

**Prequalification Team Inspection services
WHO PUBLIC INSPECTION REPORT
(WHOPIR)
Finished Product Manufacturer**

Part 1	General information
Manufacturers details	
Company information	
Name of manufacturer	Hainan Poly Pharma Co. Ltd.
Corporate address of manufacturer	Guilinyang Economic Development Area Haikou City, Hainan Province. People's Republic of China
Inspected site	
Address of inspected manufacturing site if different from that given above	Guilinyang Economic Development Area Haikou City, Hainan Province. People's Republic of China
Unit / block / workshop number	Building No 2 (FPPs)
Manufacturing license number, (delete if not applicable)	Qiong 20150024
Inspection details	
Dates of inspection	16 to 20 April 2018
Type of inspection	Routine inspection
Introduction	
Brief summary of the manufacturing activities	Production and quality control of FPPs and APIs
General information about the company and site	<p>Hainan Poly Pharm. Co., Ltd. (hereinafter referred to as POLY) was founded in 1992 and became a public company listed on the Shenzhen Stock Market in 2017. The site produces API, oral dosage forms, ointments, terminal sterile injections, and lyophilized powders for injection. A new manufacturing site named Zhejiang Poly Pharm located in Hangzhou City, Zhejiang Province was under construction at the time of inspection.</p> <p>No hormones, steroids, cephalosporin's, beta-lactams or cytotoxins were produced and no high potency /or hazardous materials were manufactured or handled at the Hainan Poly site subject to this inspection.</p>

	At the time of the inspection, the site employed approximately 276 full time employees, 83 of whom worked in the Quality Unit.
History	<p>The site had previously been inspected by the WHO inspection team in 2011, 2012 and 2014 for FFPs; and in 2011 and 2014 for APIs.</p> <p>The site had been inspected by the following authorities with positive outcomes:</p> <ul style="list-style-type: none"> • Hainan provincial Food and Drug Administration in 2013 for injections • Dutch inspectorate in March 2016 • US Food and Drug Administration in January 2016
Brief report of inspection activities undertaken	
Scope and limitations	
Areas inspected	<ul style="list-style-type: none"> • Document review • Production block for powder for injection -Building No 2 • QC including chemical and microbiological laboratories • Warehouse • Water system
Restrictions	NA
Out of scope	Products not submitted to WHO for Prequalification
WHO product covered by the inspection	Sterile powder for injection

Abbreviations	AHU	air handling unit
	ALCOA	attributable, legible, contemporaneous, original and accurate
	API	active pharmaceutical ingredient
	APQR	annual product quality review
	BDL	below detection limit
	BMR	batch manufacturing record
	BPR	batch packaging record
	CAPA	corrective actions and preventive actions
	CC	change control
	CFU	colony-forming unit
	CoA	certificate of analysis
	CpK	process capability index
	DQ	design qualification
	EM	environmental monitoring
	FAT	factory acceptance test
	FBD	fluid bed dryer
	FMEA	failure modes and effects analysis
	FPF	finished pharmaceutical product
	FTA	fault tree analysis
	FTIR	Fourier transform infrared spectrometer

GC	gas chromatograph
GMP	good manufacturing practice
HACCP	hazard analysis and critical control points
HPLC	high-performance liquid chromatograph
HVAC	heating, ventilation and air conditioning
IR	infrared spectrophotometer
IQ	installation qualification
KF	Karl Fisher
LAF	laminar air flow
LIMS	laboratory information management system
LoD	limit of detection
LOD	loss on drying
MB	microbiology
MBL	microbiology laboratory
MF	master formulae
MR	management review
NMR	nuclear magnetic resonance spectroscopy
NRA	national regulatory agency
OQ	operational qualification
PHA	process hazard analysis
PM	preventive maintenance
PpK	process performance index
PQ	performance qualification
PQR	product quality review
PQS	pharmaceutical quality system
QA	quality assurance
QC	quality control
QCL	quality control laboratory
QRM	quality risk management
RA	risk assessment
RCA	root cause analysis
SOP	standard operating procedure
TAMC	total aerobic microbial count
TFC	total fungi count
TLC	thin layer chromatography
URS	user requirements specifications
UV	ultraviolet-visible spectrophotometer

Part 2**Brief summary of the findings and comments****1. Pharmaceutical quality system**

A formal documented system of quality assurance was established, with procedures covering all expected key quality elements being in place. Operations were specified in written form and GMP requirements were essentially being met. The procedures that were reviewed and discussed during the inspection were generally of a satisfactory standard. Product and processes were monitored and these results considered during batch release; regular monitoring and reviews of the quality of pharmaceutical products were being conducted according to documented schedules and procedures.

Quality Risk Management (QRM)

Quality risk management procedure was in place. Quality risk assessment for the the product submitted to WHO PQ was reviewed and discussed. The risk identification and sterilization of vent filters in the steam sterilizer was reviewed and discussed. Non-compliances observed during the inspection that were listed in the full report regarding risk management were addressed by the manufacturer to a satisfactory level.

Product Quality Review (PQR)

Procedures for Product Quality Review were reviewed. No PQR was available for the WHO grade product. There had been no commercial batch manufactured except the initial validation batch.

In the absence of any manufacture of WHO prequalified product the 2017 PQR report for other grade of powder for injection were reviewed. Non-compliances observed during the inspection that was listed in the full report regarding PQR were addressed by the manufacturer to a satisfactory level.

Management review

Management review followed an SOP. A management review meeting was observed to be held monthly. Meeting minutes were in place.

Change control and deviation

Change control was managed according to a SOP. CC was classified into three categories of critical, major and minor.

Deviations were managed according to an SOP. The deviation SOP included procedures for both planned (temporary changes) and unplanned deviations.

Logbooks for CCs and deviations were available for review. A change control regarding aluminum-plastic overseals used in the finished product was reviewed and discussed.

Product release

Review and release procedure of finished products and a batch release was reviewed and was found acceptable.

2. Good manufacturing practices for pharmaceutical products

Good manufacturing practices were generally implemented and followed. Manufacturing processes were defined and documented and were being performed in the facilities generally acceptable.

Necessary human and physical resources were provided, including qualified and trained personnel, adequate facility and equipment, approved procedures and instructions, laboratories and equipment for in-process and other controls.

Qualification and validation activities were performed. Manufacturing processes and batch manufacturing records were reviewed and discussed.

3. Sanitation and hygiene

Premises and equipment were maintained at a good level of cleanliness. The company had a standard operating procedure in place as the basis for its approach to personal hygiene and sanitation in its production facilities, with appropriate hand washing required and change facilities seen to be in place in the areas visited. Clean areas were cleaned frequently in accordance with an approved written programme. There was a schedule for rotating disinfectants used in clean areas.

4. Qualification and validation

Validation and qualification for injections were performed according to the in-house procedures. The batch size of the WHO product was defined and made with a single batch lyophilization process. The following documents were reviewed and were found to be generally acceptable.

- Guide to aseptic processing simulation test SOP
- PQ report of pulse vacuum steam sterilizer
- Qualification for tunnel with specified vials.
- Cleaning validation management SOP
- Non-viable particle monitoring in injection plant
- Autoclave qualification and most recent requalification
- Steam quality validation and monitoring
- Media fill SOPS and history including a detailed review of the report of the most recent study performed
- Injection visual inspection

Non-compliances observed during the inspection that was listed in the full report regarding qualification and environment monitoring of aseptic filling operations were addressed by the manufacturer to a satisfactory level.

5. Complaints

Complaint was managed according to an SOP. Log books for 2016 and 2017 were available and reviewed. A complaint regarding product packaging, as well as associated CAPAs were reviewed and was acceptable.

6. Product recalls

Product recall was managed by an SOP. There had been no product recall of any product from market since last inspection. Mock recall was performed once every two years.

7. Contract production, analysis and other activities

According to the company, there was no use of external scientific, analytical or other technical assistance in relation to the products in the inspection scope.

The company performed CMO for a foreign company. The quality agreement was reviewed and discussed.

8. Self-inspection, quality audits and suppliers' audits and approval

Self-inspections (internal audits) were performed routinely according to standard procedures and covered basic GMP topics. Internal audits of each main operational area were required to be performed on a rolling programme. The company performs audits on different systems approximately every three months with a rolling programme that covers all key areas on an annual basis.

9. Personnel

The personnel met during the inspection appeared to have a good awareness of the principles of GMP and showed that they received initial and continuing training, including hygiene instructions, relevant to their responsibilities in the production process.

Steps were taken to prevent unauthorized people from entering production and QC areas and appeared to be effective. An organization chart was available and considered acceptable. Responsibilities for production and QC/QA were well separated.

10. Training

Training was provided for all personnel whose duties take them into manufacturing areas or into control laboratories. General GMP training was not reviewed in detail in this inspection other than the review of the steps and records of monitoring and authorization of those staff working in the aseptic areas.

11. Personal hygiene

Personnel were required to undergo periodic health examination. Eye examination was required for operators who perform the visual inspection of injection products.

Changing and washing before entry to production areas followed written procedures. Direct contact was avoided between the operator's hands and starting materials, primary packaging materials and intermediate or bulk product. The protective clothing washing and sterilization operations followed standard operating procedures. Extensive hand washing was required of visitors as they entered the various areas.

12. Premises

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

The lyophilized injection production line used for the WHO product was located in building No.2 and was not dedicated. There were seven products produced on this line which included both lyophilized powder injection and small volume liquid injection products.

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.

Storage areas were of sufficient capacity. Receiving and dispatch bays were separated and protected materials and products from the weather.

QC laboratories were separated from production areas. Adequate storage space was provided for samples, reference standards, solvents, reagents and records.

13. Equipment

The equipment inspected was generally appropriately installed and of an acceptable standard. The filling line was designed using grade A in the grade B background environment. The manufacturing/compounding vessel and filter system were partially equipped with automated CIP and SIP systems.

The equipment was in operation at the time of inspection. The line appeared to be running smoothly without excessive intervention.

Equipment cleaning and maintenance procedures were in place. Cleaning procedure of a sterilization tunnel was reviewed and was acceptable.

Purified water (PW) system used for FPP manufacturing was inspected. Non-compliance observed during the inspection that was listed in the full report regarding PW system was addressed by the manufacturer to a satisfactory level.

Computerized systems were used in the QC lab to network analytical instruments HPLCs and GCs. Control over these systems was reviewed. Non-compliances observed during the inspection that was listed in the full report regarding QC laboratory management were addressed by the manufacturer to a satisfactory level.

14. Materials

Non-sterile API was made in house on the same site. Packaging materials vial and rubber stopper used for the finished product were purchased from approved suppliers.

Finished products were held in quarantine until their final release and stored under appropriate and monitored conditions.

15. Documentation

In general, documentation was managed according to an SOP on filing and storage of documentation. SOPs and log books were kept and allow for traceability.

BMRs were retained for each batch processed. Batches were numbered according to a written procedure of product batch number. The master BMR and a BMR of a selected batch of the WHO product were reviewed and discussed.

16. Good practices in production

The WHO product and several other powders for injection and small volume injection products were manufactured on the same line in the building No2. The production of the lyophilized powder for injection for another market was in operation at the time of inspection. The filling machine was not dedicated except the rubber tubes were product-dedicated.

Manufacture of Sterile preparations

For Grade A and B zones, particle monitoring was undertaken for the full duration of processing, including equipment set up and assembly. The microbiological cleanliness of Grades A–D in operation in the clean areas was monitored. Media fill simulations were performed every six months. SOPs for media simulations were reviewed and found generally acceptable. The company has had no media fill positives since commencing commercial production.

Some changes regarding the production of the WHO product had been made since the last inspection including,

- Cap sterilization had been changed from contract out by radiation to steam sterilization in house. The method was Radiation for sterilization. The in-house method had been changed to by using steam sterilization. A dossier variation has yet to be submitted to WHO but a commitment was made to update the dossier.
- A machine used for vial outer surface washing had been introduced. This was introduced in response to some complaints of exterior powder on vials from other market.

The relevant documents and risk assessment were reviewed and discussed.

17. Good practices in quality control

The general and microbiology QC laboratories were inspected. The premises were generally of an acceptable standard and well equipped.

HPLCs and GCs were networked with software. A LIMS system is under validation. Data integrity and access control of IRs were checked. They were not networked but the data was backed up by transfer and saved in the lab Server.

The OOS procedures for chemical and microbial testing were separated and reviewed. There were several confirmed OOS in 2017. They were not related to Ganciclovir injection. The QC lab errors were registered in a separated log book.

Stability study management regarding sample receipt, register and testing were in place and spot checked. They were considered acceptable.

There is a dedicated area for microbiology in the QC lab. This was generally well constructed and the areas for TVC monitoring and sterility testing of an adequate design and well maintained. The general area where media was prepared, and endotoxin testing was somewhat cramped, and the company stated it had plans for a new laboratory area where this issue would be addressed.

The media used in the aseptic areas for environmental monitoring were purchased as sterile ready to use.

PART 3

Conclusion

Based on the areas inspected, the people met and the documents reviewed, and considering the findings of the inspection, including the deficiencies listed in the Inspection Report, as well as corrective actions taken and planned: ***Hainan Poly Pharma Co. Ltd. located at Guilinyang Economic Development Area Haikou City, Hainan Province. People's Republic of China***, was considered to be operating at an acceptable level of compliance with WHO good manufacturing practices for pharmaceutical products.

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.

PART 4

List of GMP guidelines referenced in the inspection

1. WHO good manufacturing practices for pharmaceutical products: main principles. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-eighth Report Geneva, World Health Organization, 2014 (WHO Technical Report Series, No. 986), Annex 2.
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_986/en/
2. WHO good manufacturing practices for active pharmaceutical ingredients. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth Report. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957), Annex 2.
<http://www.who.int/medicines/publications/44threport/en/>
3. WHO Good Manufacturing Practices: water for pharmaceutical use. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fourth-sixth Report. Geneva, World Health Organization, 2012 (WHO Technical Report Series, No. 970), Annex 2
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_970/en/

4. WHO guidelines for sampling of pharmaceutical products and related materials. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-ninth Report. Geneva, World Health Organization, 2005 (WHO Technical Report Series, No. 929), Annex 4
http://whqlibdoc.who.int/trs/WHO_TRS_929_eng.pdf?ua=1
5. WHO guidelines on good manufacturing practices for heating, ventilation and air-conditioning systems for non-sterile pharmaceutical dosage forms. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 5
http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1
6. Supplementary guidelines on good manufacturing practices: validation. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fortieth Report. Geneva, World Health Organization, 2006 (WHO Technical Report Series, No. 937), Annex 4
http://whqlibdoc.who.int/trs/WHO_TRS_937_eng.pdf?ua=1
7. WHO Good Practices for Pharmaceutical Quality Control Laboratories. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth Report. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957, Annex 1
<http://www.who.int/medicines/publications/44threport/en/>
8. WHO Good Practices for Pharmaceutical Products Containing Hazardous Substances. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth Report. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957), Annex 2
<http://www.who.int/medicines/publications/44threport/en/>
9. WHO good manufacturing practices for sterile pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 6
http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1
10. WHO guidelines on transfer of technology in pharmaceutical manufacturing WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 7
http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1
11. Model guidance for the storage and transport of time-and temperature-sensitive pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 9
http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1
12. General guidelines for the establishment maintenance and distribution of chemical reference substances. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-first Report Geneva, World Health Organization 2007 (WHO Technical Report Series, No.943) Annex 3
http://whqlibdoc.who.int/trs/WHO_TRS_943_eng.pdf?ua=1

13. WHO good practices for pharmaceutical microbiology laboratories. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 2
http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1
14. WHO guidelines on quality risk management. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-seventh Report Geneva, World Health Organization, 2013 (WHO Technical Report Series, No. 981), Annex 2
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_981/en/
15. WHO guidelines on variation to a prequalified product. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-seventh Report Geneva, World Health Organization, 2013 (WHO Technical Report Series, No. 981), Annex 3
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_981/en/
16. WHO guidelines for drafting a site master file. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 14
http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1
17. WHO Guidelines on good manufacturing practices: validation, Appendix 7: non-sterile process validation. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-ninth Report Geneva, World Health Organization, 2015 (WHO Technical Report Series, No. 992), Annex 3
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf
18. WHO General guidance on hold-time studies WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-ninth Report Geneva, World Health Organization, 2015 (WHO Technical Report Series, No. 992), Annex 4
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf
19. WHO Technical supplements to Model Guidance for storage and transport of time – and temperature – sensitive pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-ninth Report Geneva, World Health Organization, 2015 (WHO Technical Report Series, No. 992), Annex 5
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf
20. WHO Recommendations for quality requirements when plant – derived artemisin is used as a starting material in the prosecution of antimalarial active pharmaceutical ingredients. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-ninth Report Geneva, World Health Organization, 2015 (WHO Technical Report Series, No. 992), Annex 6
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf

21. WHO good manufacturing practices for biological products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fiftieth Report Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 3
http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex03.pdf
22. Guidance on good data and record management practices. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fiftieth Report Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 5
http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex05.pdf
23. WHO general guidance on variations to multisource pharmaceutical products. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fiftieth Report* Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 10
http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex10.pdf
24. WHO good manufacturing practices for biological products. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fiftieth Report* Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 3
http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex03.pdf