



**World Health  
Organization**

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## **WHO PUBLIC INSPECTION REPORT**

**(WHOPIR)**

### **Active Pharmaceutical Ingredient Manufacturer**

#### **Part 1: General information**

Name of Manufacturer	Hainan Poly Pharma Co. Ltd
Unit number	N/A
Production Block	Building No 4
Physical address	Guilinyang Economic Development Area Haikou City, Hainan Province. China
Date of inspection	21 November - 23 November 2011
Type of inspection	Routine inspection, covering all aspects of GMP
Active Pharmaceutical Ingredient(s) included in the inspection	Ganciclovir API
Summary of the activities performed by the manufacturer	Production and quality control of injections, tablets, capsules, granules, dry suspensions, ointments and APIs

## **Part 2: Summary**

### ***General information about the company and site***

Hainan POLY Pharm. Co., Ltd. (hereinafter referred to as POLY) was found in 1992. The site is specialized for production of pellets, injections, and lyophilized powders for injection and taste masking & oral dispersible dosage forms. Marketing & sales operations 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, cephalosporins, beta-lactams or cytotoxins and no poisonous /or hazardous materials were manufactured or handled at the POLY site.

At the time of the inspection the site employed approximately 188 full time employees, 50 of which worked in Quality Assurance and Quality Control.

### ***History of WHO and/or regulatory agency inspections***

The site had never been inspected by the WHO team or other international organizations.

### ***Focus of the inspection***

The inspection focused on the production and control procedures of ganciclovir API. The inspection covered all the sections of 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 Assurance
- Sanitization and hygiene
- Qualification and validation Complaints
- Recalls
- Self-inspection
- Personnel
- Training
- Personal hygiene
- Premises
- Equipment
- Materials
- Documentation
- Production
- Rejection and reuse of materials
- Quality control

## **2.1 QUALITY MANAGEMENT**

A system for managing quality was established, documented and implemented. The Organizational structure, procedures, processes and resources were provided. Quality-related activities were defined, documented and recorded at the time they were performed. The quality unit was independent of production. The persons authorized to release intermediates and APIs were specified. Deviations were documented and explained.

### **Responsibilities of the quality and production units**

Responsibilities of the quality unit (personnel) and the responsibility of the production unit (personnel) activities were described in writing.

### **Internal audits (self-inspection)**

Regular internal audits were performed in accordance with an approved schedule. Audit findings and corrective actions were documented. Agreed corrective actions were completed in a timely manner.

### **Product quality review**

Regular quality reviews of APIs were conducted. The results of this review were evaluated and an assessment made of whether corrective action or any re-validation should be undertaken.

## **2.2 PERSONNEL**

### **Personnel qualifications**

There was 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.

Training was regularly conducted by qualified individuals. Records of training were maintained. Training was periodically assessed.

### **Personnel hygiene**

Good sanitation and health habits were observed on the site. Direct contact with intermediates or APIs was avoided. Smoking, eating, drinking, chewing and the storage of food was restricted from the manufacturing areas. Any person shown at any time to have an apparent illness or open lesions was excluded from activities where their health condition could adversely affect the quality of the APIs.

### **Consultants**

N/A

## **2.3 BUILDINGS AND FACILITIES**

### **Design and construction**

Buildings and facilities used in the manufacture of intermediates and APIs were located, designed, and constructed to facilitate appropriate cleaning and maintenance.

Facilities were designed to minimize potential contamination. Adequate space was provided for the orderly placement of equipment and materials. The flow of materials and personnel through the building was designed to prevent mix-ups or contamination. Laboratory controls were carried out in the main QC laboratory.

### **Utilities**

Adequate ventilation, air filtration and exhaust systems, and a Purified Water (PW) system were provided and these were designed and constructed to minimize risks of contamination and cross-contamination. Drawings for the systems were available.

Permanently installed pipework was appropriately identified.

### **Water**

Water used in the manufacture of API was suitable for its intended use. Appropriate specifications were established and monitored.

### **Containment**

Appropriate measures were established to prevent cross-contamination from personnel and materials.

### **Lighting**

Adequate lighting was provided in production areas to facilitate cleaning, maintenance and proper operations.

### **Sewage and refuse**

Waste was disposed in a safe and sanitary manner. Containers for waste material were clearly identified and stored separately.

### **Sanitation and maintenance**

Buildings used in the manufacture of intermediates and API were properly maintained and repaired and kept in a clean condition. Written procedures were available for sanitation of facilities and equipment.

## **2.4 PROCESS EQUIPMENT**

### **Design and construction**

Equipment used in the manufacture of intermediates and API were of appropriate design, adequate size, and suitably located for its intended use. Production equipment was used within its qualified operating range.

### **Equipment maintenance and cleaning**

Schedules and procedures were established for the preventive maintenance of equipment. Written procedures were established for cleaning of equipment. Dedicated equipment were used for ganciclovir sodium API production.

### **Calibration**

Control, weighing, measuring, monitoring and test equipment were calibrated according to written procedures and an established schedule. Records of these

calibrations were maintained. The current calibration status of critical equipment was known and was verifiable.

### **Computerized systems**

Computerized systems were not used in ganciclovir sodium API production.

## **2.5 DOCUMENTATION AND RECORDS**

### **Documentation system and specifications**

Documents related to the manufacture of intermediates and ganciclovir sodium API were prepared, reviewed, approved and distributed according to written procedures. Production, control and distribution records were retained for at least one year after the expiry date of the batch. Specifications were established and documented for raw material, intermediates, ganciclovir sodium API, labelling and packaging materials. Acceptance criteria was established and documented for in-process controls.

### **Equipment cleaning and use record**

Records of equipment use, cleaning, sanitization and maintenance were attached to all equipment.

### **Records of raw materials, intermediates, API labelling and packaging materials**

Records of raw material, intermediates, ganciclovir sodium API, labelling and packaging materials were maintained.

### **Master production instructions**

Master production instructions for ganciclovir sodium API were available and were prepared, dated and signed by one person and independently checked, dated and signed by a person from the quality unit.

### **Batch production records**

Batch production records were prepared for ganciclovir sodium API and included complete information relating to the production and control of each batch. Batch production records were numbered with a unique batch number, dated and signed when issued. Written procedures were established and followed for investigating critical deviations or the failure of a batch of intermediate or ganciclovir sodium API to meet specifications.

### **Laboratory control records**

Laboratory control records included data derived from tests conducted to ensure compliance with established specifications and standards. Records were maintained for out-of-specification (OOS) investigations.

### **Batch production record review**

Written procedures were established and followed for the review and approval of batch production and laboratory control records, including packaging and labeling. Deviation, investigation and OOS reports were reviewed as part of the batch record review before the batch was released.

### **Assessment of the Site Master 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 utilities. In general it complied with the guidelines on preparation of the SMF.

## **2.6 MATERIALS MANAGEMENT**

### **General controls**

Written procedures were available describing the receipt, identification, quarantine, storage, handling, sampling, testing and approval or rejection of materials. The system was in place for evaluating the suppliers of critical materials.

### **Receipt and quarantine**

Upon receipt each container of materials were examined visually for correct labeling damage to containers, broken seals and evidence of tampering or contamination. Materials were held under quarantine until they were sampled, tested and released for use.

### **Sampling and testing of incoming production materials**

Containers from which samples were withdrawn were marked to indicate that a sample has been taken. The decision on the number of containers to sample and the sample size was based upon a sampling plan. Sampling was carried out in the warehouse in the sampling room.

### **Storage**

Materials were stored under appropriate conditions to prevent degradation, contamination and cross-contamination. Materials stored in fiber drums, bags or boxes were stored off the floor. Rejected materials were identified.

## **2.7 PRODUCTION AND IN-PROCESS CONTROLS**

### **Production operations**

Production operations were not carried out during the inspection.

### **In-process sampling and controls**

In-process controls were not carried out during the inspection.

### **Blending batches of intermediates or APIs**

In accordance with the company policy the blending of batches of ganciclovir sodium API was not carried out.

## **2.8 PACKAGING AND IDENTIFICATION LABELLING OF APIs AND INTERMEDIATES**

Written procedures describing the receipt, identification, quarantine, sampling, examination, testing and release and handling of packaging and labelling materials were available. Records were maintained for each shipment of labels and packaging materials.

### **Packaging materials**

Packaging materials provided adequate protection against deterioration or contamination of the ganciclovir sodium API.

### **Label issuance and control**

Access to the label storage areas was limited to authorized personnel.

### **Packaging and labelling operations**

Packaging and labeling operations were not carried out during the inspection.

## **2.9 STORAGE AND DISTRIBUTION**

### **Warehousing procedures**

Facilities were available for the storage of all materials under appropriate conditions.

### **Distribution procedures**

Ganciclovir sodium API was released for production of ganciclovir sodium lyophilised powder for injection after it had been released by the QC.

## **2.10 LABORATORY CONTROLS**

QC had adequate laboratory facilities. Documented procedures describing sampling, testing, approval or rejection of materials and recording and storage of laboratory data were available. Specifications were established for ganciclovir sodium API.

OOS results obtained were investigated and documented according to a procedure.

Reagents and standard solutions were prepared and labeled following written procedures.

Official reference standards were used as well as working reference standards prepared by the manufacturer. Working standards were certified by the application of appropriate tests to ensure standardization. Reference standards were properly labeled and stored. Working standards were dispensed in amber vials for individual use. Temperature in the reference standards storage fridge was monitored continuously.

### **Testing of intermediates and APIs**

Laboratory tests were performed for all intermediates. Impurity profiles describing the identified and unidentified impurities were established for ganciclovir sodium API.

### **Certificates of analysis**

Certificates of analysis (CoA) were issued for each batch of ganciclovir sodium API. The expiry date was provided on the label and certificate of analysis. Certificates were dated and signed by authorized personnel from the QC and QA.

### **Stability monitoring of APIs**

A written programme for ongoing stability determination was developed and implemented. Stability and on-going stability samples were stored properly. Temperature in the incubators was continuously monitored. Incubators were equipped with an alarm system; alarms were registered in a log book.

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### **Expiry and retest dating**

Supporting stability information was available for expiry date assigned.

### **Reserve/retention samples**

Appropriately identified reserve samples of each batch of ganciclovir sodium API was retained for one year beyond the expiry date of the corresponding finished product. The ganciclovir sodium reserve sample was stored in the same packaging system in which the ganciclovir sodium API was stored. Retention samples were stored under appropriate conditions.

## **2.11 VALIDATION**

### **Validation policy**

The company's overall validation policy was documented in VMP.

### **Validation documentation**

A written validation protocol specifying critical processes steps and acceptance criteria was established.

### **Qualification**

Appropriate qualification of critical equipment and ancillary systems were carried out.

### **Process validation programme**

Critical process parameters were controlled and monitored during process validation studies.

### **Cleaning validation**

Cleaning validation was carried out for both molecules manufactured and sets of equipments. Equipment which had product contact surfaces was dedicated for the specific molecule being manufactured. The only common, non-product-contact-surface equipment was the drying oven, which also was covered by cleaning validation.

### **Validation of analytical methods**

Analytical methods including pharmacopoeia methods were validated.

## **2.12 CHANGE CONTROL**

A formal change control system was established.

## **2.13 REJECTION AND RE-USE OF MATERIALS**

### **Rejection**

Intermediates and APIs failing to meet established specifications were rejected.

### **Reprocessing**

According to the company policy reprocessing was not carried out.

### **Reworking**

According to the company policy reworking was not carried out.



**Recovery of materials and solvents**

According to the company policy recovery of materials and solvents was not carried out.

**Returns**

N/A. Till the date of inspection ganciclovir sodium API was manufactured only for use within POLY for development batches used for studying stability and validation purposes.

**2.14 COMPLAINTS AND RECALLS**

Quality-related complaints were recorded and investigated according to a written procedure. Records of complaints were retained. The written procedure to recall products from the market was reviewed. The authorized person responsible for the execution and coordination of recalls was designated.

**2.15 CONTRACT MANUFACTURERS (INCLUDING LABORATORIES)**

N/A. No contract manufacturers or laboratories were used.

**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 manufacture of ganciclovir sodium API at Hainan Poly Pharma Co. Ltd (Building No 4) located at Guilinyang Economic Development Area Haikou City, Hainan Province, China was considered to be operating at an acceptable level of 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.