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Prequalification Team Inspection services
WHO PUBLIC INSPECTION REPORT
of the Active Pharmaceutical Ingredient (API) Manufacturer

Part 1	**General information**
Manufacturers Details	
Company information	
Name of manufacturer and address	Chongqing Holley Wuling Mountain Pharmaceutical Co., Ltd 108 Southern Jinyuan Road, Banxi Light Industry Area, Youyang City, Chongqing, China Post code: 409800 North latitude: 28.725574 East Longitude: 108.8159
Corporate address of manufacturer	Corporate office address: 108 Southern Jinyuan Roud, Banxi Light Industry Area, Youyang City, Chongqing, China. Tel number: +86-23-7558 0288 Fax number: +86-23-64755388
Inspected site	
Address of inspected manufacturing site if different from that given above	As above
Manufacturing buildings	Building No 1 Building No 2
Manufacturing license number	YU20150012, valid until December 21, 2020, issued by Chongqing Food and Drug Administration on July 11, 2017
Inspection details	
Type of inspection	Routine
Dates of inspection	06 – 09 March 2018
Introduction	
Brief summary of the manufacturing activities	The manufacturer is involved in manufacturing, packaging, labelling, testing and storage of plant derived intermediates and active pharmaceutical ingredients (APIs) and non-sterile products – liquid dosage forms
General information	Chongqing Holley Wuling Mountain Pharmaceutical Co., Ltd was established in 1986 and was acquired by Holley Group in year 2000.

<table>
<tr><td>about the company and site</td><td>The manufacturing site was initially built in Zhongduo town of Youyang. It gained Chinese GMP certificate and was accepted by WHO inspection for compliance with WHO GMP in 2005 and 2010.

Relocation works started in August 2011. New site had been gained Chinese GMP certificate and was accepted by WHO inspection for compliance with WHO GMP in 2015.

Chongqing Holley is a member of the Pharmaceutical Division of the Holley Group of companies. This group comprised Several companies.</td></tr>
<tr><td>History</td><td>The site was inspected by WHO:
April 2014
December 2014
The site was also inspected by the following authorities:<table><tr><th>Authority</th><th>Dates of inspection</th><th>Inspection outcome</th></tr><tr><td>Chongqing FDA</td><td>July 22, 2013</td><td>Compliance</td></tr><tr><td>Chongqing FDA</td><td>March 11, 2014</td><td>Compliance</td></tr></table></td></tr>
<tr><td>Brief report of inspection activities undertaken</td><td></td></tr>
<tr><td>Scope and limitations</td><td></td></tr>
<tr><td>Areas inspected</td><td>Pharmaceutical Quality System
Documentation system
Production System
Facilities and Equipment System
Laboratory Control System</td></tr>
<tr><td>Restrictions</td><td>Inspection focused only at manufacture and quality control of prequalified API used for malaria treatment</td></tr>
<tr><td>Abbreviations</td><td><table><tr><td>AHU</td><td>air handling unit</td></tr><tr><td>ALCOA</td><td>attributable, legible, contemporaneous, original and accurate</td></tr><tr><td>AQL</td><td>Acceptance quality limit</td></tr><tr><td>API</td><td>active pharmaceutical ingredient</td></tr><tr><td>APQR</td><td>annual product quality review</td></tr><tr><td>BDL</td><td>below detection limit</td></tr><tr><td>BMR</td><td>batch manufacturing record</td></tr><tr><td>BPR</td><td>batch packaging record</td></tr><tr><td>CAPA</td><td>corrective actions and preventive actions</td></tr><tr><td>CC</td><td>change control</td></tr><tr><td>CFU</td><td>colony-forming unit</td></tr><tr><td>CoA</td><td>certificate of analysis</td></tr><tr><td>CpK</td><td>process capability index</td></tr></table></td></tr>
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DQ	design qualification
EM	environmental monitoring
FAT	factory acceptance test
FBD	fluid bed dryer
FG	finished goods
FMEA	failure modes and effects analysis
FPP	finished pharmaceutical product
FTA	fault tree analysis
FTIR	Fourier transform infrared spectrometer
GC	gas chromatograph
GMP	good manufacturing practice
HACCP	hazard analysis and critical control points
HPLC	high-performance liquid chromatograph
HVAC	heating, ventilation and air conditioning
ID	identity
IR	infrared spectrophotometer
IPC	In process control
IQ	installation qualification
KF	Karl Fisher
LAF	laminar air flow
LIMS	laboratory information management system
LoD	limit of detection
LOD	loss on drying
MACO	maximum allowable carry over
MB	Microbiology
MBL	microbiology laboratory
MF	master formulae
MR	management review
NIR	near-infrared spectroscopy
NMR	nuclear magnetic resonance spectroscopy
NRA	national regulatory agency
OQ	operational qualification
PHA	preliminary hazard analysis
PM	preventive maintenance
PpK	process performance index
PQ	performance qualification
PQR	product quality review
PQS	pharmaceutical quality system
PW	purified water
QA	quality assurance
QC	quality control
QCL	quality control laboratory
QMS	Quality management system
QRM	quality risk management

RA	risk assessment
RCA	root cause analysis
RH	relative humidity
RM	raw materials
RS	reference standard
SAP	system applications products for data processing
SFG	semi-finished goods
SOP	standard operating procedure
STP	standard test procedure
T	Temperature
TAMC	total aerobic microbial count
TFC	total fungal count
TLC	thin layer chromatography
TMC	total microbial count
TOC	Total organic carbon
URS	user requirements specifications
UV	ultraviolet-visible spectrophotometer
VMP	Validation Master Plan
WFI	water for injection
WS	working standard

Part 2	**Brief summary of the findings and comments**

1. Pharmaceutical quality system

The quality management system is generally established and documented; the system encompassed organizational structure, procedures and processes. QA and QC departments were independent of production. In general, deviations from established procedures were documented and explained. A procedure was in place for notifying responsible management of regulatory inspections, serious GMP deficiencies, product defects and related actions.

Data integrity

SOP "Data Control Management Procedure" was briefly discussed. SOP explained ALCOA and ALCOA + principles. List of persons trained on SOP was presented to the inspectors.

Management review (MR)

SOP "Quality Management Review" was briefly discussed. According to the SOP, MR meeting should be performed annually with the following items covered.

- Deviations
- Complaints
- Recalls
- Change controls, returns and rework/reprocessing
- Validation management
- Suppliers
- GMP audits

- APQR
- QRM
- Documentation
- Training
- Quality targets
- Regulation and law update
- Outside environment
- Product quality
- Production compliance to GMP

Product Quality Review (PQR)

SOP "Annual Product Review procedure" was briefly discussed. The PQR covered:

- Critical Process parameter
- Deviations investigation
- Changes
- Product recalls
- Customer complaints, including quality complaints and adverse event complaints
- Rejected, partially released, discussed and reprocessed lots
- Events related to regulatory
- Change controls
- Validation review
- Follow up of previous PQR
- Stability data
- Contract production and analysis
- Technical agreements
- OOS investigations
- Materials quality
- In-process control data
- Specifications and test methods
- Yield
- Equipment maintenance, calibration and performance
- Water system trends
- HVAC system trends
- Returns
- Suppliers
- Product quality agreements (suppliers)

According to the SOP the PQR should be prepared from 1st Jan to 31st December and shall be completed by the end of March of the following year.

APR for XXX was briefly discussed.

Quality risk management (QRM)

SOP "Quality Risk management" was briefly discussed. RA was applicable for product lifecycle. The SOP identified the following tools for RA review:

- Flow chart
- Check list
- HACCP
- HAZOP
- FMEA

According to the company, FMEA was mainly used. Scoring from 1 to 3 was used with RAs checked annually when performing PQR.

Before Quality Risk Assessments were performed Severalreports were made on the basis of FMEA assessments. Reports were briefly discussed.

Several RAs were presented to the inspectors.

Deviations (Incidents)

SOP "Deviation investigation procedure", flow chart and log sheet were briefly discussed. Deviations were classified as:

- Unplanned deviations
- Serious errors
- Major deviations
- Minor deviations

According to the SOP CAPAs were classified as:

- Class A – actions that must be completed and documented prior the closure of investigation closure
- Class B - actions that do not be completed and documented prior the closure of investigation closure
- Class C – action that requites longest time to implement and does not require completion prior to further processing.

According to the SOP on deviations a monthly report should be prepared at the beginning of each month and trending should be done annually. Deviation monthly and annually reports were presented to the inspectors.

Several deviation investigation reports were briefly discussed.

Corrective actions and preventive actions

SOP "Corrective actions and preventive actions" was briefly discussed. Scope of the document was:

- Product design control
- Process control
- Material management
- Facility and equipment management
- Employees
- Documentation
- Records
- Change control

- Returns
- Internal/external audits
- OOS
- Complaints

Root cause analysis (RCA)
SOP "Root cause analysis" was briefly discussed. According to the SOP RCA should be performed using the following tools:

- 5 WHYs
- Brainstorming
- Ishikawa diagram
- FAT

Change control (CC)
SOP Change control was briefly discussed. The log sheets of change controls did not mention if a change was "Major" or "Minor". Trending of these categories was not possible on the basis of the log sheets. Management of open changes was weak.

Several CCs were briefly discussed.

Complaints
SOP "Complaints" and complaints register for 2017 were briefly discussed. There were no complaints registered in 2016 and only one complaint registered in 2017. A complaint XX investigation report was briefly discussed.

Recalls
SOP "Recall" was briefly discussed. No product recalls were recorded. Recalls were classified as:

- Class I –initiated within 24 hours
- Class II - initiated within 48 hours
- Class III - initiated within 72 hours

SOP specified that in the event of a serious or potentially life-threatening situation CFDA should be informed. Recall effectiveness was evaluated every year for domestic market.

Self-inspection
SOP "Internal audit" was briefly discussed. According to the SOP conflict of interests should be avoided – only individuals who have no direct responsibility for the matters to be audited shall conduct the audit. According to the SOP, a 5-system audit should be performed twice a year. Audit report was drafted by an audit team. Observations were classified as critical, major and other. Internal audit report dated.

Supplier qualification

SOP "Supplier Management Process", flow chart and approved suppliers list were briefly discussed. Material suppliers were categorized on three levels:

- Level A – directly affect product quality; starting materials for APIs
- Level B – indirectly affect product quality; solvents, some packaging materials
- Level C – do not affect product quality

Personnel

Current organization chart of the company was available. Personnel were wearing suitable clothing applicable to the manufacturing activities.

According to the SMF and company presentation, the site employed approximately 152 full time employees.

SOP "Department Training Procedure" was briefly discussed. Several types of training were identified:

- Orientation training
- Training for newly promoted or transferred employees
- Retraining
- External training
- General GMP training plan

Training effectiveness was evaluated by written assessment and performance observation/verification.

2. Documentation system

Documentation system was generally established. Documents related to the manufacture of intermediates and APIs were prepared, discussed, approved and distributed according to written procedures. The issuance, revision, superseding and withdrawal of documents were controlled with maintenance of revision histories. Specifications were established for raw materials, intermediates and APIs.

SOP "Production planning and packaging instructions" was briefly discussed. SOP also described the batch numbering system.

SOP "Batch production record issuance, review and approval" was briefly discussed. Check list was used for batch production record and analytical test report review. According to the SOP QA manager was responsible to verify according to the check list that batch production and packaging instructions were followed and that analytical raw data was complete, true and traceable. SOP also explained blending of batches. The expiry of the blended batch was based on the manufacturing date of the oldest batch in the blend.

SOP "Laboratory testing" was briefly discussed. According to the SOP QC manager was responsible for review and approval of analytical test reports/results including audit trails for every batch. To perform manual integration the analyst should request written permission from QA. Back-up of electronic data was done every 3 months. Back-up was done on hard discs which were stored in QC office. According to the SOP a check on readability of the data should be performed every time when additional data was stored on hard disc.

SOP "HPLC operation and maintenance" was briefly discussed.

SOP "Returned or exchanged products management procedure" and the returned product register were briefly discussed. Returned products were placed in returned products storage room and quarantined.

SOP "GMP related Documentation Retention and Destruction" was briefly discussed.
Some documents, i.e. product Specifications and Batch Records were retained for the product life cycle + 1 year. Production, control and distribution records were retained for 7 years (re-test dates for APIs were 3 years).

3. Production system
In general, production operations followed defined procedures. Process flows (with IPCs) and routes of synthesis were available. Deviations from procedures were recorded; major deviations were investigated.

Process Validation report XX and cleaning validation report ZZ were briefly discussed.

Reprocessing and Reworking
SOP "API re-processing and re-working" was briefly discussed. The company claimed no reworks performed on any APIs.

Recovery of solvents
SOP "Recovery of solvents" was briefly discussed. Recovery of solvents was recorded. According to the SOP recovered solvents specifications should be the same as fresh solvents specifications. Recovery of solvents was recorded. Recovered Ethanol and fresh Ethanol specifications were compared; comparison showed the specifications were the same.

Validation Master Plan
Validation Master Plan for 2018 was briefly discussed.

4. Facilities and equipment system
Facilities were designed to minimize potential contamination. Adequate space was provided for orderly placement of equipment and materials to prevent mix-ups and contamination. Permanently installed pipework was not appropriately identified. Buildings were constructed of masonry with finishes appropriate to the activities carried out.

A list of equipment was presented to the inspectors.

Equipment maintenance was done according to an annual maintenance plan, which was annexed to SOP. Trending of maintenance and repairs was done for individual equipment in the respective APRs.

A tour was made of the production and storage facilities. Warehouses 1, 2, 3 and 4 and manufacturing buildings 1 and 2 were inspected.

Temperature mapping was seen for the 2 - 8ºC warehouses. The study was well designed.

Building #1 and #2 were inspected. No production was occurring during the time of the inspection. The layout was clear, and tanks were all marked with ID numbers.

Laboratory instruments
The laboratories for GC and HPLC analysis were visited. Calibration of the GCs was done according to SOP. Calibration was done yearly. Calibration certificates were seen and found in order.

Utilities
These were not covered during this inspection.

Laboratory premises
Laboratory areas and operations were separated from production areas. Microbiological laboratory premises were separated from the QC laboratory. The room with stability chambers had a 2 - 8ºC chamber for real-time studies and a 20 - 25ºC chamber for accelerated studies. The chambers were fitted with an alarm system linked to a text messages system.

5. Laboratory control system

SOP "Sampling Management" was briefly discussed. SOP was applicable for raw materials packaging materials, intermediates, API, finished product and PW sampling.

Out of specification (OOS)
SOP "Investigation of out of Specification Result" was briefly discussed. SOP was applicable to all OOS results from microbiological, physical and chemical tests conducted by laboratory.

Several OOS investigation reports were briefly discussed.

Stability studies
SOP "Stability studies management" was briefly discussed. Window period was specified plus 7 days. On-going stability studies were in place. Several stability study reports were briefly discussed.

Reference standards
SOP "Reference standards" was briefly discussed. Working standards (WS) were standardized against Pharmacopoeia standards and dispensed in 12 vials under LAF. One vial was used within one month.

Retention samples
SOP "Sample management" was briefly discussed. Starting materials and APIs retention samples were stored retest date + two years. APIs retention samples were stored in the same packaging system in which the APIs were stored.

Environmental monitoring (EM)
SOP "Environmental monitoring of clean area" was briefly discussed. Settle plate method and active air sampling was used. Settle plates were exposed for 4 hours. 4 hours exposure time was validated as recovery studies, recovery rate was 70%. Trends were performed once per year.

Microbiological laboratory was not inspected.

6. Packaging and labelling system

Packaging of the final API was performed in the cleanrooms. Dust control was not available in the packaging rooms. Packaging operations were not carried out during the inspection.

Part 3

Conclusion – inspection outcome

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, Chongqing Holley Wuling Mountain Pharmaceutical Co., Ltd, located at 108 Southern Jinyuan Road, Banxi Light Industry Area, Youyang City, Chongqing, China was considered to be operating at an acceptable level of compliance with WHO good manufacturing practices for active pharmaceutical ingredients 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.

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

PART 4

List of GMP guidelines used for assessing compliance

1. WHO good manufacturing practices for active pharmaceutical ingredients. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth Report. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957), Annex 2.
   Short name: WHO TRS No. 957, Annex 2
   http://www.who.int/medicines/publications/44threport/en/

2. WHO good manufacturing practices for pharmaceutical products: main principles. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-eighth Report Geneva, World Health Organization, 2014 (WHO Technical Report Series, No. 986), Annex 2.
   http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_986/en/
   Short name: WHO TRS No. 986, Annex 2

3. WHO Good Manufacturing Practices: water for pharmaceutical use. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fourth-sixth Report. Geneva, World Health Organization, 2012 (WHO Technical Report Series, No. 970), Annex 2
   Short name: WHO TRS No. 970, Annex 2
   http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_970/en/

4. WHO guidelines for sampling of pharmaceutical products and related materials. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-ninth Report. Geneva, World Health Organization, 2005 (WHO Technical Report Series, No. 929), Annex 4
Short name: WHO TRS No. 929, Annex 4
http://whqlibdoc.who.int/trs/WHO_TRS_929_eng.pdf?ua=1

5. WHO guidelines on good manufacturing practices for heating, ventilation and air-conditioning systems for non-sterile pharmaceutical dosage forms. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 5
Short name: WHO TRS No. 961, Annex 5
http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

6. Supplementary guidelines on good manufacturing practices: validation. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fortieth Report. Geneva, World Health Organization, 2006 (WHO Technical Report Series, No. 937), Annex 4
Short name: WHO TRS No. 937, Annex 4
http://whqlibdoc.who.int/trs/WHO_TRS_937_eng.pdf?ua=1

7. WHO Good Practices for Pharmaceutical Control Laboratories. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth Report. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957, Annex 1
Short name: WHO TRS No. 957, Annex 1
http://www.who.int/medicines/publications/44threport/en/

8. WHO Good Practices for Pharmaceutical Products Containing Hazardous Substances. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth Report. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957), Annex 2
Short name: WHO TRS No. 957, Annex 3
http://www.who.int/medicines/publications/44threport/en/

9. WHO guidelines on transfer of technology in pharmaceutical manufacturing WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 7
Short name: WHO TRS No. 961, Annex 7
http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

10. Model guidance for the storage and transport of time-and temperature-sensitive pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 9
Short name: *WHO TRS No. 961, Annex* 9
http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

11. General guidelines for the establishment maintenance and distribution of chemical reference substances. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-first Report Geneva, World Health Organization 2007 (WHO Technical Report Series, No.943) Annex 3
Short name: WHO TRS No. 943, Annex 3
http://whqlibdoc.who.int/trs/WHO_TRS_943_eng.pdf?ua=1

12. WHO good practices for pharmaceutical microbiology laboratories. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 2
Short name: WHO TRS No. 961, Annex 2
http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

13. WHO guidelines on quality risk management. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-seventh Report Geneva, World Health Organization, 2013 (WHO Technical Report Series, No. 981), Annex 2
Short name: WHO TRS No. 981, Annex 2
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_981/en/

14. WHO guidelines for drafting a site master file. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 14
Short name: WHO TRS No. 961, Annex 14
http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

15. WHO General guidance on hold-time studies WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-ninth Report Geneva, World Health Organization, 2015 (WHO Technical Report Series, No. 992), Annex 4
Short name: WHO TRS No. 992, Annex 4
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf

16. WHO Technical supplements to Model Guidance for storage and transport of time – and temperature – sensitive pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-ninth Report Geneva, World Health Organization, 2015 (WHO Technical Report Series, No. 992), Annex 5
Short name: WHO TRS No. 992, Annex 5
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf

17. WHO Recommendations for quality requirements when plant – derived artemisin is used as a starting material in the prosecution of antimalarial active pharmaceutical ingredients. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-ninth Report Geneva, World Health Organization, 2015 (WHO Technical Report Series, No. 992), Annex 6
Short name: WHO TRS No. 992, Annex 6
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf

18. Guidance on good data and record management practices. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fiftieth Report Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 5
Short name: WHO TRS No. 996, Annex 5
http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex05.pdf