WHO PUBLIC INSPECTION REPORT (WHOPIR)
API Manufacturer

Prequalification of Medicines Programme
WHO INSPECTION REPORT
API Manufacturer

Part 1: General information

<table>
<thead>
<tr>
<th>Name of Manufacturer</th>
<th>Shougang Fukang Pharmaceutical Co Ltd.</th>
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<tbody>
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<td>Unit number</td>
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| Production Block                          | • Workshop 101 - Building W32, W19 and W47 for TMP  
|                                           | • Workshop 102 - Building E04, E07, E05, E06 and E03 for SMZ |
| Physical address                          | North-East of Dongwaihuan Road, Dongcheng Industrial Area, Shouguang City, Shandong, China |
| Postal Address                            | Same as above                                 |
| Contact person and email address.         | Mr. Li Hongcheng                             |
|                                           | export@shouguangpharm.com                    |
| Dates of inspection                       | 2 to 5 February 2015                         |
| Type of inspection                        | Initial inspection (New site)                |
| Active Pharmaceutical Ingredient(s)       | Trimethoprim (API for FPP)                   |
| included in the inspection                | Sulfamethoxazole (API for FPP)               |
| Summary of the activities performed by the manufacturer | Production, quality control and storage of intermediates, APIs and finished pharmaceutical products |
Part 2: Summary

General information about the company and site

Shouguang Fukang Pharmaceutical Co., Ltd. was established in 1993. It is located at North-East of Dongwaihuan Road, Dongcheng Industrial Area, 262700, Shouguang City, Shandong Province of China. The whole site occupies an area of approximately 508,500 m² including workshops for API and FPP manufacturing. The site was divided into east and west parts by a road. Approximately 1200 staff was employed at the site at the time of the inspection.

Shouguang Fukang Company manufactures a range of APIs, but no betalactams, steroids or hormones. A limited range of formulations (tablets and pellets) are also manufactured at this site. The main products manufactured on the site include Trimethoprim (TMP), Sulfamethoxazole (SMZ), Omeprazole, Metformin HCl, Itrazonazole, Clozapine, Vildagliptin and Dutasteride Clozapine Tablets, Omeprazole pellets etc. The API facilities included dedicated blocks (synthesis, purification and finishing) for SMZ and TMP APIs.

The above mentioned two APIs were produced as the following different grades of APIs, each grade using the same processes. There was a code number system to differentiate the different grades:

TMP: CP, EP, BP, USP with three manufacturing steps.
     Production Block: Workshop 101
     Micronisation might be applied subject customer’s request.

SMZ: CP, EP, BP, USP with five manufacturing steps.
     Production Block: Workshop 102,

No computer system was used in production and quality control.

History of WHO and/or regulatory agency inspections

This was the first inspection conducted by WHO PQP. The site had been licensed by the Local Food and Drugs Administration, and had also been inspected and approved by USFDA (2011 and 2014), Poland FDA (2012) and TGA (2014). However the inspection scope in terms of facilities and products did not fully overlap the WHO inspection scope.

Focus of the inspection

The inspection focused on the production and control of Trimethoprim and Sulfamethoxazole APIs. The inspection covered most of the sections of WHO GMP for Active Pharmaceutical Ingredients, including Quality Management; Personnel; Buildings and Facilities; Process Equipment; Documentation and Records; Materials Management; Production and In-Process Controls; Packaging and Identification Labelling of APIs and Intermediates; Storage and Distribution; Laboratory Controls; Validation; Change Control; Rejection and Reuse of Materials and Complaints and Recalls.
**Areas inspected**

The inspection covered the following areas according to an inspection plan sent to the company in advance and modified as necessary:

**Opening meeting**
**Scope of inspection**
**Overview of activities at site**

**Facility tour:**
- Warehouses: solid and liquid raw materials, tank farm, finished APIs, packaging materials.
- Workshop 101 Production including finishing and packaging
- Workshop 102 Production including finishing and packaging
- Purified water system
- HAVC (TMP)
- QC Laboratory: Chemical and Physical Lab - Sampling and sample handling, work allocation, specifications and test methods, SOPs, logbooks, records, worksheets and test reports, stability program, OOS results, evaluation of results, release and rejection procedures, chemicals and reagents, reference standards, retention samples, equipment, instruments and devices, microbiology Lab – Facility, media preparation, test procedures and results, OOS

**Document review:**
- Quality Risk Management
- Product Quality Reviews (PQR)
- Change Control
- Deviations
- Complaints
- Recalls
- Supplier approval
- Reprocessing and reworking
- Out of Specification Results
- Self-inspections
- Validation master plan
- Process validation
- Cleaning validation,
- Equipment qualification
- Engineering Preventive maintenance
- Review of batch documents
- Batch manufacturing Records
- Batch Release

**2.1. QUALITY MANAGEMENT**

The quality management system was generally well established, documented and implemented. The site organizational structure was reviewed and was acceptable.
Quality-related activities were defined and documented. The Quality Assurance department was independent from production. The persons authorized to release intermediates and APIs were specified.

**Product quality review (PQR)**
PQRs were conducted on an annual basis according to a documented SOP. The 2013 PQRs for TMP API as well as SMZ API were reviewed. The required elements had been considered and documented. Preparation of the 2014 PQRs were still in progress at the time of inspection.

**TMP PQR 2013**
Product code: A-001. For starting materials, different suppliers used the same material code, and the different codes are used for different grades of the finished APIs. No OOS, no recall, two deviations, reprocessing and reworking, one change. Long term stability study condition 25°C/60% and, starting from August 2014, 30°C/75% RH had been added into the stability study. Purified water system was used for TMP production. The purified water met CP and EP specifications.

**SMZ PQR 2013**
Product code: A-002. There was one major deviation and three changes. There had been no OOS, no recall, and one batch reprocessed.

The codes for different grades of SMZ API were:
1 for CP, 2 for EP, 3 for USP, 4 for BP

**Quality Risk Management**
QRM was conducted according to SOP and covered all aspects of API production. Responsibilities were clearly defined and the SOP included an organization chart for this activity. Various forms were attached to the SOP and included one for listing all processes and locations for a particular API and a separate form for listing all documents associated with a particular API processes. The approach described in the above mentioned SOP included fishbone analysis to identify potential risks and an FMEA model to analyze and quantify the risks and reassess them after any action was taken. Probability, severity and detectability were quantified on a scale of 5 with guidance for each level.

QRM reports for TMP and SMZ storage and for clean area processing and cleaning were selected for review, and were generally satisfactory.

**Out of specifications (OOS)**
The general OOS procedure, 2014 OOS log book and OOS records were reviewed. An OOS investigation was reviewed and discussed.

**Deviations**
Deviations were handled according to SOP and covered unplanned deviations only. A deviation example regarding the crystal size was reviewed. The corrective and
preventive actions had been conducted according to the CAPA procedure and considered acceptable.

**Internal Audit (self-inspection)**
Internal audits were performed according to SOP with responsibility for this activity stated as being the Quality Department Manager. Checklists were used with a clear decision regarding comply/non-comply required for each item reviewed. After each internal audit a non-compliance report was required to be issued and any action required handled through the CAPA system.

The internal audit plan for 2015 was reviewed and various dates in July had been allocated to the various areas for inspection. Workshops 101 and 102 had been included. Although detailed records of findings were not reviewed, the system for allocating responsibility for corrective actions and tracking progress to established target completion dates was reviewed and found satisfactory.

**2.2 PERSONNEL**

**Personnel qualifications**
According to the SMF, key personnel were suitably qualified with appropriate tertiary qualifications and experience in the manufacture of APIs and pharmaceutical products.

**Training**
Training was conducted according to the procedures in the SOP. As an example of training and the records maintained, the job description and Annual training plan for 2015 were reviewed. The acceptance criterion for assessing training effectiveness was in place.

**Personnel Hygiene**
Requirements for entry to manufacturing areas were documented with the level and type of protective clothing required dependent on the nature of the API and step of manufacture. Adequate change rooms were provided for entry into Grade D manufacturing areas with hand washing facilities provided.

**2.3 BUILDINGS AND FACILITIES**

**Design and construction**
The design and interior finishes of the two workshops visited were suitable for API production and packaging. The inspected workshops and facilities dedicated to the manufacture of TMP and SMZ APIs were clean and maintained to an acceptable level. The final purification and packaging took place in a clean area with a Grade D environment. Entry to the clean area of manufacturing and packaging areas was through appropriate change rooms.

The following facilities were inspected:
- TMP: Workshop 101 including Building W32, W19 and W47
- SMZ : Workshop 102 including Building E04, E07, E05, E06 and E03
- Purified Water System: at ground floor of Workshop 101
- Solvent recovery plant

Utilities
The HVAC system was dedicated in the workshops 101 and 102 respectively with G4, F8 and terminal HEPA filtration. The HVAC system appeared clean and well maintained.

Compressed air was appropriately controlled and the system included a 0.22µ filter. Compressed air was tested every 3 months, including for particulates, moisture, oil and microbiology.

Water
There were three purified water stations on the site. Purified Water was used as a solvent in different manufacturing steps including the last stages of the processes.

Purified water was produced by double RO with 2000, 5000 and 10000l/hr capacities. Distribution was through a SS loop at ambient temperature. The system was regularly sanitized by heating circulating water to >80°C by steam heat exchangers. Sampling points were identified throughout the system. Records of monitoring were reviewed and indicated that the system was under good control.

Lighting
Lighting in all areas visited was appeared to be adequate.

Sanitisation and maintenance
All manufacturing areas visited appeared to be well maintained and clean in general. Cleaning and sanitization were performed according to documented procedures using materials approved by QA. Records were maintained.

Containment
As claimed by the company, there were no penicillin, cephalosporin or other highly sensitizing materials or APIs of high pharmacological activity (such as steroids or cytotoxic) produced or handled at the site.

2.4 PROCESS EQUIPMENT
Design and construction
Equipment used for the APIs within the scope of the inspection was generally of a good standard and suitable for intended use. The equipment used for manufacturing TMP and SMZ were dedicated.

Equipment maintenance and cleaning
Equipment was maintained by the engineering department according to a written SOP. Equipment was classified into 3 levels depending on maintenance requirements and risk. A schedule of equipment requiring maintenance and requirements for each equipment was documented.
The schedule for 2015, procedures and records for selected sample of equipment were reviewed. These were generally acceptable.

**Calibration**
Where necessary, measuring equipment was labelled with a calibration tag. All of those reviewed indicated that the calibration was within date. The system appeared to be working effectively.

### 2.5 DOCUMENTATION AND RECORDS

**Documentation system and specifications**
Documents were prepared and approved according to SOP. This SOP described the format to be used and requirements for review and approval. A distribution list was maintained with signature of the recipient details of recall or return.

The SOP required documents to be kept up to date and formally reviewed every 5 years. Batch production records were required to be issued according to SOP.

The sample of documents reviewed during the inspection indicated that the documentation system was working effectively.

**Equipment cleaning and use record**
SOPs for cleaning each type of equipment were available and suitable records were maintained. There was a usage log book for each major piece of equipment and the sample reviewed was up to date and satisfactory.

**Records of raw materials, intermediates, API labeling and packaging materials**
All records reviewed relating to materials, including intermediates and APIs were acceptable.

**Master production instruction (master production and control records)**
Master production batch records for each API were available. These were photocopied for use in batch manufacturing. Similarly there were master QC worksheets that were photocopied in the lab for use in batch testing.

**Batch production records (batch production and control records)**
The approved master formula of the inspected API’s were checked and compared to the ones used in practice. The in-process BMRs and the completed BMRs reviewed had been properly completed and were acceptable.

**Laboratory control records**
The in-process QC records and the completed QC records reviewed had been properly completed and were generally acceptable.

### 2.6 MATERIALS MANAGEMENT
General controls
Suppliers of materials were required to be approved according to SOP. The approval process included a questionnaire, a sample for trial and analysis, and an audit of critical suppliers. An annual audit schedule was available. Critical suppliers were required to be re-evaluated on a regular basis. An audit report for a raw material was reviewed. The quality agreement with a raw material supplier was reviewed.

Receipt and quarantine
Starting materials were received and quarantined according to SOP. There was a quarantine area for starting materials on site. Although not for long term storage, the construction material for this area was sheet metal only. The starting materials were classified as GMP and non-GMP types.

Sampling and testing of incoming production materials
Sampling of starting materials was performed by QC personnel according to a documented sampling plan. Appropriate environmentally controlled sampling areas were available in the warehouses.

2.7. PRODUCTION AND IN-PROCESS CONTROLS
Production of TMP and SMZ took place in dedicated and self-contained facilities.

Production operations
Production operations in Workshops 101 and 102 were reviewed and generally found acceptable. Most reactors and material tanks were labelled with the batch in progress in general and the associated batch documentation was up to date.

Time limits
Time limits were specified in the BMR where necessary.

In-process sampling and controls
In-process sampling and testing was conducted as specified in the relevant BMR. IP tests were either conducted in the IPC lab close to workshop 102, or sent to the central QC lab, depending on the test to be performed.

2.8 PACKAGING AND IDENTIFICATION LABELLING of APIs AND INTERMEDIATES
Packaging materials
Packaging materials were purchased from approved suppliers and placed in quarantine before sampling, testing and release by QC. The storage and labelling of these materials was acceptable.

Packaging and labeling operations
Packaging and labelling was performed in areas dedicated for this purpose. These areas were appropriately designed and classified as Grade D. There was a documented line clearance check before packaging and labelling operations commenced.

2.9 STORAGE AND DISTRIBUTION
Warehousing procedures
Starting materials and APIs were stored in temperature monitored but not controlled areas. A risk assessment had been conducted for storage of these materials and included the worst case hottest months (July, August and September). This assessment concluded that any risk to the type of materials stored, was acceptable and no further action was required. Packaging materials were stored in segregated areas with appropriate labelling and controls.

2.10 LABORATORY CONTROLS

General controls
The company had an organized and suitably equipped QC laboratory. Equipment included HPLC, GC and other testing instruments.

Testing of intermediates and APIs
QC testing was conducted as specified in the relevant specification and according to documented test methods. The sample receiving and distribution log book was checked. Samples for testing were kept in a designated area.

Primary pharmacopoeial reference standards were available and working standards prepared according to a SOP.

A Waters HPLC was used for RS testing of EU grade TMP and SMZ APIs. The computer access control, authorization of the functions and testing method validation were checked during the inspection.

Stability monitoring of APIs
A range of stability chambers were available. Following initial stability studies to determine re-test date; at least one batch of API per year was required to be placed on on-going stability study. The records for stability samples in the chambers were available for review.

Reserve/retention samples
There was a designated temperature controlled area for storage of retention samples. Access to this area was restricted. A sample of each batch of API manufactured was kept. Retention samples were stored in container systems that were comprised of the same materials as those used for the final API.

Handling of out of specification (OOS) results
The OOS/OOT handling procedure was reviewed and discussed. For an example reviewed a CAPA had been made and appeared to be acceptable.

Microbiology labs
There was no microbiological limit in the product specifications of TMP and SMZ APIs. Media preparation and testing procedure for PW were reviewed.
12. VALIDATION

Validation policy
The company’s validation policy was described in a Validation Master Plan. Responsibilities were well defined and an annual validation plan was required to be prepared. Various types of validation were described with guidance on when each should be used.

Qualification
Requirements for the qualification of equipment and utilities were included in the abovementioned Validation Master Plan. Periodic requalification was required, depending on criticality.

Process validation programme
The 2015 validation plan as relevant to TMP and SMZ was reviewed and appeared to be satisfactory. This showed the recent history of validation, current status and the due date for re-validation.

Process validation for the production of SMZ was reviewed and had been conducted according to Protocol. The conclusion was based on a summary report of the 8 batches and had been approved by all relevant personnel.

Cleaning validation
Requirements for cleaning validation were adequately described in the above mentioned VMP and were applicable to any equipment in direct contact with product. Acceptable limits were described, including guidance on a MACO calculation as well as a maximum carry over limit of 10ppm. Microbiological limits had also been established at max 10cfu/10cm² by swab method. Swab recovery was also required.

Cleaning validation and the report for TMP was reviewed. Equipment cleaning procedures were cross-referenced and there was a diagram for each piece of product contact equipment showing the hardest to clean area and total product contact surface area. Swab recovery had been determined and the analytical methods used had been validated for LOD, precision, linearity and range. The study appeared to have been appropriately done and all results were within specified limits.

2.12 CHANGE CONTROL

There was a procedure for change control. A change control register and records were maintained. The change control register 2014 was reviewed. A major change for SMZ process and equipment was reviewed.

The SOP for handling Deviations and the CAPA procedure were reviewed. A deviation reviewed was acceptable in general.
2.13 REJECTION AND RE-USE OF MATERIALS

Rejection
There were locked dedicated areas in the warehouses for rejected materials. They were empty at the time of inspection.

Reprocessing
Reprocessing was controlled according to SOP. Any reprocessing had to be approved by the Quality Department and by the QP before implementation. A form was used to record and obtain approval for reprocessing. Completed forms were filed by the Quality Department and a copy said to be filed in the relevant BPR, however this was not specified in the above SOP.

Reworking
Rework was not permitted by the company.

Recovery of materials and solvents
Solvents and other chemicals used in TMP or SMZ production were recovered, with the process included in the BMR. It was collected in separate storage tanks and a sample tested by the QC lab before approval. Recovered materials and solvents were only used in the same step of production.

2.14 COMPLAINTS AND RECALLS

Complaints were handled according to SOP. The Quality Department was responsible for entering complaints in a register, allocating a reference number and instigating investigations. Complaints were required to be classified according to risk and a complaint form was used to record the complaint and subsequent processing by the company. The records relating to two complaints about TMP API were reviewed and considered acceptable.

Recalls were required to be handled according to SOP. Three levels of recall were described timeframes for notifying customers and regulatory authorities specified. A mock recall had been carried out in March 2014. There had been no recalls of TMP or SMZ APIs.

2.15 CONTRACT MANUFACTURERS (INCLUDING LABORATORIES)
No manufacturing and testing activity is outsourced for the inspected APIs.

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, APIs of Trimethoprim and Sulfamethoxazole manufactured at Shouguang Fukang Pharmaceutical Co Ltd located at North-East of Dongwaihuan Road, Dongcheng Industrial Area, Shouguang City, Shandong, China were considered to be manufactured in compliance with WHO GMP for Active Pharmaceutical Ingredients.
All the non-compliances observed during the inspection that were listed in the full report as well as those reflected in the WHOPIR, were addressed by the manufacturer, to a satisfactory level, prior to the publication of the WHOPIR.

This WHOPIR will remain valid for 3 years, provided that the outcome of any inspection conducted during this period is positive.