## Part I
### General information

<table>
<thead>
<tr>
<th>Manufacturers details</th>
<th></th>
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<tbody>
<tr>
<td>Company information</td>
<td></td>
</tr>
<tr>
<td>Name of manufacturer</td>
<td>Changzhou Yabang-QH Pharmachem Co. Ltd.</td>
</tr>
<tr>
<td>Corporate address of manufacturer</td>
<td>18 Jinlong Road, Chunjiang Town, Xinbei District, Changzhou, Jiangsu. P. R. China 213127</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Inspected site</th>
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<tbody>
<tr>
<td>Address of inspected manufacturing site if different from that given above</td>
<td>DUNS 527929456</td>
</tr>
<tr>
<td></td>
<td>Latitude 31.9744N</td>
</tr>
<tr>
<td></td>
<td>Longitude 119.9663E</td>
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</tbody>
</table>

| Unit / block / workshop number | Plant 1, |
|-------------------------------| Plant 3 Line 1 and |
| | Plant 3 Line 2 |

<table>
<thead>
<tr>
<th>Inspection details</th>
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<tbody>
<tr>
<td>Dates of inspection</td>
<td>4 to 7 July 2016</td>
</tr>
<tr>
<td>Type of inspection</td>
<td>Routine</td>
</tr>
</tbody>
</table>

### Introduction

<table>
<thead>
<tr>
<th>Brief summary of the manufacturing activities</th>
<th>Manufacture of APIs and API intermediates for human and veterinary use.</th>
</tr>
</thead>
</table>

| General information about the company and site | The company was established in 2004 to make anthelmintic APIs. Products at the time of the inspection were anthelmintic and antifungal APIs and high value intermediates. |

### History

<table>
<thead>
<tr>
<th>Previous WHO Inspection 16th to 18th September 2013</th>
<th>EDQM 20th to 22nd April 2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>CFDA 24th to 25th March 2014</td>
<td>CFDA 24th to 26th March 2016</td>
</tr>
<tr>
<td>Ministry of Agriculture 10th to 11th June 2015.</td>
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### Brief report of inspection

This inspection report is the property of the WHO
Contact: prequalinspection@who.int
<table>
<thead>
<tr>
<th>activities undertaken</th>
<th></th>
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<tbody>
<tr>
<td><strong>Scope and limitations</strong></td>
<td></td>
</tr>
</tbody>
</table>
| **Areas inspected** | • 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  
  • Complaints and recalls  
  • Contract manufacturers (including laboratories) |
| Site visit: | Warehousing, (solids RMs, tank farm, Finished Goods, Packing Materials, Production Cartridge Filters, Maintenance Spares), Plant 1 and Plant 3, Purified Water System (Plant 1 and plant 3), QC labs |
| **Restrictions** | NA |
| **Out of scope** | Plants 2 & 5 were outside the scope of the inspection. |
| **WHO product numbers covered by the inspection** | Mebendazole API (APIMF 220) |

<table>
<thead>
<tr>
<th>Abbreviations</th>
<th>Description</th>
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<tbody>
<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>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>
<tr>
<td>DQ</td>
<td>design qualification</td>
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</table>

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<table>
<thead>
<tr>
<th>Acronym</th>
<th>Definition</th>
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<tbody>
<tr>
<td>EM</td>
<td>environmental monitoring</td>
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<tr>
<td>FAT</td>
<td>factory acceptance test</td>
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<tr>
<td>FBD</td>
<td>fluid bed dryer</td>
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<tr>
<td>FMEA</td>
<td>failure modes and effects analysis</td>
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<tr>
<td>FPP</td>
<td>finished pharmaceutical product</td>
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<tr>
<td>FTA</td>
<td>fault tree analysis</td>
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<tr>
<td>FTIR</td>
<td>Fourier transform infrared spectrometer</td>
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<td>GC</td>
<td>gas chromatograph</td>
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<td>GMP</td>
<td>good manufacturing practice</td>
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<td>HACCP</td>
<td>hazard analysis and critical control points</td>
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<td>HPLC</td>
<td>high-performance liquid chromatograph</td>
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<tr>
<td>HVAC</td>
<td>heating, ventilation and air conditioning</td>
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<tr>
<td>IR</td>
<td>infrared spectrophotometer</td>
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<tr>
<td>IQ</td>
<td>installation qualification</td>
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<tr>
<td>KF</td>
<td>Karl Fisher</td>
</tr>
<tr>
<td>LAF</td>
<td>laminar air flow</td>
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<tr>
<td>LIMS</td>
<td>laboratory information management system</td>
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<tr>
<td>LoD</td>
<td>limit of detection</td>
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<tr>
<td>LOD</td>
<td>loss on drying</td>
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<tr>
<td>MB</td>
<td>microbiology</td>
</tr>
<tr>
<td>MBL</td>
<td>microbiology laboratory</td>
</tr>
<tr>
<td>MF</td>
<td>master formulae</td>
</tr>
<tr>
<td>MR</td>
<td>management review</td>
</tr>
<tr>
<td>NMR</td>
<td>nuclear magnetic resonance spectroscopy</td>
</tr>
<tr>
<td>NRA</td>
<td>national regulatory agency</td>
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<tr>
<td>OQ</td>
<td>operational qualification</td>
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<tr>
<td>PHA</td>
<td>process hazard analysis</td>
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<tr>
<td>PM</td>
<td>preventive maintenance</td>
</tr>
<tr>
<td>PpK</td>
<td>process performance index</td>
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<tr>
<td>PQ</td>
<td>performance qualification</td>
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<tr>
<td>PQR</td>
<td>product quality review</td>
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<tr>
<td>PQS</td>
<td>pharmaceutical quality system</td>
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<tr>
<td>QA</td>
<td>quality assurance</td>
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<tr>
<td>QC</td>
<td>quality control</td>
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<tr>
<td>QCL</td>
<td>quality control laboratory</td>
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<tr>
<td>QRM</td>
<td>quality risk management</td>
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<tr>
<td>RA</td>
<td>risk assessment</td>
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<tr>
<td>RCA</td>
<td>root cause analysis</td>
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<tr>
<td>SOP</td>
<td>standard operating procedure</td>
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<tr>
<td>TAMC</td>
<td>total aerobic microbial count</td>
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<tr>
<td>TFC</td>
<td>total fungi count</td>
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<tr>
<td>TLC</td>
<td>thin layer chromatography</td>
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<tr>
<td>URS</td>
<td>user requirements specifications</td>
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<tr>
<td>UV</td>
<td>ultraviolet-visible spectrophotometer</td>
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</table>
Brief summary of the findings and comments

1. Quality management

Principles
Responsibilities of the quality Unit(s)
The Quality Unit was divided into QA and QC with management responsibilities shown in an approved organization chart. Responsibilities were suitably described, including in position descriptions for key staff. The position descriptions reviewed were acceptable. The responsibilities of the Quality Director included all those topics specifically stated in the WHO Guidelines. The Quality Director reported to the General Manager and was responsible for supervising the QA and QC managers. In the absence of the Quality Director, the QA Manager would act as deputy.

Responsibility for production activities
The structure and management responsibility for production activities was shown in an approved organization chart. Responsibilities were suitably described, including in position descriptions for key personnel. The position descriptions reviewed were acceptable.

Internal audits (self-inspection)
Not covered by this inspection.

Product quality review
The product quality review was performed according to a SOP. PQRs of Mebendazole were conducted on a yearly basis. Plant 1 and Plant 3 reviews were conducted separately.

Mebendazole PQR 2013 for Plant 1 and Plant 3 were reviewed. There were no rejected raw materials, packing materials, batches of APIs and no complaints or returns of Mebendazole APIs.

PQR of Mebendazole 2014 in Plant 1 and Plant 3 were also reviewed. No product return or recall occurred. The major change was to introduce a new production line in Plant 3. This was reviewed.

PQRs of production in 2015 showed all details to be satisfactory. Non-compliances observed during the inspection, that were listed in the full report regarding PQR, were addressed by the manufacturer to a satisfactory level.

Quality risk management
There was a written procedure for Quality risk management. Various approaches to risk assessment were allowed. The risk management had not been fully implemented at the time of inspection. Non-compliances observed during the inspection, that were listed in the full report regarding quality risk management, were addressed by the manufacturer to a satisfactory level.

Deviation
Procedure for Handling Deviation was reviewed. There were two types of deviation, critical and non-critical, mentioned in the procedure. Deviations in 2015 were reviewed. Non-compliances observed
during the inspection, that was listed in the full report regarding deviation, were addressed by the manufacturer to a satisfactory level.

2. Personnel
   Personnel qualifications
   There were sufficient personnel who were suitably qualified through qualifications, experience and training. 327 persons were employed by the company at the time of inspection.

   Job Description, Preparation and Management were described in an SOP. All employees and contractors were covered. Responsibilities were well described, including position descriptions for all personnel. Position descriptions for selected key staff were reviewed and generally found satisfactory.

   Personnel hygiene
   Personnel were required to wear protective clothing suitable for the type and stage of manufacturing. Suitable sanitation and change room facilities were provided. Photographs of the requirements were on display.

   Training
   Training was performed according to an SOP. All employees were covered. QA & HR would check the qualifications of trainers. For new employees, the relevant department and QA would give the training requirements to HR. New employees were issued with a company handbook which included legal requirements. The training plan for 2015 of a process operator in Plant 3 was checked and was completed. The company training plan for 2016 was in place.

3. Buildings and facilities
   Design and construction
   The buildings and facilities inspected were designed and constructed to facilitate cleaning, maintenance and operations as appropriate to the type and stage of manufacture. The site was observed to be maintained to a satisfactory standard.

   Buildings were constructed of masonry with both internal and external finishes appropriate to the activities conducted. Housekeeping and maintenance were observed to be satisfactory. Where required, flying insect insectocutors, rodent and pest traps/barriers were installed.

   HVAC systems
   A dedicated HVAC system provided filtered air to supply to the clean area in Plant 3 to meet requirements for Grade D environment for final crystallization, drying and packaging of Mebendazole API. This was a circulatory system with specified make-up.

   All filters were monitored using Magnehelic gauges. When readings, showed that the maximum pressure drop had been reached, the filter was changed. No filters were cleaned for re-use after filter is changed. AHU systems were revalidated annually Details were not inspected.
**Water system**

Purified water was used in the final stages of Mebendazole API manufacture. The system was a design using reverse osmosis and EDI to produce purified water meeting EP and CP specifications. The water system appeared to be well maintained and the results of regular monitoring indicated that it was under control.

The last review of data, available at the time of the inspection, was from 4th January 2015 to 28th December 2015 and was reported in a document. Results from samples were reviewed for microbiological results. All samples showed results <10 cfu/ml. The sampling plan for 2016 was checked.

The final stage Qualification report for the PW system performed during 2014 to 2015 was reviewed and considered acceptable.

**Compressed air**

Compressed air was used for micronisation of Mebendazole and was reviewed during the inspection.

**Computer system**

Computer system was used in the QC lab for networking HPLC and GC only.

4. **Process equipment**

**Design and construction**

Process equipment in the finishing areas of Plant 1 and Plant 3 were inspected. In all areas, process and utility pipelines were observed to be adequately supported and labeled. Reactor systems were designed for reflux, distillation and stirring operations, as required.

**Equipment maintenance and cleaning**

Preventative Maintenance of Production Equipment was described in an SOP. This covered all equipment and a maintenance schedule was drawn up. As an example, a maintenance plan for a reactor was reviewed and found acceptable.

**Calibration**

Instrument/gauge calibration was covered in an SOP. A tachometer on the agitator of a reactor as an example was reviewed. Calibration recheck was due in July 2016.

5. **Documentation and records**

**Documentation system and Specifications**

Documents were managed according to an SOP. Activities were documented in SOPs and other appropriate documents such as batch manufacturing records (BMRs). These were approved and version controlled. All records and other documentation requested during the inspection were readily available.
Equipment cleaning and use record
Equipment was required to be cleaned according to documented procedures for each type of equipment. Records were maintained and all equipment viewed appeared to be clean and suitably labelled with cleaning status. An SOP for centrifuge bag cleaning was reviewed.

Records of raw materials, intermediates, API labelling and packaging materials
Suitable records of raw materials, intermediates, API labelling and packaging materials were maintained.

Master production instructions (Master production and control records)
Approved master production instructions were available for all production lines used for Mebendazole production.

Batch production records and batch production record review
The batch numbering system was described in an SOP. All raw materials, packing materials, intermediates and finished products were included.

BMRs were available and up to date as reviewed during the inspection. The productions records for a batch of Mebendazole and the associated records for the intermediates used in this batch were reviewed. These records appeared to have been properly completed and reviewed.

Laboratory control records
Laboratory testing records were kept and available in general.

6. Materials management

General controls
Procedures for the receipt, quarantine, storage, handling, sampling, testing and approval or rejection of materials were inspected and generally found satisfactory. Materials were issued in full containers to production according to a Material Request Form. No dispensing was done by warehouse staff.

Receipt and quarantine
On receipt, materials were checked for damage and against the approved supplier list controlled by an SOP. They were labelled segregated and quarantined appropriately.

Sampling and testing of incoming production materials
Materials were sampled by QC following a documented sampling procedure and sampled by QC before release. The containers sampled were labelled with a sampled label. Sampling was described in an SOP.

Vendor approval
Managing the Qualification of Suppliers was detailed in an SOP. All materials were covered and contractors were also included. Suppliers of critical materials (key materials) would be audited. For other materials, a “desk-top” audit would be conducted. Samples would be analysed. The company was understood to have satisfactory agreements with the suppliers.
Storage
Materials were stored in designated warehouses that were generally well organized, clean and tidy. Warehouses were equipped, as required, with proprietary racking. Materials were stored on plastic pallets. Insect and rodent traps etc. were installed, as appropriate. At the time of the inspection, the locked “Reject Area” in Building E was empty.

Warehouse for solid, liquid materials and bulk solvent tanks were inspected and considered acceptable. Mebendazole API product was stored in a warehouse provided with environmental control. Records indicated that the specified conditions had been maintained.

7. Production and in-process controls

Production operations
Production of Mebendazole API took place in the Plant 1 and Plant 3 including chemical synthesis in chemical areas, and purification, drying and packaging in Grade D clean areas.

They were not dedicated to Mebendazole API production. Different grades, of Mebendazole API, including those for human and veterinary use, were manufactured in both plants, by the same process. The specification for WHO grade is the same as EP.

All of the above production areas were inspected and generally found to be of suitable standard, clean and logically organized to suit their intended purpose.

Holding time
A Hold-Time study was conducted before the WHO inspection in 2013. Details were reported in a document. The holding time in routine production was specified and reported.

In-process sampling and controls
In-process sampling and testing was performed at defined stages during processing. In-process samples were tested in the QC laboratory.

Blending batches of intermediates or APIs
Blending operation were only performed for tailing material of Mebendazole.

Contamination control
Plant 1 and plant 3 were not dedicated to production of Mebendazole. Adequate precautions to minimize the likelihood of contamination, including final stages taking place in a Grade D controlled environment, were in place.

8. Packaging and identification labelling of APIs and intermediates

Packaging materials
Packaging materials were appropriately stored and subjected to quality control testing before release.

Label issuance and control
Labels were printed and issued according to an SOP and were adequately controlled.
Packaging and labelling operations
Packaging and labelling operations were described in batch packaging instructions. Polyethylene bag was used for the primary packing of intermediates and final API.

9. Storage and distribution
Warehousing procedures
There were documented procedures for the receipt, quarantine, sampling and release of materials. Computerized systems were not used for material control and a manual bin-card system was used. The materials reviewed had been controlled according to the procedures and no issues were noted.

Finished API products were stored in a temperature-mapped room. Inventory was recorded on QA-issued log sheets.

Distribution procedures
Product release and BPR review was described in an SOP. Product release was the responsibility of QA. The release procedure was comprehensive, including review of BMRs, BPRs, any deviations, OOSs etc., QC results including chromatograms. A final product label was included. Requirements were detailed in a check-list. An example of the release of a recent batch was reviewed and found satisfactory, apart from details on the label.

10. Laboratory controls
General controls
Procedures for sampling, testing and approval were documented. Material and product specifications and laboratory records were maintained.

Reference standards
Reference standards were available and used for Mebendazole testing.

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

Agilent GCs and HPLCs were networked with OpenLab EZchrom software. The computer access, control and authorization of the functions were spot checked during the inspection.

Microbiological testing
The microbiology laboratory was part of QC Laboratory. Media preparation and sterilization were spot checked. Microbial testing procedure for PW was reviewed.

Stability monitoring of APIs
Stability study was managed according to an SOP. Stability chambers were housed in a dedicated room. Included were chambers set to 25±2°C/60±5%RH and 30±2°C/75±5%RH used for Mebendazole stability testing. Cabinet logbooks were maintained and stability samples logs recorded the start of the study and when samples were removed. Location parameters were also given.
The data from the chambers was recorded automatically. Print-outs were kept in a logbook. Out-of-range alarms were fitted. Also, the stability chambers were connected to a UPS and the back-up diesel generator.

**Reserve/retention Samples**
Reserve/retention samples were stored in proprietary draw system in a temperature controlled, dedicated room. As an example, it was requested to look at a Mebendazole batch. The sample was satisfactory. The room was controlled with specified temperature and RH.

**11. Validation**

**Validation policy**
Validation policy for Mebendazole was described in VMP and the SOP for process validation approaches was reviewed and acceptable in general.

**Qualification**
A reactor, as an example of equipment qualification, was reviewed and found acceptable.

**Process validation**
Documentation (including protocol, report and BMRs) regarding the validation of the Mebendazole process operated in Plant 3 Line 2, was reviewed.

**Cleaning validation**
Cleaning validation was performed according to an SOP. Cleaning validation protocol and report of a line in Plant 3 were reviewed. Non-compliances observed during the inspection, that were listed in the full report regarding cleaning validation, were addressed by the manufacturer to a satisfactory level.

**Computerized system validation**
Computer validation for QC software was spot checked. Non-compliances observed during the inspection, that was listed in the full report regarding computerized system in QC lab, were addressed by the manufacturer to a satisfactory level.

**Periodic review of validated systems**
The status of validated systems was considered annually during Product Quality Review. In addition the need for revalidation after e.g. process or major equipment change was defined.

**12. Change control (CC)**
Change control was managed according to an SOP. Major changes made since last inspection related to Mebendazole were documented. The change control log book and several changes, including major changes to introduce a new production line in Plant 3, were reviewed and found acceptable in general.

**13. Rejection and re-use of materials**

**Reprocessing and reworking**
Reprocess and reworking were managed according to an SOP. The OOS material handling SOP covered reprocessing and rework of products. Regulatory approval was required before a batch was
reworked and a concurrent validation plan would been in place before a reworking took place. However, in general, reworking was not conducted.

Recovery of materials and solvents
Routinely, solvent was recovered from the mother liquor of manufacturing process. The specifications and recovery processes of recovered solvents were documented and found satisfactory.

14. Complaints and recalls
A complaint was made in 2014 and the relevant batches returned in June 2015. The investigation report was reviewed during the inspection. The investigation was performed and root cause identified. The CAPA included the requirement for operator retraining.

15. Contract manufacturers (including laboratories)
Contract manufacturing and contact testing were not applied to Mebendazole API.

PART 3
Conclusion
Based on the areas inspected, the people met and the documents reviewed, and considering the findings of the inspection, including the deficiencies listed in the Inspection Report, as well as corrective actions taken and planned. Mebendazole API (APIMF 220) manufactured at Changzhou Yabang-QH Pharmachem Co. Ltd., located at Survey Number DUNS 527929456 Latitude 31.9744N Longitude 119.9663E, 18 Jinlong Road, Chunjiang Town, Xinbei District, Changzhou, Jiangsu. P. R. China 213127 was 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.

PART 4
List of GMP guidelines referenced in the inspection report

http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_970/en/

http://whqlibdoc.who.int/trs/WHO_TRS_929_eng.pdf?ua=1

http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

http://whqlibdoc.who.int/trs/WHO_TRS_937_eng.pdf?ua=1


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http://whqlibdoc.who.int/trs/WHO_TRS_943_eng.pdf?ua=1

http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_981/en/

http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_981/en/

http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1


   http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex03.pdf

   http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex05.pdf


   http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex03.pdf