



WHO PUBLIC INSPECTION REPORT

(WHOPIR)

Finished Product Manufacturer

Part 1: General information

Name of Manufacturer	Hainan Poly Pharma Co. Ltd
Production Block	Building 2
Physical address	Guilinyang Economic Development Area Haikou City, Hainan Province. China
Contact person and email address.	Mrs. Minhua Fan Chief Executive Officer fmh@hnpoly.com
Date of inspection	14 to 16 May 2012
Type of inspection	Follow up inspection
Dosage forms(s) included in the inspection	Powder for injection
WHO product categories covered by the inspection	HIV/AIDS (HA) Ganciclovir Sodium 500mg
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, injection, and lyophilized powder for injection, 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, 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 188 full time employees, 50 of which worked in Quality.

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 of Ganciclovir Sodium 500mg lyophilised powder for injection. The inspection covered all the sections of the WHO GMP text, including premises, equipment, documentation, materials, validation, sanitation and hygiene, production, quality control, utilities, manufacture of sterile products, terminal sterilization of garments and utensils, aseptic processing and sterilization by filtration, freeze drying and finishing of sterile products

Inspected Areas

Briefly list inspected areas.

- Quality Assurance
- Sanitization and hygiene
- Qualification and validation
- Complaints
- Recalls
- Self-inspection
- Personnel
- Training



- Personal hygiene
- Premises
- Equipment
- Materials
- Documentation
- Production
- Quality control

2.1 QUALITY ASSURANCE

A system for quality assurance in general was established:

- pharmaceutical products were designed and developed in a way that takes account of the requirements of GMP
- production and control operations were clearly specified in a written form
- arrangements were made for the manufacture, supply and use of the correct starting and packaging materials
- all necessary controls on materials, calibrations, and validations were carried out
- there was a procedure for self-inspection that regularly appraises the effectiveness and applicability of the QA system
- there was a system for Quality Risk Management (QRM)
- quality reviews were conducted

2.2 GOOD MANUFACTURING PRACTICES (GMPs) FOR PHARMACEUTICAL PRODUCTS

Good manufacturing practices generally were implemented. The necessary resources were provided. Manufacturing processes were clearly defined and systematically reviewed. Qualification and validation were 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. The company had a standard operating procedure as the basis for its approach to personal hygiene and sanitation in its production facility.

Clean areas were cleaned frequently in accordance with an approved written programme. More than one type of disinfectants was employed. Monitoring was regularly undertaken. Interactions between different cleaning materials were validated. Disinfectants used in Grade A and B areas were sterile before use.

2.4 QUALIFICATION AND VALIDATION



The company identified what qualification and validation work was required. The key elements of a qualification and validation programme were defined and in a validation master plan (VMP). Documentary evidence was available that the premises, supporting utilities, equipment and processes have been designed, installed, operated in accordance with their design specifications.

2.5 COMPLAINTS

Complaints and other information concerning potentially defective products were reviewed according to written procedures and the corrective actions were taken. A person responsible for handling the complaints and deciding the measures to be taken was designated. Complaints concerning a product defect were recorded and investigated. Consideration was given to whether other batches should be checked in order to determine whether they were also affected.

2.6 PRODUCT RECALLS

The written procedure to recall products from the market was reviewed. The authorized person responsible for the execution and coordination of recalls was designated.

2.7 CONTRACT PRODUCTION AND ANALYSIS

Production or quality control operations were not contracted out.

2.8 SELF INSPECTION AND QUALITY AUDIT

Self-inspections were performed routinely. Self inspection covered basic GMP topics. The frequency at which self-inspections were conducted was stated in the procedure. A report was made at the completion of a self-inspection.

The system was in place for approving suppliers. Before suppliers were approved and included in the approved supplier's list they were evaluated. Critical materials suppliers' audits were carried out.

2.9 PERSONNEL



The manufacturer had an adequate number of personnel with the necessary qualifications and practical experience. Responsible staffs, specific duties were recorded in written job descriptions. Personnel were aware of the principles of GMP and received initial and continuing training, including hygiene instructions, relevant to their needs. Steps were taken to prevent unauthorized people from entering production, storage and QC areas. An organization chart was available - and was appropriate.

2.10 TRAINING

Training was provided in accordance with a written programme for all personnel whose duties take them into manufacturing areas or into control laboratories. Newly recruited personnel received training appropriate to the duties assigned to them. Continuing training was given, and its practical effectiveness periodically was assessed. Approved training programme were available. Training records were kept. A procedure for Analyst qualification and periodic proficiency verification was in place.

2.11 PERSONAL HYGIENE

All personnel employed received initial and regular training in disciplines relevant to the correct manufacture of sterile products. Personnel involved in the manufacture of sterile preparations were instructed to report any conditions that may cause the shedding of abnormal numbers or types of contaminants. Periodic health checks were carried out. Changing and washing followed a written procedure. 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. The protective closing washing and sterilization operations followed standard operating procedures. Sterile garment washing operations were validated.

2.12 PREMISES

Exposed surfaces were smooth, impervious and unbroken to minimize the shedding or accumulation of particles or microorganisms and permitted the repeated application of cleaning agents and disinfectants, where used. Changing rooms were designed as airlocks and used to provide physical separation of the different stages of changing. Changing rooms were flushed with filtered air. The final stage of the changing room was in the at-rest state, the same grade as the area into which it leads. Changing rooms were equipped with mirrors. Airlock doors did not opened simultaneously.

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. There was separate sampling area for starting materials and rubber stoppers. Ganciclovir Sodium API samples were taken in the API production clean area.

Weighing areas

The weighing of Ganciclovir API was carried out in separate weighing room next to compounding room.

Quality control areas

QC laboratories were separated from production areas. Sufficient space was given to avoid mix ups and cross-contamination. Adequate storage space was provided for samples, reference standards, solvents, reagents and records. Separate air-handling units were provided for microbiological laboratories.

2.13 EQUIPMENT

Fixed pipework was clearly labelled to indicate the contents and the direction of flow. Balances and other measuring equipment of an appropriate range and precision were available for production and control operations and were calibrated on a scheduled basis. Production equipment was cleaned on a scheduled basis. Laboratory equipment and instruments suited to the testing procedures undertaken.

All equipment such as sterilizers, air-handling and filtration systems, air vent and gas filters, water treatment, generation, storage and distribution systems were subject to planned maintenance.

2.14 MATERIALS

Incoming materials and finished products were quarantined after receipt until they were released for use or distribution. Materials and products were stored under the appropriate conditions

Starting materials



Starting materials were purchased from approved suppliers. For each consignment, the containers were checked for integrity of package and seal. Damage to containers and any other problem that might adversely affect the quality of a material recorded and reported to the QC department. If one delivery of material was made up of different batches, each batch was considered as separate for sampling, testing and release. Starting materials in the storage area were appropriately labelled.

There were appropriate procedures in place to ensure the identity of the contents of each container of API. Bulk containers from which samples were drawn were identified.

Packaging materials

Packaging materials were purchased from approved suppliers. Printed packaging materials were stored in secure conditions. Each delivery of batch of printed or primary packaging material was given a specific reference number or identification mark.

Finished products

Finished products were held in quarantine until their final release, and stored under conditions established by the manufacturer.

Rejected, recovered, reprocessed and reworked materials

Rejected materials and products were marked as such and stored separately. Finished product was not reprocessed or reworked.

Recalled products

Recalled products were stored separately in a secure area.

Returned goods

Returned goods were stored separately in a secure area.

Reagents and culture media

Records for the receipt and preparation of reagents and culture media were available. Reagents made up in the laboratory were prepared according to written procedures and appropriately labelled. Positive and negative controls were applied to verify the suitability of culture media each time they were prepared and used.

Reference standards



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 use. The temperature in the reference standards storage fridge was monitored continuously.

2.15 DOCUMENTATION

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. Records were made or completed when any action was taken.

Labels

Labels applied to containers, equipment and premises were clear and unambiguous.

Specifications and testing procedures

Testing procedures were validated and were appropriately authorized and dated. Approved, signed and dated testing procedures and specifications were available for starting and packaging materials and for finished products as well as for intermediate and bulk products.

Master formulae

Authorized master formula was available.

Packaging instructions

Authorized packaging instructions existed.

Batch processing records

Batch manufacturing records (BMRs) were kept for each batch processed. Before any processing begins, checks were made that the equipment and work station were clear of previous products, documents, or materials, and that the equipment was clean and suitable for use. Checks were recorded and were part of the BMR.

Batch packaging records

A batch packaging record (BPR) was kept for each batch processed. Before any packaging operation begins, checks were made that the equipment and work station were



clear of previous products, documents or materials, and that equipment was clean and suitable for use. Checks were recorded and were part of the BPR.

Standard operating procedures and records

SOPs and associated records of actions taken were available.

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 utilizes, such as the water systems. In general it complied with the guidelines on preparation of the SMF.

2.16 GOOD PRACTICES IN PRODUCTION

There was no manufacture of ganciclovir sodium lyophilised powder for injection scheduled during the visit by the WHO team, because it was not yet commercialized. However, POLY organized for a simulation of the entire aseptic manufacturing steps from dispensing, filling, lyophiliser loading, to crimping, torque testing and transfer to inspection to simulate the API powder.

Deviations from instructions or procedures were done in accordance with an approved procedure. The authorization of the deviation was approved in writing. Checks on yields and reconciliation of quantities were carried out. During processing, all materials, bulk containers, major items of equipment and rooms were labelled.

Manufacture of Sterile preparations

Clean areas for the manufacture of sterile products were classified according to the required characteristics of the environment. Clean rooms and clean-air devices were routinely monitored while in operation. For Grade A and B zones, particle monitoring was undertaken for the full duration of critical processing, including equipment assembly. To control the microbiological cleanliness of Grades A–D in operation the clean areas were monitored. Appropriate alert and action limits were set for the results of particulate and microbiological monitoring.

Aseptic preparation

Components after washing were handled in a Grade D or better environment. The preparation of solutions which were to be sterile-filtered during the process was carried out in a Grade C or better environment, such as Grade A with C background. The



handling and filling of aseptically prepared products, was carried out in a Grade A environment.

Aseptic processing and sterilization by filtration

Ganciclovir sodium solution was filtered through a sterile filter of 0.22 micron into a previously sterilized container. A second filtration through a further sterilized microorganism-retaining filter prior to filling was carried out. The final sterile filtration was carried out close to the filling point. The integrity of the sterilized filter was verified before use and immediately after use.

Finishing of sterile products

Containers were closed by validated methods. Crimping of the caps was performed after lyophilisation. Containers were subject to 100% integrity testing. Filled containers were inspected individually. Inspection was carried out visually in a qualified and adequately maintained light inspection station, to ensure proper illumination and background of matt black and white panels. Operators doing the inspection were qualified by periodic practical testing against a “blind” test panel of vials containing acceptable and unacceptable samples, passed regular eyesight checks and were allowed frequent breaks from inspection.

Packaging operations

Before packaging operations begun, steps were taken to ensure that the work area, packaging line, printing machine and other equipment were clean and free from any products, materials or documents used previously. The line clearance was performed and recorded in BPR. Production records were reviewed as part of the approval process of batch release before transfer to the authorized person.

2.17 GOOD PRACTICES IN QUALITY CONTROL

The QC function was independent of other departments. Adequate resources were available to ensure that all the QC arrangements are effectively and reliably carried out. QC personnel had access to production areas for sampling and investigation as appropriate.

Control of starting materials and intermediate, bulk and finished products

Tests followed the instructions given in the relevant written test procedure. The result was checked by the QC supervisor before the material or product was released. Samples were representative of the batches of material from which they were taken. Out-of-specification results and out of trend results obtained during testing of materials or



products were investigated in accordance with an approved procedure. Records were maintained.

Test requirements

Starting and packaging materials

Before releasing a starting or packaging material for use, the QC manager ensured that the materials have been tested for conformity with specifications. An identity test was conducted on a sample from each container of starting material. Each batch of printed packaging materials was examined following receipt.

In-process control

In-process control records were maintained and formed a part of the batch records.

Finished products

For each batch of medicines product, there was an appropriate laboratory determination of satisfactory conformity to its finished product specification prior to release.

Batch record review

QC records were reviewed as part of the approval process of batch release. Retention samples from each batch of finished product as well as related documents were kept for one year after the expiry date. Finished products were kept in their final packaging and stored under the recommended conditions. Samples of active starting materials were retained one year beyond the expiry date of the corresponding finished product. Retention samples were stored under appropriate conditions.

Stability studies

The quality and stability of finished pharmaceutical product were evaluated. Expiry dates and shelf-life specifications were established on the basis of stability tests related to storage conditions. 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 alarm system; alarms were registered in log book.

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, of Hainan Poly



Pharma Co. Ltd (Building No 2) 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.

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 2 years, provided that the outcome of any inspection conducted during this period is positive.