

WHO PUBLIC INSPECTION REPORT

(WHOPIR)

Finished Product Manufacturer

The report is the property of the organization responsible for performing the inspection.

Part 1: General information about the inspection

Name of manufacturer	Beijing Novartis Pharma Ltd.
Physical address	No. 31 Yong'an Road, Changping District, Beijing 102200. P. R. China
Postal address	See above
Telephone number	+86 10 6974 4888
Fax number	+86 10 6974 4887
Summary of activities of manufacturer (e.g. manufacturing, packing).	Manufacturer of non-sterile medicinal products (including anti-malaria products)
Indicate dosage forms and type of products (e.g. tablets; cephalosporin containing products)	Oral solid dosage forms (tablets and hard gelatin capsules) and semi-solids
Focus of inspection - products in WHO PQ program covered in the scope at the time of inspection with the WHO reference num- ber	MA
Scope and type of inspection	Routine inspection, focusing on the recent extension of the solids' production unit and related validation and qualification activi- ties
Date of inspection:	16 - 17 March 2009
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. This was the sixth inspection by WHO of the referred site in approximately 4 years.

At the time of the inspection, there were approximately 300 employees working on site.

The extension project was completed and three validation batches had been produced in the new premises with the new equipment

Primary and secondary packaging was carried out in the new extension.

History of WHO or regulatory agencies inspections

The site was last inspected by the WHO team on 21 - 24 July 2008. The Beijing Novartis Pharma Ltd manufacturing site was approved by various authorities:

- SPAC and MOH
- TGA (Australia)
- Uganda
- Nigeria
- Botswana
- MHRA (UK)

Focus of the inspection

The inspection focused on the recent extension and related validation and qualification activities.

Inspected Areas

The specific areas inspected are listed below; related documents (i.e. SOP's, log books, batch records, and validation and qualification protocols and reports) were assessed.

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.

A change control procedure and change register was available for inspection. Change control was adequately managed; however the change records were complicated and difficult to review. It was noted that the company was going to introduce a new database for change control.

A system for deviation management was described in writing. Deviations were recorded also in the Manufacturing Instruction Records (MIR) and Packaging Instruction Records (PIR). A deviation register was available. Deviations were adequately managed.

Annual product review included all batches manufactured during the calendar year and contained sufficient information and trends.

A general procedure addressing "Total quality risk management" was available. On spot checks the risk management was implemented and root causes were identified. During the inspection the following risk assessment (RA) documents were reviewed:

- RA for Purified Water (PW) system: Chloride out of limits
- RA for Fluid Bed Drier (FBD): pre- and post-qualification stages.



- RA cleaning validation status for new processing equipment chain
- Tools were used for the risk assessment.

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
- operators were trained
- manufacturing processes were clearly defined and reviewed. Manufacturing steps were recorded in MIRs and PIRs.

2.3 Sanitation and Hygiene

The topic was not specifically covered during the inspection. No notable concerns were identified during the "walk through".

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
- analytical methods validation
- cleaning validation
- compressed air system validation
- equipment/facilities/utilities validation

Re-validation policy was defined by the matrix table as following:

- processes, cleaning and compressed air system - re-validation had to be carried out every 3 years
- if no changes, analytical methods were not re-validated
- HVAC system was re-validated annually.

Process validation

Process validation report and raw data were reviewed during the inspection. Batch size was increased. Primary packaging materials had not been changed.

Cleaning validation

Granulation equipment was inspected. Cleaning validation appeared to be extensive from the analytical aspect, critical locations were clearly identified in the validation documents.

The inspection focused on the validation and qualification of the following systems and equipment:

- The PW system: PQ1 and PQ2 phases were completed, reports and raw data were available. The PQ3 phase was in progress
- HVAC system



- FBD Glatt
- Metal detector

2.5. Complaints

There had been no complaints in 2008-2009 related to the inspected tablets.

2.6 Product Recalls

There had been no recalls in 2008-2009 related to the inspected tablets.

2.7 Contract production and analysis

Production, quality control and storage activities were not subcontracted in relation to the inspected tablets.

2.8 Self inspection and Quality Audits

The self inspection procedure was described in an SOP. The self inspection plan for the year 2008 was presented. A self inspection plan for the year 2009 will be drawn up in April. Self inspection was performed on an annual basis, using the check list.

CAPAs implementation would be monitored during the next self inspection.

Suppliers' audits and approval

A written procedure was in place. SOP "Supplier approval, qualification for reduced testing and monitoring including TSE requirements" was reviewed and found to be acceptable. The suppliers were classified as:

- Approved
- Qualified
- Certified
- Disqualified

Approved suppliers - full testing of each batch was required before release. Identity (ID) tests were performed on each container.

Qualified suppliers and Certified Suppliers – supplier's certificate of analysis (CoA) was accepted in lieu of full testing. "Critical" and identity (ID) tests were required before release. "Critical" tests were defined for each material. Sampling for ID tests was performed in accordance to the formula $\sqrt{n} + 1$.

ID tests were performed on each of container of Lumefantrine and Artemeter API used for manufacture of the inspected tablets. Formula $\sqrt{n} + 1$ was applied for excipients' ID tests.

2.9 Personnel

A new Quality Assurance (QA) manager had been appointed recently. The QA manager had appropriate education, training and experience to fulfill the duties.

For general information please see previous reports.

2.10 Training

The topic was not covered during the inspection. For general information please see previous reports.

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 each production room were available.

An environmental monitoring programme was in place and was followed. Environmental monitoring (surfaces and air) was carried out quarterly for all production rooms. 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. Temperature mapping was carried out.

New sampling unit was in operation. IQ, OQ and PQ was performed. The sampling unit had independent air handling system. Before the sampling wooden pallets were changed for Aluminum pallets in a separate part of the sampling unit. After sampling containers were placed back to wooden pallets.

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. A new Microbiological control laboratory was under construction.



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

The 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.

Incoming goods and finished products were quarantined until tested and released by QC.

Materials and products were generally stored in a proper manner.

Each container of starting material used for production of the inspected tablets were sampled for identity test purpose.

ID tests were performed on each of container of Lumefantrine and Artemeter API used for manufacture of the inspected tablets. Formula $\sqrt{n + 1}$ was applied for excipients' ID tests.

Reference and working standards were stored appropriately. Use of reference and working standards was recorded; log books on use of standards were available. Stability studies had been performed on reference standard solutions.

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.

2.16 Good practices in production

Production operations were done following clearly defined procedures.

Deviations from instructions or procedures were handled in accordance with approved procedures.



Necessary checks on yields and reconciliation of quantities were carried out. Operations on different products were not carried out simultaneously in the same room.

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.

Access to production areas was restricted to authorized personnel.

Line clearances were performed and recorded before processing operations were started.

2.17 Good practice in Quality Control

For general information please see previous reports. During this inspection attention was not paid to quality control activities, except dealing with reference standards.

Out of Specification (OOS) results were evaluated and investigated in accordance with a written procedure. The company also applied a concept of Out of Expectation (OOE) results. Two OOS reports were reviewed and found to be comprehensive.

Stability studies

The three validation batches were subjected to stability studies (short term accelerated and long term). Stability studies had been started on 14.01.2009. Results for the first testing period were available, test results met specification limits.

Utilities

The HVAC system

The new HVAC system was designed in accordance with current state of the art recommendations, to avoid possible contamination and cross contamination.

The HVAC system was designed in a way that production corridors were at a positive pressure with respect to production rooms.

Filters were not washed for cleaning, replacing with the new ones was the practice.

The dust collector for the granulation room was placed on the technical floor and was attended by the production personnel. Cleaning operations were inspected briefly, as no cleaning/replacement of collector bags had taken place yet.

Purified water (PW) system

The new PW system was designed in accordance with current state of art recommendations.

The „old“ solids manufacturing unit had been connected to the new water production plant. Functioning parameters of the RO unit were monitored, sanitisation processes were established.



Validation of the purified water production had an inappropriate design - please see section "observations". It was noted that the company had applied the procedure because of the understanding that as the sampling points were located in an unclassified area, unrelated contamination might occur; however no incidents had been identified, other measures can be applied to avoid the issue.

Compressed air

Two new compressed air generation systems were located in the plant. Oil-free compressors were used and 0.01 µm filters were installed at the user points.

Maintenance of the compressed air unit No 11 (in the „old“ manufacturing unit) and monitoring of the air quality was inspected. No remarks regarding the activities were made by the inspectors.

Part 3: Conclusion

Based on the areas inspected, the corrective actions evaluated, the people met and the documents reviewed, and considering the findings of the inspection, reflected in the observations listed in the inspection report, 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

The WHOPIR is valid for a maximum of 3 years, unless the site is found to be non-compliant in another inspection before the 3 years had lapsed.