

**WHO PUBLIC INSPECTION REPORT  
(WHOPIR)  
Finished Product Manufacturer**

**Part 1: General information**

|   |  |
|---|--|
| Name of manufacturer                                    | Beijing Novartis Pharma Ltd.   |
| Physical address  | No. 31 Yong'an Road,<br>Changping District,<br>Beijing 102200. P. R. China |
| Postal address  | As above   |
| Date of inspection:                                     | 26 - 29 September 2011   |
| Type of inspection                                      | Routine inspection   |
| Dosage form included in the inspection                  | Tablets (Uncoated )  |
| WHO product categories covered by the inspection        | Malaria  |
| Summary of the activities performed by the manufacturer | Production and quality control of oral solid dosage forms                  |
| Project (if any):                                       | Prequalification of Medicines Programme                                    |

**Part 2: Summary**

*Background information*

Beijing Novartis Pharma Ltd. was inspected by a WHO prequalification team on the above mentioned days.

There were approximately 320 employees currently working on site.

***History of WHO or regulatory agencies inspections***

The site has been inspected by the WHO team on regular basis, the last inspection being performed by WHO in March 2009. The Uganda Authority and MHRA also performed inspections in 2011. The Beijing Novartis Pharma Ltd manufacturing site was licensed by the Chinese Drug Regulatory Authorities.

***Focus of the inspection***

The inspection focused on the production and control of oral solid dosage forms, in particular uncoated tablets. The inspection covered most of the sections of the WHO GMP text, including premises, equipment, documentation, materials, qualification and validation, sanitation and hygiene, production and quality control

### *Areas inspected*

- Warehouse storage areas for starting materials, finished products, packaging materials; sampling room, returned goods and rejected goods room.
- Solid/Semi-solid production unit including segregated areas of weighing and dispensing, granulating and drying, compressing, first and secondary packaging areas and in-process control.
- HVAC system;
- Purified water manufacturing and distribution networks;
- Quality control laboratory (Wet chemistry and microbiology);
- Documentation as listed below but not limited to

- Organization Chart
- Job descriptions
- Staff training programme & records

#### Quality Management System

- Product Quality Reviews (2009 and 2010)
- Deviations
- Customer complaints
- Recalls system
- Out of Specification investigations
- Change Control
- Warehouse agreements
- Product release

#### Quality Control

- Specifications, sampling & testing
- QC Labs
- Microbiology lab
- Dissolution, HPLC etc.
- Stability study

#### Environmental monitoring

- Environmental monitoring results of production areas

#### Validation

- Process validation
- Validation Master plan, programme, protocols
- Facility & equipment qualification
- Cleaning validation
- Equipment preventive maintenance programme

#### Materials Management

- Transport & Distribution
- Supplier approval and supplier complaints
- Supplier audit program
- Sampling, testing & raw material release

#### Review of batch documents

- Example batch record review
- Batch Release systems

#### Review of procedures from facility tour

- Production / cleaning procedures
- Self-inspection procedures and plan
- Pest control

### ***2.1. Quality Assurance (QA)***

A quality assurance system was implemented and maintained.

The QA and QC units were independent from production.

Managerial responsibilities were specified in job descriptions.

Annual product review included all batches manufactured during the calendar year and contained sufficient information and trends. Reviews demonstrated the adherence to the WHO guidelines. There were no batch failures. Starting raw materials showed a fully documented change of supply of Artemether. In process controls showed no adverse trends.

A system for deviation management was described in writing. Deviations were recorded and appeared to be adequately managed. Deviations and any non-conformity triggers a risk assessment following WHO guidelines.

Change control of identifying raw materials and the training of operators using NIR was also well documented.

### ***2.2. Good manufacturing Practices for Pharmaceutical products***

Good manufacturing practices were implemented and maintained:

- Qualifications and validations were performed
- Adequate premises and equipment were available for production, in-process controls and storage
- Instructions and procedures were written in clear and unambiguous language
- Manufacturing processes were clearly defined and reviewed.

### ***2.3 Sanitation and Hygiene***

A good level of sanitation and hygiene was in place on site. The scope of sanitation and hygiene procedures covered personnel, premises, equipment and apparatus, production materials and containers, products for cleaning and disinfection, and anything that could become a source of contamination to the product.

### ***2.4 Qualification and Validation***

The Validation Master Plan was a general document and declared the company's validation policy. Separate Validation Master Plans were available for:

- process validation
- cleaning validation

- equipment/facilities/utilities validation

#### Process validation

The process validation protocol and report and raw data were reviewed during the inspection. It was noted that critical and non-critical parameters were defined.

#### Cleaning validation

The cleaning validation of granulation equipment was inspected. Cleaning validation protocol and report were in place.

#### HVAC qualification

Qualification reports and raw data were available for inspections. The SOP of handling the AHUs and parameters had been checked:

- Pressure differentials of rooms
- Pressure drops over filters
- HEPA filter integrity
- System function test, access & security

For the re-qualification of the HVAC system the following tests were listed:

- Air velocity
- HEPA filter integrity
- Non viable particle counts

### ***2.5. Complaints***

Complaints were managed using SOP. A flow diagram gives guidance for the necessary action to take. QA/QC was involved with any assessment concerning the suitability of a return to be reprocessed as saleable stock.

### ***2.6 Product Recalls***

There had been no recalls in 2009-2010 related to the inspected product.

### ***2.7 Contract production and analysis***

Production, quality control and storage activities in relation to the inspected product were not subcontracted. There was a contract for using an outsource warehouse.

### ***2.8 Self inspection and Quality Audits***

The self inspection procedure was described in an SOP. The self inspection plan for the year 2011 was presented. Self inspection was performed on an annual basis, using the check list.

## ***2.9 Personnel***

There were sufficient numbers of personnel to carry out all the tasks for which the manufacturer was responsible at the time. Organization charts and job descriptions were in place. Individual responsibilities were defined and recorded as written descriptions. Delegated duties were clearly defined. The people met during inspection were competent and had good understanding of the GMP requirements.

## ***2.10 Training***

Training was provided. Training records were generally kept. Assessments after training were not recorded in sufficient detail in the training files.

## ***2.11 Personal Hygiene***

The level of hygiene observed and the measures taken to maintain this were considered sufficient.

Changing rooms were provided with photos describing the gowning procedures.

## ***2.12 Premises***

Premises were designed to minimize the risk of errors, potential contamination and cross-contamination, to facilitate proper cleaning and maintenance and ensure the logical flow of materials and personnel.

Cleaning records for selection production rooms were available.

An environmental monitoring programme was in place and was followed. Environmental monitoring was carried out on the regular base. Alert and action limits were established.

Premises were protected from entry by insects, birds and animals. Premises were clean and well maintained.

### **Storage areas**

Sufficient space was provided for storage of different materials. Appropriate storage conditions were provided.

The new sampling unit was inspected. The sampling unit had independent air handling system. Two sampling booths, both housing LAF cabinets, were available.

### **Production areas**

Production area was laid out to allow the production to take place in a logical order. The surfaces were smooth and free from cracks.

Production areas were effectively ventilated. Temperature, relative humidity and pressure differentials were regularly monitored.

#### Quality control areas

Quality control areas were separated from production areas.

#### **2.13 Equipment**

Process equipment was installed and maintained in a way that minimizes risk of error, contamination and cross contamination.

A preventive maintenance program was in place and was followed.

Production and quality control equipment was identified as to its content or purpose and cleanliness status and appropriately indicated by labels.

The cleaning procedures were available.

#### **2.14 Materials**

Procedures describing the receipt, identification, quarantine, storage, handling, sampling, testing and approval or rejection of materials were available. Materials in the warehouse were handled by the SAP system.

Materials and products were generally stored in a proper manner. Each container of starting material used for production of the inspected tablet was sampled for identity test purpose.

#### Purified Water System

The construction of the system was confirmed as that given in the Site Master File. The plant room was of a high order of construction and finish.

The system was controlled according to SOPs. The water quality was constantly monitored and recorded.

Water microbial quality was tested. Microbiological trends for the past year were assessed later in the audit. Results for take off points in the manufacturing loop showed no adverse trend. Trend data was summarised in Document.

#### **2.15 Documentation**

In general, the documentation system was well established and maintained.

Documents were designed, prepared, reviewed and distributed with care. Documents were approved, signed and dated by the appropriate responsible persons. Documents

had unambiguous contents and were laid out in an orderly fashion and were easy to check. Documents were regularly reviewed and kept up to date. Batch manufacturing records included sufficient data.

The generation of SOP's was controlled. It addresses all the conventional requirements regarding layout, authorisation and circulation control etc. All SOP's were held as electronic copies with electronic signatures. Hard copy can only be accessed for printing off by authorised personnel.

Throughout the inspection, all documentation was noted to be properly annotated. Those seen included but were not limited to, BMR's, SOP's for cleaning records of rooms and equipment, test specifications, purified water plant control and monitoring.

### ***2.16 Good practices in production***

The site was essentially a multi-product facility which handled a large number of APIs. The finish of the floors, walls and ceilings confirm the Site Master File descriptions. Access to production areas was restricted to authorized personnel.

Production operations were done following clearly defined procedures. The manufacturing of the inspected tablet was not being performed during the time of inspection. The manufacture of another tablet product was observed as an example of a similar process.

During processing the materials, bulk containers, major items of equipment, rooms and packaging lines were labeled and indicated the product being processed, its strength and batch number. Operations on different products were not carried out simultaneously in the same room.

#### **Tablet Manufacture uncoated tablets**

Being an uncoated tablet, the coating process was not inspected.

Primary change rooms were separate for female operators (ground floor) and male operators (1st.floor). Men then descend a "clean" stairway to the ground floor. Entry to the manufacturing area was then via a communal secondary clothing room. Instructions for gowning and washing were clearly displayed on the wall. The exit route was the reverse of the entry route

#### **Dispensary**

Entry for men and materials was through the same sliding door. The room was equipped with two floors to ceiling LAF weighing booths, each having a yellow demarcation line set in the floor. Air flows and filter pressure drops were clearly displayed on magnahelix gauges. All were operating within the set specification. The cleaning log was up to date.

Materials being dispensed were properly entered into the BMR with each weight verified by a second operator. Materials were placed in labelled plastics bags and then into clearly labelled drums. Balances and weighing machines were regularly calibrated with certified weights.

#### Blending and Compression

The materials were remixed and blended in equipment linked by a vacuum transfer system. The BMR records the separate stages of the process.

The tablet press had been set up as noted in the BMR. Correct tooling had been verified. Continuous metal detection was in place. Blend containers and tablet containers were clearly marked. In process weight checks were regularly performed. Tablets were sampled for In-process control.

#### Tool Storage

Punch and die sets were stored in a locked room in custom-built cabinets. Use and maintenance was managed using SOP.

#### In-process Control

The laboratory was equipped with several sets of apparatus for testing average tablet, weight, thickness, hardness, friability and disintegration. All were calibrated.

#### Packaging

Primary packaging was carried out in rooms with a controlled environment.

Blister packers were cleaned and operated using SOPs. Line clearance and machine set up checks were recorded. Packing materials were collated and start quantities were recorded. Secondary packaging was carried out in an open hall.

### **2.17 Good practice in Quality Control**

#### Quality control

The quality control laboratories were inspected. The laboratory comprised separate chemistry, microbiology and stability storage areas and was equipped with the necessary calibrated measuring instrumentation to test packaging materials. The company maintained a range of standard analytical equipment (HPLC, HP-TLC, G C, UV-spectroscopy, FRIR spectroscopy, dissolution testing). The labs were found to be generally well controlled.

The microbiology laboratory tested raw materials, water samples and environmental monitoring samples.

#### Components Testing

Authorised reference standards were available and include primary cartons and labels. Specimen colour references were also available.

#### Chemistry Laboratory

The laboratory was well equipped with well maintained benches, shelves and cupboards. Fume extraction cupboards showed a strong updraft when in operation.

Samples requiring analysis were fully identified by name and control number. Work was distributed to technicians on a prioritised basis. Technicians were multi skilled and were capable of carrying out any analysis required.

#### Wet Chemistry

All volumetric glassware was grade A and in good condition, all reagents were properly labelled and referenced to a method of preparation. General laboratory equipment was properly maintained and calibrated (e.g. pH meter, melting point apparatus. Viscometers). Analytical balances were well maintained and serviced and checked daily with standard reference weights.

#### Instrumentation

UV and IR spectrometers were maintained and calibrated. Any IR spectrum was compared to a standard trace generated by Novartis global QA group. Tablet dissolution equipment was calibrated in house except for the shaft eccentricity check. This was performed by a contractor.

#### HPLC Laboratory

One laboratory was dedicated to accommodating several HPLC stacks. Each was a stand-alone unit comprising of a pump, detector, oven and automatic sample injector. Each stack was validated.

#### Microbiology

The microbiology laboratory was entered through an air lock operating at a positive  $\Delta P$  to the outside.

The autoclave used for sterilising media was validated and data for empty and loaded chamber studies for porous loads were available.

Incubator temperatures were continually monitored with a weekly print out from data loggers.

### **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, Beijing Novartis Pharma Ltd., Changping District, Beijing 102200. P. R. China was considered to be operating at an acceptable level of compliance with WHO GMP.

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.

