERSONNEL

The manufacturer had an adequate number of personnel with the necessary qualifications and practical experience. Responsible staff's specific duties were recorded in written job descriptions.

Job description of the Quality director & qualified person was reviewed.

2.9 TRAINING

Not covered during this inspection.

2.10 PERSONAL HYGIENE

During inspection it was noted that personnel was familiar with hygiene requirements in both manufacturing buildings.

2.11 PREMISES

Exposed surfaces of production areas for APIs were generally smooth, impervious and unbroken to minimize the shedding or accumulation of particles or microorganisms.

Ancillary areas

Rest and refreshment rooms were separate from manufacturing and control areas.

Storage areas

Storage areas were of sufficient capacity. Receiving and dispatch bays were separated and protected materials and products from the weather. Segregation was provided for the storage of rejected, recalled, or returned materials or products. Ganciclovir Sodium API samples were taken in Building 4, in the API production clean area.

Quality control areas

QC laboratories were separated from production areas. Sufficient space was given to avoid mix ups and cross-contamination.

2.12 EQUIPMENT

No issues of significance were found regarding production equipment during this inspection.

2.13 M ATERIALS

Materials were generally stored appropriately. Packaging materials were sampled according to an SOP reflecting ISO recommendations.

2.14 DOCUMENTATION (common for FPPs and APIs)

In general documents were designed, prepared, reviewed and distributed with care. Documents were approved, signed and dated by the appropriate responsible persons. Documents were regularly reviewed and kept up to date.

Assessment of the Site Mater File

The Site Master File was available in electronic form before the visit was made to the manufacturing site. It included detailed schematic plans and drawings of the buildings and utilizes, such as the water systems. In general it complied with the guidelines on preparation of the SMF.

2.15 GOOD PRACTICES IN PRODUCTION

There were no activities carried out during the inspection in the API manufacturing block.

2.16 GOOD PRACTICES IN QUALITY CONTROL

The QC function was independent of other departments. Adequate resources were available. QC personnel had access to production areas for sampling and investigation as

appropriate. Special attention during this inspection was paid to the HPLC data reliability and data integrity.

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, Hainan Poly Pharma Co. Ltd, located at Guilinyang Economic Development Area Haikou City, Hainan Province, China was considered to be compliant with WHO GMPs for Active Pharmaceutical Ingredients published by WHO for the manufacture and packaging of Ganciclovir sodium API.

All the non-compliances observed during the inspection that were listed in the full report 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.

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