



WHO PUBLIC INSPECTION REPORT

(WHOPIR)

Finished Product Manufacturer

Part 1: General information

Name of Manufacturer	Guilin Pharmaceutical Co., Ltd
Unit number	Oral solid Dosage forms site
Production Block	⇒ Workshop 1. ⇒ Workshop 2.
Physical address	Guilin Pharmaceutical Co. Ltd, No. 17, Shanghai Road, Guilin, Guangxi, P.R of China
Contact person and email address.	Mr. Jimmy He Mobile: Tel: +86-773-3555935 Fax: +86-773-3832783 E-mail: Hem@guilinpharma.com
Date of inspection	25 and 26 February 2010
Type of inspection	Routine Inspection
Dosage forms(s) included in the inspection	Coated and uncoated single layer, bilayer and trilayer Tablets
WHO product categories covered by the inspection	FPPs used in the management of Malaria (MA)
Summary of the activities performed by the manufacturer	Manufacturing, packaging, quality control and batch release of coated and tablets.



Part 2: Summary

General information about the company and site

The facility inspected was the **Tablet Workshops 1 and 2 of Guilin Pharmaceutical Co. Ltd, No. 17, Shanghai Road, Guilin, Guangxi, P.R of China**, hereafter referred to as **Guilin OSD**. According to the Site Master File, Doc No.:SMP-QA-006001-04 effective 08.01.2010 and the company presentation, **Guilin Pharmaceuticals Co. Ltd** was largely owned by Shanghai Fosun Pharmaceutical (Group) Co. Ltd, as the major shareholder. **Guilin Pharmaceuticals Co. Ltd's** headquarters was at this site **No. 17 Shanghai Road, Guilin, Guangxi, China**, which also hosted the API manufacturing facilities. The other production site was **No. 43 Qilidian Road, Guilin (Guilin INJ)** which produced powders for injection, SVP, LVP and lyophilised injections. Both sites produced cephalosporin, penicillin and non-penicillin based materials and/or products. Both sites were operated under one management and were approved by Chinese SFDA under one licence No. Gui HabZb20060060, expiring 31 December 2010.

The factory site of **Guilin OSD consisted of the following workshops and warehouses:**

- Workshop 1: Tablets (Simple, bilayer, trilayer or co-blistered tablets).
- Workshop 2: Tablets (granules and tablets).
- Warehouse dedicated for Artesunate.
- Workshop 3: Tablets (non-penicillin for domestic market).
- Workshop 4. Tablets (Non-β-lactam dedicated)
- Workshop for hard gelatine capsules (HGC) and soft gelatine capsules
- Workshop for Penicillins
- Warehouse for Penicillin APIs
- Warehouse for Penicillin FPPs
- API Workshops (7)

According to the SMF, the company employed a total of 993 people at both No. 17 Shanghai Road and No. 43 Qilidian Road distributed as follows:

- | | |
|---------------------------|-----|
| • Quality assurance | 28 |
| • Engineering Technicians | 181 |
| • Quality control | 53 |
| • Production | 630 |
| • Warehouse | 29 |
| • Sales department | 70 |

History of WHO and/or regulatory agency inspections

This was the eighth inspection of this site by WHO Prequalification team. The previous inspections were in December 2002 (compliant), November 2005 (compliant), August 2006 (compliant), April 2007 (compliant), March 2008 (compliant) and September 2008 (compliant). The manufacturing facility was inspected and licensed by the Chinese SFDA.

Focus of the inspection

The inspection generally focused on the activities related to the production and control of coated and uncoated tablets with particular focus on Workshop 1 dedicated to antimalarial simple WHO Public Inspection report (WHOPIR):

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tablets, FDC tablets and co-blister packaging and Workshop 2 - also for antimalarial tablets and various other products.

Inspected Areas

Day I

On arrival, the inspectors were directed into the conference room, introduced themselves and exchanged business cards with the key staff of **Guilin Pharmaceutical Co. Ltd.** The inspectors explained the procedure for WHO Prequalification Programme, the procedures and standards used for inspection and timelines for the processing of the inspection report and company responses to the inspection observations. The procedures for closing the inspection including the WHO public inspection report (WHOPIR), Notice of Concern (NOC) and Notice of Suspension (NOS) were explained. The tentative inspection plan was discussed and confirmed. The company made a presentation about the company and the site to be inspected. The presentation highlighted the company's overview, site description, production and QC capacities, quality management and assurance systems, summary of manufacturing processes, major equipment, product range, inspection history and changes and CAPAs since the last WHO inspection.

The major changes since the last inspection included the following:

1. Reconstruction of the PW system (Double RO system)
2. New QC equipment: HPLC and GC.
3. New metal detector.
4. Control of temperature and RH in the warehouse.
5. Constructed buffer room for receiving area of the Artesunate warehouse.
6. Reconstructed the floor for the production line.
7. New trolley desk for transfer of products between blocks.
8. Recruited new staff.

A copy of the presentation was obtained and will be filed in the company file.

Since this site was under the same management as the injection site which had just been inspected, a numbers of quality management systems were similar and hence were not reviewed again. The batch numbering system was the same as the Injectable site:

- SOP on assignment of Batch Numbers and Control numbers, where:
 - Format for batch number for export: CC-YYMMNN where YY = the last two digits of the year of manufacture, MM = two digits representing the month of manufacture, NN = serial number per product starting from 01, ML = added as a prefix to a blended API batch and MR = added only if the batch is reworked or reprocessed.
 - Format for domestic batch: YYMMNN as defined above.
 - Date of manufacture for freeze dried injectables and injectable solution was the date of compounding while it was the date of filling for sterile API powders filled for injection.
 - ⇒ Export: DD/MM/YY, where DD = day and the rest as above
 - ⇒ Domestic: YYYY/MM/DD, where YYYY = year and the rest as above.
 - Expiry date format:
 - ⇒ Export: DD/MM/YY as defined above.
 - ⇒ Domestic: YYYY.MM.DD as defined above.

Inspectors proceeded with document review for the following areas:

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- Annual Product Review reports for 2009 on selected products:
- Change Control SOP, register for 2009 and review of selected examples of changes.
 - For example, addition of supplier of PVC.
- Complaints handling and product recall systems. There had been no recall and there was only one complaint in 2009.
- Packaging

The inspection of the following areas followed:

- Vendor approval and qualification system and audit reports of selected suppliers.
- Receiving, quarantine and sampling of RM and PM
- Warehouses for RM, PM and FG + Temp/RH monitoring.
- Workshop 2: dispensing, pre-blending, milling, sieving, granulation, drying, compression, IPC laboratory, handling and issuance of punches and dies
- Workshop 1: handling punches and dies, compression, blister packing

At the end of the day, the team reviewed progress of the activities of the day, gave feed back, received reactions from the management of the company and agreed on the tentative programme for the next day.

Day 2

The inspectors started by reviewing the following outstanding areas on the previous day's programme:

- Reviewed some changes:
 - Monitoring temperature of supply and return for AHU 1 & 2 for workshop No. 1 and Workshop 2.
 - Change from distiller to double pass RO for production of PW and combining it as a source PW for workshops 1 & 2. Its qualification was reviewed in detail.
 - Change in assay analytical method for one API: from titration to HPLC and addition of test for one residual solvent. Comparative studies done were reviewed.
 - Change from weight variation to uniformity of content for the FPP to comply with USP monograph. There was evidence that this variation was submitted to WHO-PQ.
- Reviewed deviations registers for 2009 and selected examples of deviations:
 - Pin holes observed on some blisters due to incorrect control of temperature for heat sealing AL-PVC sheet.
 - Printing error on small unit box.
- Reviewed complaint investigation:
 - Complaint on deformed blisters of two different products.
- Reviewed batch manufacturing records (BMR) of selected batches.
- Reviewed process validation reports of selected products.
- Reviewed stability monitoring results for selected batches.
- Reviewed CAPAs;
- Reviewed validation of purified water system;
- SOP for microbial limits testing.
- SOP on preparation and sensitivity testing of media used in microbial limits testing.
- SOP for handling reference bacteria.

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Inspectors proceeded to inspect the following areas:

- **Quality control laboratory**
 - Sample receiving and distribution procedures
 - Wet chemistry laboratory,
 - Instrumental laboratory
 - Qualification, calibration, preventive maintenance of IR, Dissolution Tester,
 - Laboratory materials management (Samples, Reagents, Stock Solutions, Reference and Working Standards). SOP and records of preparation of selected working standards were reviewed in detail:
 - Starting materials and finished products specifications, testing and release.
 - Testing of Packaging Materials and Components
 - Microbiological laboratory
 - Validation of Analytical methods
 - Stability testing programme (*Protocols, programme, records and data*)

At the end of the day, the team reviewed progress of the activities of the day and the entire inspection, gave feed back and wrap up for the inspection and received reactions from the management of the company. There was consensus of the all the observations made.

2.1 QUALITY ASSURANCE

The company had established basic elements of a quality management system in the form of an organization chart and job descriptions; written and approved procedures; systems to control and ensure the quality of starting materials, intermediate products and finished goods; procedures for equipment qualification, processes validation, change and deviation control; a self inspection and annual product review.

Weaknesses were noted in the documentation and depth of investigation and evaluation of changes, deviations and incidences. Appropriate corrective actions have been taken.

2.2 GOOD MANUFACTURING PRACTICES (GMPs) FOR PHARMACEUTICAL PRODUCTS

The site had adequate facilities and procedures for the production and quality control of the products in focus. They were generally well executed and/or maintained to ensure products of consistent quality.

Although the level of GMP compliance was acceptable, there were several observations noted that required attention as part of continuous improvement. Appropriate corrective actions have been taken.

2.3 SANITATION AND HYGIENE

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The level of sanitisation and hygiene at the site was generally adequate to keep the production and quality control facilities at a reasonable level of cleanliness. Care had to be taken in cleaning places where pallets were used. The cleaning of equipment and premises was guided by approved procedures and appropriate records were maintained.

There were changing facilities and procedures requiring personnel to change into clean gowns and wash hands before entering production and quality control facilities.

2.4 QUALIFICATION AND VALIDATION

Validation and Qualification activities were guided by policies and schedules outlined in the Validation Master Plan. The conventional approach to qualification was used and included definition of user requirements and specifications (URS), Design Qualification (DQ), Installation Qualification (IQ), Operation Qualification (OQ) and Performance qualification (PQ). Selected protocols and reports were reviewed which showed that the specific equipment had been adequately qualified. The blister packaging equipment was requalified and following modifications, the Purified Water system was adequately qualified.

Cleaning procedures had also been validated and requalification was provided for whenever there was a change in the cleaning procedure.

The VMP provided for prospective process validation using three consecutive production scale batches. However, one range of products was considered not completely validated because of the small batch size used without validation of the minimum effective operating capacity of the equipment and the inadequate number of samples taken throughout the process. Appropriate corrective actions have been taken.

2.5 COMPLAINTS

There was a system to record and investigate market complaints. A complaint received by WHO-PQ related to the poor sealing of blisters of one product was presented to the company for investigation and an acknowledgement letter was received. Review of records of previous complaints indicated that similar complaints had been received but the investigations and corresponding CAPAs were not comprehensive. Complaints handling was identified as one area that required strengthening. A comprehensive investigation report has been received.

2.6 PRODUCT RECALLS

There was a written procedure for handling recalls and it provided for notifying local and foreign authorities, as appropriate, in case of a recall.

There had not been any recall in the past two years but the effectiveness of the procedure had been tested through a mock recall.

2.7 CONTRACT PRODUCTION AND ANALYSIS

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This aspect was not inspected in detail but according to the site master file, the company did not carry out any contract production or analysis and none of their production or analysis activities were contracted out.

2.8 SELF INSPECTION AND QUALITY AUDIT

Self inspection was guided by an SOP which gave guidance on the frequency of the audits and the GMP elements to be covered.

Vendor evaluation and approval procedures provided for use of a questionnaire filled by the supplier, full analysis of the first 3 batches and vendor audits when considered necessary.

2.9 PERSONNEL

There were adequate numbers of skilled personnel to conduct production and most quality control procedures. They were guided by organization charts and job descriptions. The responsibilities of the key personnel e.g. head of production, head of quality control and head of quality assurance were well defined and there were personnel designated to deputise the key personnel in their absence. The responsibility for batch review and release was assigned to head of QA.

2.10 TRAINING

The training program for employees included induction training, cGMP training, on the job training (SOPs Training), training on specific skills, and continuing training. The training programme was coordinated by Human Resource department.

The selected records reviewed, the practices observed and the experience gained from interaction with staff at various levels indicated an acceptable level of basic knowledge with a need for continuous training programmes to be strengthened.

2.11 PERSONAL HYGIENE

Personnel hygiene was part of the basic training received by all personnel during induction and basic GMP training. Personnel entered production areas where they were required to wash their hands and change into clean factory garments. The facilities were generally adequate and the procedures were well enforced. Production staff were required to undergo health checks on recruitment and thereafter regularly every year.

2.12 PREMISES

Storage areas

There was a receiving area which had a shade to ensure that materials were protected from adverse weather conditions. A buffer room had been constructed at the entrance into the warehouse for inspection and dedusting received goods.

Materials in the warehouse were stored in good order on shelves and pallets. There were separate and secure storage areas for rejected materials.

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A sampling room was built in the warehouse dedicated for Artesunate. Material and personnel flow was separate. Appropriate gowning needed to be used when sampling in the room. Sampling tools were kept in the QC laboratory. The room was equipped with dust extraction system and weighing balances.

Production areas

There were change room for staff to clean their hands and change into factory clothing. There were separate personnel and material air-locks. There were separate room for different stages of production and packaging provided with filtered air to class D (class 100,000) level and appropriate pressure differentials. There were separate AHUs for the different workshops and continuous monitoring of temperature of supply and return air had been instituted. Temperature, RH and pressure differentials were monitored frequently and regularly.

The floor in the production area had been changed from terrazzo to modified polyurethane (PU). Production facilities were smooth, free from cracks and open joints and permitted effective cleaning. Generally, facilities were designed to achieve unidirectional flow of production activities, except in Workshop 2 where the material flow was not unidirectional and effective after the coating process. Nevertheless, the design was adequate to minimize the risk of cross – contamination and contamination.

Quality control (QC) areas

QC laboratories were located in the main building and separated from the production areas. There were separate rooms or facilities for wet analytical laboratory, instrumentation, balances, microbiological laboratory, stability chambers and reference sample storage.

Adequate space was provided for storage of samples, laboratory reagents and reference standards, solvents, reagents and records. Although the laboratory was used to analyse β -lactam and non- β -lactam samples, the samples were adequately packed and segregated to avoid cross-contamination.

Water purification system

The purified water system had been changed from the distillation process to a double pass RO system with appropriate qualification. The restructured system was used to supply PW to both Workshop No.1 and No. 2. to replace the previous separate systems. It was regularly monitored and sanitised.

2.13 EQUIPMENT

Guilin OSD site had adequate numbers of equipment for the production and testing products manufactured at the site. For tableting, these included sifter, pre-blender, Multi-mill, Rapid High-shear Mixer Granulator, Tray driers, Granule Resizer (Shaft Granulator), V-blender, Manesty tableting machines, double rotary compression machines, metal detectors, auto coaters and blister packing machines. They were generally well designed, installed, qualified and were covered by a preventive maintenance programme. There were 2 exceptions, one on the observed

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rusty exhaust of the miller and the other on the observed gaps between the filters in the tray dryers in Workshop 2. These were subsequently adequately rectified.

There were procedures for equipment set up, operation, cleaning and maintenance. There were also logbooks for their use, cleaning and maintenance.

2.14 MATERIALS

Starting materials

Guilin has put in place a procedure for Vendors/Suppliers Audit. Under this procedure, vendors of critical materials (e.g. APIs and excipients, labels, packaging insert, primary packaging materials, which could have significant impacts on the quality of products) must be audited prior to approval; Vendors of non-critical materials (e.g. Secondary Packaging Materials, etc.), the approval shall be decided based on the assessment, in the way of an on-site audit when deemed necessary (e.g. if the supplier is also the manufacturer of the material) or questionnaires filled by suppliers or qualification reports from a third party.

A list of approved vendors was available at the receiving area and was always followed in procurement and receiving of materials reviewed.

All containers of active pharmaceutical ingredients were sampled individually and tested for identity while full testing was done on a composite sample.

Packaging materials

Packaging materials were purchased from approved vendors. Each consignment was quarantined, sampled and tested before release for use although the sample size was not in line with ISO2859 or BS6001. This deficiency was subsequently addressed.

Intermediate and bulk products

Granules could be kept up to 3 months which had been validated. Some granules and/or bulk tablets were transferred in sealed drums from Workshop 1 to Workshop 2 for compression or co-packaging. The conditions under which film coated tablets were left overnight to dry were not monitored. This was subsequently adequately rectified.

Finished products

Products were not released for distribution unless each batch was tested and its production, packaging and testing records reviewed and found in compliance with GMP and regulatory requirements.

2.15 DOCUMENTATION

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The preparation, review, distribution and retrieval of Standard Operating Procedures were under the control of QA. Most SOPs were in Chinese language although some had been translated into English. SOPs were available or easily accessible at the points of use.

Validation and qualification activities were guided by approved protocols and corresponding reports were in place. The details in these protocols and reports could be improved.

Production and control of products was guided by master formulae, specifications of starting and packaging materials, production and packaging instructions, batch processing and packaging records, finished product specifications, standard testing procedures and corresponding records were maintained.

Weaknesses which had been observed in the comprehensiveness of some documents and lack of policy to guide translation of documents were subsequently addressed. The long timeline (12 months) for completion and implementation of CAPA was reviewed.

2.16 GOOD PRACTICES IN PRODUCTION

Tablets production generally included sieving, pre-mixing, milling, wet granulation using a Rapid High-shear Mixer Granulator, drying in a tray dryer, resizing of granules, blending, compression, coating and packaging. This was supported by BMRs.

Milled materials were collected in cloth bags but there was no indication of the previous product and there was no indication that they were dedicated. These deficiencies were later addressed. Some granules and/or bulk tablets were produced in workshop 2 and transferred in drums placed in a closed trolley to workshop 1 for compression into bilayer tablets with another API or for co-packaging with other tablets.

There were provisions for conducting in-process checks (mass variation, hardness, friability, disintegration and tablet dimensions) and calculation of yield at various stages of production.

In workshop 2, only one compression machine out of 3 had a metal detector. It was indicated that it was not a requirement for products meant for local market to go through a metal detector. Punches and dies were well controlled.

Packaging was done in blisters which were tested for leakage and correct labelling. Packing was accompanied by pre and post line clearance. Incidences of poor sealing were noted towards the end or at the beginning of a roll of Aluminium or PVC foils. Inspection was done on line visually by one of the staff but it was observed that this was not effective and chances of defective blisters passing unnoticed were likely.

2.17 GOOD PRACTICES IN QUALITY CONTROL

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The quality control and quality assurance departments were independent of production and were located in a separate building from Workshops 1 and 2. The laboratory served both the penicillin and non-penicillin blocks but with adequate segregation of samples. It had adequate facilities in the form of space, equipment, reagents and chemicals to test all starting materials, packaging materials, intermediates and finished products before release for use or distribution.

Retention samples from each batch of starting materials and finished products were kept to facilitate any future investigation, if necessary.

There was a stability testing programme supported by stability chambers set at 40⁰C/75%RH and 30⁰C/65%RH. Weaknesses were also noted in the records to support traceability of stability samples from charging, withdrawing and testing, but appropriate corrective action were latter taken.

General and wet chemistry laboratory

The laboratory had a fume hood for safe handling of volatile chemicals.

The calibration and maintenance programme of the QC equipment was evaluated using the dissolution testing equipment which was found to have been adequately calibrated by regularly checking the temperature probe, shaft eccentricity, RPM and paddle clearance, performance checks using the standard USP tablets (Salicylic Acid).

Instrumentation

The instrument laboratory was stocked with HPLCs, UV-Visible spectrophotometers and IR Spectrophotometer instruments. They were routinely maintained and calibrated and the performance of the HPLC column was monitored.

Reference standards

Primary reference standards were used to standardize Working standards. There was a standard method of preparation of working standards to a high purity level by recrystallization in the appropriate solvent and retesting carefully selected APIs.

Microbiology

There was a microbiology laboratory for testing water samples and other materials for microbial limit test. At the time of inspection, there was, unexpectedly, hardly any activity and this made the assessment of this area difficult. However, the inadequate control of the reference standards used to control the media for environmental and product testing and the inadequate control of autoclaved products were of significant concern. These deficiencies were subsequently addressed.



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, **Guilin Pharmaceutical Co. Ltd, Tablet Workshops 1 and 2, No. 17, Shanghai Road, Guilin, Guangxi, P.R of China** was considered to be operating at an acceptable level of compliance with WHO GMP guidelines.

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

The WHOPIR is valid for a maximum of 3 years, unless the site is found to be non-compliant in another inspection before the 3 years had lapsed.