



**WHO PUBLIC INSPECTION REPORT  
(WHOPIR)**

**Finished Product Manufacturer**

**Part 1: General information**

Name of Manufacturer	<b>Guilin Pharmaceutical Co., Ltd</b>
Unit number	Injectable site
Production Block	⇒ Workshop No. 8 dedicated for Artesunate 60mg powder for injection. ⇒ Workshop No. 7 for small volume Parenterals, including Sodium Bicarbonate 5% Ampoule.
Physical address	<b>Guilin Pharmaceutical Co., Ltd No. 43 Qilidian Road, Guilin, Guangxi, China</b>
Contact person and email address.	<b>Mr. Jimmy He</b> Mobile: Tel: +86-773-3555935 Fax: +86-773-3832783 E-mail: Hem@guilinpharma.com
Date of inspection	23, 24, 25 and 26 August 2010
Type of inspection	Follow up Inspection
Dosage forms(s) included in the inspection	Powder for injection and injectable solutions
WHO product categories covered by the inspection	<b>Powder for injection Finished product used in the management of Malaria (MA)</b>
Summary of the activities performed by the manufacturer	Manufacturing, packaging, quality control and batch release of injectable products.

## **Part 2: Summary**

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

The facility inspected was the **Injectable Workshop 7 and 8 of Guilin Pharmaceutical Co. Ltd No. 43 Qilidian Road, Guilin, Guangxi, China**, here after referred to as **Guilin INJ**. According to the Site Master File, Doc No.: SMP-QA-006001-05 effective 06.07.2010 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 **No. 17 Shanghai Road, Guilin, Guangxi, China**, which also hosted the API and OSD manufacturing facilities. The production site at **No. 43 Qilidian Road, Guilin (Guilin INJ)** produced sterile bulks, powders for injection and Small Volume Parenteral (SVP) injections. Both sites produced cephalosporin, penicillin and non-penicillin based materials and/or products in dedicated production blocks. 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 INJ** consisted Workshop 8 (dedicated for the powder for injection), Workshop 7 [for many SVPs including injection the solution co-packaged with powder for Injection], Workshop 6 (Penicillin block and Cephalosporin block), and Cephalosporin block (joint venture). A new facility was under construction and was expected to be completed at the end of 2011.

According to the SMF, the company employed a total of 989 people at both No. 17 Shanghai Road and No. 43 Qilidian Road distributed as follows:

• Quality assurance	30
• Engineering Technicians	181
• Quality control	53
• Production	667
• Warehouse	28
• Sales department	73

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

This was the fifth inspection of this site by WHO Prequalification team. The previous inspections were in August 2006, April 2007, September 2008 and February 2010. It also received technical assistance arranged by WHO-PQ. The API production facilities at No. 17 Shanghai Road site, which supplied the API used in the powder for injection, were inspected by WHO-PQ in November 2005, April 2007 and March 2008.

The site at **No. 43 Qilidian Road** had GMP Certificates from SFDA:

- K4986 valid until 02.09.2014 for powders for injection and Lyophilised powder for injection
- J4519 valid until 28.02.2013 for Small Volume Parenteral Solutions

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According to the company's presentation, the API production facilities at No. 17 Shanghai Road site had also been inspected in September 2008 and approved by the USFDA with respect to Bumetanide.

### *Focus of the inspection*

This was a follow up of the observations of the inspection carried out in February 2010. The inspection focused on production and control activities in Workshop No. 8 (dedicated for compounding, lyophilisation and aseptic filling of the powder for injection) and Workshop No. 7 (used to manufacture a variety of small volume parenterals, including ampoules of the solution for injection, which are co-packed with the powder for injection). Spot checks were made to the neighboring Cephalosporin and Penicillin blocks to evaluate facilities for the treatment of exhaust air.

### *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 gave an update on the procedure for WHO Prequalification Programme. 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, summary of manufacturing processes, inspection history and changes and CAPAs since the last WHO inspection. A copy of the presentation was obtained and will be filed in the company file.

The major changes highlighted include the following:

1. Workshop 8: Installed new filling line with a bigger hopper to accommodate the batch in one load, filling quantity control and automatic vial sampling. The loading of the hopper was still by manual scooping.
2. Workshop 8: Installed 5 continuous monitoring devices for non-viable airborne particle at the outlet of the vial depyrogenation tunnel (No. 29); vial turn table (No. 28); filling station (No. 27), LAF for storage of sterilized rubber stoppers (No. 31) and under the LAF in the crystallization room (No. 32).
3. Workshop 8: Changed the compounding tank to one of SS316L.
4. Increased batch of the MFT from 5,500 vials to 12,000 vials. Only one run had been done.
5. Standardized the batch sizes for the powder for injection and Solution for Injection.
6. Installed in the warehouse sampling booths for sampling some non-sterile raw materials, ethanol, Rubber stoppers and vial caps.
7. Conducted training in microbiology facilitated by USP and Guilin Institute for Drug Control. A post graduate student in Microbiology was employed as an intern in the QC department. The same person found during the previous inspection was still the head of the Microbiology laboratory, but had undergone intensive training, as mentioned above.
8. Workshop 7: Installed interlocking devices on doors of airlocks separating areas of different cleanliness. The gaps between doors were removed and wooded furniture replaces with SS furniture. The UV intensity of the ampoule inspection stations was now regularly checked.
9. On-line conductivity meter and temperature sensors in the return water loops were installed.

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10. Training was conducted by Bayer Technology on HVAC and Water Systems.
11. Pantone colour standard charts were purchased and sampling of packaging materials was consistent with ISO2859 was adopted.
12. The road within the site was given a new coat of tarmac and the outside walls of some building were repainted.
13. A GMP consultant was engaged and his CV showed that he was highly qualified and with wide experience in GMP.

This was followed by document review for the following areas:

**Quality Management System review:**

- Personnel Policies:
  - *Organization charts for the site, Injection Workshop, Quality Management and Quality Control department:* these, together with lists of employees showed separate staff for production and analysis of penicillins, cephalosporins and other products.
  - *Job descriptions of key personnel: e.g. Head of QC2 (Microbiology).*
  - *Training (induction and continuing): Records of selected staff were reviewed, e.g. training of F06106 on 16.07.2010 on the protocols for filling and preparation of sterile API.*
  - *Health and Hygiene:* For example, regular check on the visual acuity of F06145 involved in visual inspection of filled ampoules.
- Change control procedure and register for 2010. The procedure classified changes as major and minor. The change on HVAC system related to the CAPA to an observation of the previous inspection was reviewed in detail. The HVAC requalification report was also reviewed in detail.
- Deviations + related SOPs and registers for 2010. A deviation related to wrong installation of F8 filter instead of G4 as primary filter was reviewed in detail. The report discussed the impact of the deviation on 28 batches of the powder for injection produced during this period. Increased documentation was introduced as a CAPA.
- OOS + related SOPs and registers for 2010: Examples of OOS were reviewed in detail.
- Self inspection SOP, Plans, reports for 2010: these were up to date up to August 2010.
- Validation Master Plan (including status and planned): effective date 01.01.2010.

**Inspection of Receiving and storage areas:**

- Vendor approval and qualification system
- Starting materials, packaging materials and components receiving, quarantine, sampling and storage areas +SOPs:
  - A shade had been erected above the loading and off-loading bay.
  - Records of receiving and sampling of selected materials were reviewed. Raw materials were held under quarantine, sampled and tested before release for use in production. Packaging materials were sampled and tested according approved SOPs which defined AQLs and sampling plans consistent with ISO 2859/MIL Standard 105D. Records of selected consignments of ampoules, vials, small boxes, vial labels, ampoule labels and APIs were reviewed and they had been sourced from approved suppliers and sampled and tested according to the SOPs before release.
  - A LAF cabinet was available as sampling booth and it was fitted with a dust extraction system modified from a vacuum cleaner.

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- The storage conditions for Non-sterile API for preparation of sterile powder for injection were specified as  $\leq 20^{\circ}\text{C}$  and 45 - 75%RH.
- Finished goods warehouse: The date of manufacture on the label was the date of preparation of the sterile API.
- Temperature + RH mapping and monitoring: Thermo hygrometers capable of taking Temperature and RH every hour had been recently installed. Actual conditions at the time reading were recorded in the log book but readings were also downloaded on the computer programme. There was no evidence that this data was not regularly reviewed for trending.

At the end of the day, the team reviewed progress of the activities of the day and agreed on the tentative programme for the next day. Feedback was deferred to the following day.

## Day 2

The inspectors started by giving feed back on observation of the previous day and obtained preliminary clarifications from management where deemed necessary. The inspection then proceeded as below.

### **Review of Plant Layout and Production activities in Workshops 8:**

- Block layout, area classification, AHU distribution and material and personnel flow.
- Inspection of areas for compounding, lyophilisation, aseptic filling and packaging of bulk sterile API. Inspectors witnessed the filling, sealing with rubber stoppers and crimping of batch of vials of a batch of the Powder for Injection. The transfer of the sterile API powder into the hopper was done by manual scooping. Records of continuous particle monitoring during this period were reviewed and copies taken. There were all within limits except for some unexplained gaps.
- Media fill tests, process validation/revalidation: It was conducted using a simulated batch of 11,956 vials filled in 4 sessions from 8:30 to 17:05 On 18.07.2010. Each session included a different operator (F01117, F01123, F01016 & F06106) and several interventions on the filling line that were well documented. The entire period was covered by continuous viable and non-viable particle monitoring. The 11894 vials packed in 73 trays were incubated in 4 incubators. Results showed no growth in any vial. Only one run was reported.
- Review of BMRs for selected batches. Out of 19 batches manufactures since January 2010, a few were selected for detailed review.

### **Inspection of Utilities for Workshop 8**

#### **1. HVAC system for Workshop 8:**

- Requalification/Monitoring the HVAC System
  - Report dated 14.08.2010 for the last area requalification done on 09.08.2010 was reviewed. It was based on an approved SMP and used particle counters with capacity of 28.3L/min $\pm$ 5%. Raw data for viable and non-viable particle counts **at rest** for the following areas were reviewed:
    - LAF for the filling machine (Class A)
    - LAF for storage of rubber stoppers (Class A)
    - LAF for crystallization room (Class A)
    - Storage room for rubber stoppers (Class B)
    - Crystallization room (Class B)

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- Filling room (Class B)
- Class B Corridor

It was required to use at least 1000L for Grade A areas and 690L for Grade B areas. The prints from the particle counters (capacity 28L/min) showed that sampling times used were 2160 sec (36 min) for Grade A and 1500 sec (25 min) for Grade B. This is consistent with the minimum volume required by ISO14644-1(B.4.2.1).

TSA/SCDA media was used in settle plates (cfu/4h) and plates with air samples (cfu/m<sup>3</sup>) which were then incubated for 5 days at 30<sup>0</sup> - 35<sup>0</sup>C. All the results were within limits of section 4.9 of WHO sterile guideline (TRS957).

- Following changes in the filling line and related LAF, the installed filter system was tested for leakage using a Discrete Particle Counter (DPC), (Ref. ISO14644-3, B.6.3)
- Inspection of the HVAC technical area: AHU1 and AHU 2
- Prevention of penicillin/cephalosporin cross-contamination. Inspected the technical area of the Joint venture Cephalosporin Workshop to establish the filtration of the exhaust air. It was established that a HEPA (H13, 99.99% EN1882) filter had been recently installed, but was not working since the AHU had been switched off because there was no production.

## **2. Water purification system for Workshops 8:**

- PW system drawings and summary of specifications and capacities
- Qualification/Requalification/Monitoring the PW and WFI system (*Sampling and trend analysis*). Records showed that the PW and WFI system were commissioned in April 2008. Records of its validation and x-rays of selected weld were reviewed.
  - China National Standard for radiographic test method, Doc. No. JB4730.2-2005.
  - Radiographic test reports: GLNY/QHZS-GX-RT/BG-01-2010 and GLNY/QHZS-GX-RT/BG-02-2010.
- Inspection of Water Generation and Purification System installations. Online conductivity meter had been installed in the PW and WFI return loops.

## **3. Pure steam system for Workshops 8:**

- Inspection of the pure steam system installations. The diagram and testing of the jacketed section of the system piping system was reviewed.

## **4. Compressed air system for Workshops 8:**

- Qualification/Requalification/Monitoring the Compressed Air systems
- Inspection of the Compressed Air system installations

## **Equipment qualification and preventive maintenance:**

- Equipment qualification/Requalification (DQ, IQ, OQ and PQ for major equipment)
- Preventive maintenance schedules and records

At the end of the day, the team reviewed progress of the activities of the day and agreed on the tentative programme for the next day. Feedback was deferred to the following day.



### **Day 3**

The inspectors started by giving feed back on observation of the previous day and obtained preliminary clarifications from management where deemed necessary. The inspection then proceeded in the following areas.

#### **Review of Plant Layout and Production activities in Workshops 7:**

- Block layout, area classification, AHU distribution and material and personnel flow.
- Ampoule washing and sterilization, compounding, filtration, filling, sterilization, visual inspection, drying ampoules at 40<sup>0</sup>C for 24 hours (this was supported by accelerated stability studies), labelling and packaging of solution for injection. The system for issue, use, control and reconciliation of pre-printed labels was reviewed.
- In-process quality control laboratory.
- Drying and holding storage of filled ampoules.
- Review of BMRs for selected batches.

#### **Inspection of Utilities for Workshop 7:**

##### **1. HVAC system for Workshop 7:**

- Requalification/Monitoring the HVAC System
- Inspection of the HVAC technical area

##### **2. Compressed air system for Workshops 7:**

- Qualification/Requalification/Monitoring the Compressed Air systems
  - Inspection of the Compressed Air system installations: The system consisted of air inlet, compression, cooling, freezing and serial filtration (3µm → 1 µm → Carbon filter → 0.01 µm → 0.2 µm near point of use). The validation report dated 20.06.2010 for one of the Air Compression System ZW-3/7 was reviewed.
3. Nitrogen for ampoule purging - vendor approval, quality control, storage and use was reviewed.

#### **Equipment qualification and preventive maintenance:**

- Equipment qualification/Requalification (DQ, IQ, OQ and PQ for major equipment).
- Preventive maintenance schedules and records.
- Integrity testing of filters for Nitrogen, compressed air, WFI, NaHCO<sub>3</sub>.

#### **Quality control laboratory**

- Analyst competencies and training
- Sample receipt, storage and allocation
- Wet chemistry laboratory
- Instrumental laboratory
  - Qualification, calibration, preventive maintenance. Calibration of standard weights used for daily verification of balance was reviewed (SOP and certificate)
- Laboratory materials management (Samples, Reagents, Stock Solutions, Reference and Working Standards)
- Starting materials and finished products specifications, testing and release.

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- Testing of Packaging Materials and Components
- Stability testing programme (*Protocols, programme, records and data*): At least one batch of each product was put on stability every year.
- Retention samples: samples (3 times quantity need for a full analysis) of each FPP were kept for at least 1 year after the expiry of the batch. The environmental conditions of their storage room were not being continuously monitored.

At the end of the day, the team reviewed progress of the activities of the day and agreed on the tentative programme for the next day. Feedback was deferred to the following day.

#### **Day 4**

The inspectors started by giving feed back on observation of the previous day and obtained preliminary clarifications from management where deemed necessary. The inspection then proceeded in the following areas.

#### **Workshop 7:**

Entrance and changing procedures for compounding and filling areas in workshop.

#### **Water purification system for Workshops 7:**

- PW system drawings and summary of specifications and capacities
- Qualification/Requalification/Monitoring the PW and WFI system (*Sampling and trend analysis*)
- Inspection of Water Generation and Purification System installations

#### **Microbiological laboratory**

- Room and equipment: There were room and equipment to support adequate segregation of activities. The lab had an adequate number of incubators with adequate temperature capacity ranges. Reference cultures were labelled to indicate their generation and there was policy not to exceed the 5<sup>th</sup> generation.
- Media preparation and product testing.
- PW monitoring: The membrane filtration method was used.
- Environmental monitoring: Plates were referenced to the location in the workshop and were incubated for 5 days at both 25<sup>0</sup>C and 35<sup>0</sup>C.
- Reviewed the documents related to qualification and testing of compressed air.
- Preparation of the sterile powder through compounding, aseptic filtration, crystallization, washing, filtration by vacuum, lyophilisation and bulk packaging. Inspectors observed the manual transfer of the powder from the vacuum drier onto trays, sampling and loading into the lyophiliser.

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. Management reaction included:

- Acknowledgement of the observations made by the inspectors.
- A commitment to continuous improvement.

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- Pledge to ensure translation of documents in both English and Chinese.
- Resolve to improve the comprehensiveness of documents to enhance traceability and audit trail.
- To continue to work to on the improvement of the aseptic procedures. To this end it was said that stability studies were in advanced stages aimed at using the sterile API storage Aluminium container as a hopper for the filling and provide automatic loading of the sterile API after crystallization.
- Commitment to continuous improvement in the skills of staff.
- Commitment to achieve WHO prequalification so as to provide quality products to those patients who need them.

## **2.1 QUALITY ASSURANCE**

There was an organization chart and job descriptions specifying the responsibilities and reporting relationships of the various staff. Improvements were noted in segregating staff and responsibilities for  $\beta$ -lactam (penicillins & cephalosporins) and non- $\beta$ -lactam products.

There were documented and approved procedures to guide routine operations and activities. Starting materials, intermediate products, finished goods were generally controlled and approved by QC/QA before release for use or distribution.

Policies and procedures were in place for qualified and validation of equipment and systems, change control and deviation management, self inspection, annual product review and evaluation of trends. Most had been recently revised with marked improvements.

## **2.2 GOOD MANUFACTURING PRACTICES (GMPs) FOR PHARMACEUTICAL PRODUCTS**

There was noted improvement in the facilities on site, especially in Workshop 7, though this improvements need to continue. Improvements were noted in the training of personnel, aseptic procedures, general production procedures and microbiology activities but gaps still existed in control and validation of aseptic procedure, handling utilities and general documentation to provide adequate product history and audit trail.

It was noted that numerous improvements had been made since the previous inspection and most CAPAs were adequately implemented, though the CAPAs focused on the specific examples mentioned in the previous report with limited system-wide review. Satisfactory CAPAs have been submitted to the observations made during this inspection to further improve the level of GMP compliance.

## **2.3 SANITATION AND HYGIENE**

The production and quality control facilities were generally maintained at a reasonable level of cleanliness. There were cleaning procedures for the equipment and the premises. Improvements were noted in waste collection and management procedures in workshop 7.

Personnel changing procedures and related gowning were generally appropriate, except for some minor issues. There were facilities and requirements for washing and sanitising hands before entering key production areas in workshop 8.

## **2.4 QUALIFICATION AND VALIDATION**

There was a Validation Master Plan (VMP2010) which outlined the policy and approaches to be followed in qualification of equipment and validation of systems and processes. The policies with respect to application of retrospective and concurrent validation were not consistent with WHO GMP. Qualification included definition of user requirement and specifications (URS), Design Qualification (DQ), Installation Qualification (IQ), Operation Qualification (OQ) and Performance qualification (PQ). Validation and qualification were guided by approved protocols. The schedules and frequencies for planned requalification, validation and revalidation were outlined in the the VMP.

Evaluation was done to identify the worst case products for the purpose of cleaning validation. The documentation of the limit setting procedures and evidence of sensitivity of the analytical methods used during cleaning validation has been strengthened.

## **2.5 COMPLAINTS**

This area was not inspected in detail as there were no complaints recorded since the last inspection.

## **2.6 PRODUCT RECALLS**

This area was not inspected in detail as there was no record of any product recalled since the last inspection.

## **2.7 CONTRACT PRODUCTION AND ANALYSIS**

According to the site master file, the company did not carry out any contract production or analysis. The API manufactured at the sister site (i.e. No. 17 Shanghai Road) was accepted and released for compounding, sterile filtration, re-crystallization, and lyophilisation based on the certificate of analysis from the sister company. Preparation and qualification of Working Standards was still done at the sister site (No. 17 Shanghai Road). These two activities were not considered by management to require a formal agreement since both sites were operating under the same management and overall QA system.

The company however, contracted out coding of some primary product labels (not for WHO-PQP products) but the documentation and control of these activities needed strengthening.

## **2.8 SELF INSPECTION AND QUALITY AUDIT**

Internal audits were conducted following a written and approved SOP and schedule. Contradicting systems existed on the required frequency of self inspection. From the records seen and reviewed the impression gained was that the inspection audits were conducted on schedule.

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Vendor evaluation and approval procedures provided for a questionnaire to be filled by the vendor, followed by a review of technical documents from the supplier, audit of suppliers of critical materials and full analysis of the first 1 - 3 batches of the materials supplied.

## **2.9 PERSONNEL**

There was an organization chart and job description to guide personnel. The responsibilities of the key personnel like head of production, head of quality control and head of quality assurance were defined and there were personnel designated to deputise the key personnel in their absence. The responsibility for batch review and release was assigned to QA Manager and the deputy QA Managers. Improvements were noted in segregating staff and responsibilities for  $\beta$ -lactam (penicillins & cephalosporins) and non- $\beta$ -lactam products.

Improvement were generally noted in, knowledge, skills and compliance with SOPs and other quality assurance measures.

## **2.10 TRAINING**

There had been intensive training of staff since the last inspection, focused on the revised procedures and general improvements. There were conducted by internal expert, contracted GMP consultant and external bodies like USP and Guilin Institute for Drug Control.

The records reviewed, the practices observed and the experience gained from interaction with staff at various levels indicated that training programmes plus their evaluation had improved.

## **2.11 PERSONAL HYGIENE**

Personnel were trained in personal hygiene procedure and facilities were provided in form of change rooms, protective garments and disinfectants. It was a policy for the health of staff to be checked on recruitment and thereafter every year. Records reviewed showed that staff involved in visual inspection underwent eye checks every six months.

## **2.12 PREMISES**

There were two workshops involved in the production of the sterile Powder for injection (co-packed with an ampoule of solution for injection):

⇒ **Workshop No. 8** was dedicated for compounding, lyophilisation and aseptic filling of the powder for injection. The premises were protected from entry by insects, birds or animals and had separate personnel and material air-locks. The production facilities were smooth, generally free from cracks (with minor exceptions) and open joints. There were separate areas for the different stages of production appropriately separated by airlocks, pressure differentials and they were generally designed to facilitate unidirectional processing flow. The doors were interlocked and were fitted with automatic sensors. Premises generally were fairly maintained (with minor exceptions) and clean. It was supplied by two AHUs: one for class A & B areas and the other for class C & D areas. The ceiling of the building was so narrow that it could not be used for servicing most of the fixtures. Therefore HEPA filters and light

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fixtures could only be serviced through the production areas. The control of grilles between rooms and the monitoring of  $\Delta P$  across filters have been to avoid uncontrolled changes in  $\Delta P$  between different rooms.

In close proximity to workshop 8 were four blocks: One block was used for quarantining and co-packaging vials of the vials powder for injection with ampoules the solution for injection and labeling; two blocks were known as Workshop No. 6 - one block for production of Cephalosporins and the other for Penicillins; the third block housed a joint venture company (Auspicious Pharma) which produced Cephalosporin products. Exhaust air from these blocks were filtered through HEPA filters and wet scrubber with alkaline solution (NaOH).

⇒ **Workshop No. 7** was used for the manufacturing of a variety of small volume parenterals, including ampoules of the solution for injection, which was co-packed with vials of the powder for injection. It was designed with separate areas for the different stages of production. It was supplied by one AHU for all the clean A, B, C and D areas with pressure differentials.

Interlocking devices had been fitted on doors of the airlocks and improvements had been made on these premises. Appropriate CAPAs have been submitted to provide hand washing facilities for staff entering certain parts of this workshop where the product is already packed in the primary container/ampoule, repair the floor of rooms after sterilization, identify and provide facilities monitoring environmental conditions the holding room for filled ampoules. Part of the building that was previously used for producing large volume parenterals was still sealed off.

Construction was still going on within the vicinity of Workshop 7 for the new production facilities, but these construction activities were appropriately barricaded to reduce their impact on production activities in workshop 7.

The warehouse for the APIs and other related materials was located in the building also housing the microbiology laboratory. A shade had been constructed above the loading and offloading bay but the same entrance was still used for materials and personnel. Materials at different status were segregated by different coloured chains (yellow for quarantine and green for approved). Sampling booths had been installed in this ware house and the one for ethanol. Sampling of penicillins and cephalosporins was still done in dedicated sampling rooms within the microbiology laboratory. Pest control measures were in place. The storage conditions in the warehouse were monitored and recorded twice daily.

Each workshop had a dedicated water purification system. It was designed to produce Purified Water (PW) and Water for Injection (WFI). On-line conductivity meter and temperature sensors in the return water loops were installed.

There was a separate building for QC laboratories with different rooms to facilitate appropriate segregation for different activities. It was used for testing penicillin, cephalosporin and non- $\beta$ -lactam raw materials and products.

## 2.13 EQUIPMENT

There were adequate numbers of equipment for the production and testing of products manufactured at the site. The compounding tank in Workshop 8 had been changed from glass-lined to one made of SS316L. The filling line had been changed to increase the capacity of the powder hopper and install an automatic vial sampler. Devices for continuous monitoring for non-viable airborne particle had been installed at the outlet of the vial depyrogenation tunnel (No. 29); vial turn table (No. 28); filling station (No. 27), LAF for storage of sterilized rubber stoppers (No. 31) and under the LAF in the crystallization room (No. 32).

The equipment for production of solution for injection (scoops, trolley, wooden furniture, visual inspection stations, etc) that had been observed as inappropriate had been replaced or repaired. Appropriate CAPAs have been submitted to address the weaknesses observed in the identification and status labelling of some equipment plus preventive maintenance of some of the equipment (e.g. Air conditioners for the warehouses).

Appropriate CAPAs have been submitted to improve documentation of the qualification of air compressors including ID numbers, standards used, linkage with testing devices used and their calibration status.

## 2.14 MATERIALS

### *Starting materials*

There was a system for approval and qualification of vendors of Raw Materials and Packaging Materials. This was based on a questionnaire sent to all suppliers and audit of the manufacturing facilities when deemed necessary. The list of approved vendors was always followed in procurement and receiving of materials reviewed.

All actives, except non-sterile API from the sister site, were identified and fully tested upon receipt and provision of an officially authorized CoA by the supplier was mandatory.

Appropriate CAPAs have been submitted for regular testing of utilities like Nitrogen, compressed air and dye used in ampoule leak test.

### *Packaging materials*

Packaging materials were purchased from approved vendors. Each consignment was quarantined, sampled and tested before release for use. The sampling used was now equivalent to BS6001 or ISO2859. Appropriate CAPAs have been submitted to address weaknesses noted in the control of the issue, use and reconciliation of labels.

### *Finished products*

Each batch of finished products was held in quarantine until it was tested and its production, packaging and testing records reviewed and found in compliance with GMP and regulatory requirements.

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### *Rejected materials and products*

There were separate facilities designated for storage of rejected material until either they were disposed off by return to the supplier or destruction, or they were reviewed and approved by QA for further testing and repackaging.

### *Reference Standards*

There were dedicated facilities (*refrigerator and desiccators*) for storage of working standards. All primary reference standards were stored in the QC laboratories at Guilin OSD at No. 17 Shanghai Road where all the working standards were prepared and supplied to Guilin INJ at No. 43 Qilidian Road. They were clearly labelled and the records for use of working standards were maintained.

## **2.15 DOCUMENTATION**

The preparation, formats, review, distribution and control of Standard Operating Procedures and other documents was guided and controlled by an SOP. Chinese was the preferred language for most documents but some were written in both Chinese and English. SOPs were provided with reference and version numbers plus effective and review dates.

It was noted that most documents and related records had been recently revised and were now comprehensive to provide adequate product or activity history and support an audit trail. Appropriate CAPAs have been submitted to ensure that documents and forms were brought in line with the changes made (e.g. change in equipment ID numbering system).

In view of the long time it took to provide requested documents, there were still weaknesses in archiving and retrieval of documents and records. Documentation control was under the quality assurance department.

## **2.16 GOOD PRACTICES IN PRODUCTION**

There were written procedures and records to manage the receipt, quarantine, sampling, labelling, storage and dispensing of materials; cleaning of equipment and premises; processing, packaging and distribution of products. Limits for yield had been set at different stages of production and packaging to facilitate investigation of any results beyond the limits.

Production of the FPP for injection included compounding, aseptic filtration, crystallization, dehydration and washing, freeze drying/lyophilisation, filling, stoppering and capping in cleaned and pre-sterilized vials, stoppers and caps, and labelling. The transfer of the sterile powder into the filling hopper was now done in one session, though still manually by scooping. Filling, rubber stopping and vial crimping were done under LAF with a provision for automatic vial sampling. The batch had been fixed. Measures have been put in place to ensure that all incidences and deviations were documented. The process of documenting, assessing the impact/risk of incidents, deviations and changes have been strengthened.

The production of the solution for injection included dissolution, filtration and vacuum transfer, filling and sealing in cleaned and pre-sterilized ampoules, sterilization and leak testing, visual inspection and labelling.

The co-packaging included placing one labelled vial of the powder for injection and one labelled ampoule of the solution for Injection into a plastic tray, and the tray was in turn packed in a pre-coded small box together with a package leaflet. Five (5) small boxes were then packed in one middle box and 100 middle boxes were in turn packed into a shipping carton.

Improvements have been made in the status labelling of labelling lines (e.g. in Workshop 7) and related line clearance. The documentation of approval of printed labels and online coding has been strengthened. Coding of lot number, manufacture and expiry dates for labels of primary containers for products under WHO-PQ was done on line, although for some other products coding was contracted out. Coding of lot number and expiry date for small, medium and shipper boxes was done off line using stereos.

IPQCs were performed at different stages of production and packaging.

## **2.17 GOOD PRACTICES IN QUALITY CONTROL**

There were quality control and quality assurance departments whose functions were independent of other units including production. The quality control laboratory was located in a separate block and served both  $\beta$ -lactam (penicillins & cephalosporins) and non- $\beta$ -lactam production blocks.

Quality assurance staff reviewed all the production and testing records for each batch before it was released for distribution. Retention samples were kept from each batch of starting materials and finished products to facilitate any future investigations, if necessary.

There was a stability testing programme supported by  $5^{\circ}\pm 3^{\circ}\text{C}$ ,  $25^{\circ}\text{C}/\text{Ambient RH}$ ,  $25^{\circ}\text{C}/60\%\text{RH}$ ,  $30^{\circ}\text{C}/70\%\text{RH}$ , and  $40^{\circ}\text{C}/\text{Ambient RH}$  stability chambers.

### ***General and wet chemistry laboratory***

The laboratory was generally in a good state of repair and had a fume hood for safe handling of volatile chemicals.

There was a calibration and maintenance programme for balances and other QC equipment. There were SOP and records for the preparation of reagents and standard solutions. Reagents and standard solutions were labelled with name, date of preparation and expiry date.

### ***Instrumentation***

The instrument laboratory was stocked with HPLCs, UV-Visible spectrophotometers and GC instruments. There were records for their routine maintenance and calibration. HPLC column logs were well maintained. Records of issue, performance and maintenance were available.



### ***Components and packaging material testing laboratory***

Sampling of components followed approved SOPs, the sampling plans for the items reviewed (vials, ampoules, package leaflets, vial and ampoule labels) were consistent with BS6001/ISO2859 and all had been tested to the relevant authorized specification. Pantone colour standard charts had been purchased.

#### **Microbiology**

##### ***a) Premises and equipment***

The microbiology laboratory had separate areas for solid media storage, liquid media preparation; sterility testing; water testing, microbial limit tests, positive controls; endotoxin testing and incubation. Access to the clean areas was via three level change rooms for appropriate gowning.

There was an autoclave dedicated for media sterilization and autoclave tape with a sterilization indicating card were used in each load to distinguish the sterilization status and indicate the sterilization efficiency. A bio-indicator was added to confirm the sterilization efficiency and verify the autoclaving integrity once every 3 months.

##### ***b) Routine Testing reagents and procedures***

Growth promotion controls were done for media using reference cultures and were routinely carried out. The SMP for generation and usage of culture species had been revised to provide for identification tests to be done on reference cultures on receipt and individual species to be given a specific/unique number. The species were tentatively sealed in liquid paraffin and kept at 2 ~ 8<sup>0</sup>C. The next generation was produced at intervals of 2 months and each vial of culture species had to be used only once after opening.

##### ***c) Water Testing***

The sampling plan followed an approved SOP and applied the membrane filtration testing procedure.

##### ***d) Environmental Monitoring***

The environmental monitoring programme included routine active air sampling and settle plates which covered all aseptic procedures. The records reviewed showed that the clean rooms met the conditions claimed at the time of recording. Finger dabs were also taken from operators and the record showed accepted levels.

Improvements were noted in the management of this laboratory in documentation of the procedures and lot numbers of the media and cultures used; management of samples (e.g. date and time of picking of water samples) and reagents (e.g. water used in media preparation); compliance with testing and aseptic procedures; filling, archiving and retrieval of records.



### **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, **Injectable Workshop 7 and 8 of Guilin Pharmaceutical Co., Ltd No. 43 Qilidian Road, Guilin, Guangxi, 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.