

**Prequalification of Medicines Programme
WHO INSPECTION REPORT
Finished Product Manufacturer**

Part 1: General information

Name of Manufacturer	Beijing Novartis Pharma Co., Ltd.
Unit number	N/A
Production Block	Builing 12, 12 A, 12 B & B 16
Physical address	No. 31 Yong'an Road, Changping District, Beijing 102200. P. R. China
Contact address	As above
Date of inspection	24 to 26 June 2014
Type of inspection	Routine inspection
Dosage forms(s) included in the inspection	Tablets
WHO product numbers covered by the inspection	MA026: Artemether/Lumefantrine 20/120mg Tablets MA069: Artemether/Lumefantrine 20/120mg dispersible tablets
Summary of the activities performed by the manufacturer	Production and quality control of non-sterile oral solid dosage forms (tablets and hard gelatine capsules) and semi-solids

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Part 2: Summary

General information about the company and site

The Changping manufacturing site of Beijing Novartis Pharma Co., Ltd was established in 1987. It is located 45km away from Beijing airport. Approximately 340 staff was employed by the site at the time of inspection.

The site manufactures a range of non-sterile solid and semi-solid dosage forms, as well as packaging of imported drug products. The site operates 3 shifts.

Major changes since the last WHO-PQP inspection include:

- Manufacturing science and technology department was established.
- Head of speciality unit and head of manufacturing science and technology were filled the positions in 2013; head of compliance was changed from 2012.
- Dispensing area was renovated for increasing dispensing capacity.
- A manufacturing execution system-MES (dispensing) was validated and implemented in 2013.
- The room monitoring system for clean zone was installed and qualified in 2013
- A company global training web application (LMS) was implemented in 2013
- Perform container wise ID check for incoming drug substance and excipients in November 2011.

History of WHO and/or regulatory agency inspections

The Beijing Novartis Pharma Ltd manufacturing site was licensed by the Chinese Drug Regulatory Authorities. The site has been inspected by the WHO team on regular basis, the last inspection being performed by WHO in September 2011. The Kenya Authority and South Africa MCC also performed inspections in 2012 and 2013 respectively.

Focus of the inspection

The inspection focused on the production and control of products. The inspection covered most of the sections of the WHO GMP text, including premises, equipment, documentation, materials, validation, sanitation and hygiene, production, quality control and utilities.

Inspected Areas

The inspection included:

- Warehouse for starting materials, finished products, and 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.
- QC labs including microbiology lab.
- Documentation as listed below but not limited to

- Product Quality Review
- Quality Risk Management
- Deviation control
- Change control
- Complaints
- Recalls
- Supplier approval
- Rework or reprocessing
- Document Control
- IT systems used in GMP activities
- Validation and qualification
- Contracts / agreements
- Water system
- HVAC and environment monitoring

2.1 QUALITY ASSURANCE

The company had a well-established quality system that was implemented and maintained.

Annual product review was performed as per SOP on Product Quality Review (PQR). Annual product review of Coartem tablet of 2012 and 2013 were reviewed. There was no batch failure for this period. All starting raw materials and packaging materials were compliant.

Annual product review of Coartem/Riamet dispersible tablet was reviewed. As the bulk is manufactured in Novartis Suffern USA, and packaging operations are performed in Novartis Beijing, documents were available on site.

The policy for handling the deviations was presented. A risk assessment is performed to classify the deviations, using several tools. Deviations are logged in an IT system AQWA. The deviation during the reviewed period (2012-2013) has been discussed during inspection. A weekly meeting is scheduled to assess deviations trend. There was also annual report of deviations. 3 examples of non-critical deviations observed in 2013, were presented with the raw data of investigation.

The change control policy was presented with SOP and the reference change of Lumefantrine. This change was found well documented. Checking the effectiveness of the change is a requirement of the Company.

The quality risk management was explained through the SOP following the ICH and WHO guidelines. An annual review report of risk assessments is written to have an overview of the events on site during the previous year. The report for 2013 was presented.

2.2 GOOD MANUFACTURING PRACTICES (GMPs) FOR PHARMACEUTICAL PRODUCTS

All of the necessary aspects of GMPs were covered. The necessary resources were provided, including qualified and trained personnel, suitable equipment, services and premises. Appropriate controls were performed for finished products, raw materials, containers and labels as well as in-process. Manufacturing processes were clearly defined and shown to be capable of consistently manufacturing pharmaceutical products of the required quality that complied with their specifications. Qualification and validation were performed.

2.3 SANITATION AND HYGIENE

A high level of sanitation and hygiene was observed at the plant. All surfaces in production were cleaned on a regular basis. There were no traces of dust or residue.

2.4 QUALIFICATION AND VALIDATION

The Validation Master Plan was a general document and declared the company's validation policy. Revalidations were conducted according to product lifecycle management concept, e.g. continuous process verification, periodic cleaning validation, etc.

Process validation

Protocol signed in April 2011 and report signed in August 2011 to validate the process using new grade of Lumefantrine and Artemether, were reviewed.

Protocol signed in December 2011 and report signed in February 2012 to validate the holding time of Coartem granulate were reviewed to address deficiency of previous report.

Cleaning validation

SOP, cleaning validation matrix table, planning for 2014 and cleaning validation master plan were presented. The policy for revalidation was explained. The calculation to address deficiency of previous report was added in the SOP.

Computer validation

GMP computerised system were validated and managed based on the V-model, GAM5 and company guidelines. SOP on Computer System Validation was reviewed and found to be acceptable in general.

Equipment qualification

SOP on Commissioning, Qualification and Decommission of Equipment and Facilities were reviewed. The qualification status of equipment was available for review and considered acceptable.

2.5 COMPLAINTS

SOP on Handling of Customer Complaints for Novartis Pharma Products and the complaint list of 2013 was reviewed. Two complaints of Coartem tablets regarding the loss of efficacy were reviewed and considered to be handled acceptable.

2.6 PRODUCT RECALLS

There had been no recalls in 2012 to 2013 related to the Coartem tablets. A mock recall was performed in November 2013 and the report was reviewed.

2.7 CONTRACT PRODUCTION AND ANALYSIS

Production activities in relation to Coartem tablets FPP were not subcontracted.

A contract warehouse located in Beijing was used. Part of Artemether API was stored in the warehouse (2 to 8°C).

The National Institutes for Food and Drug control (NIFDC) and Beijing Institute of Drug Control were used as contract labs for testing of Artemether by X-ray diffract meter and other analysis.

2.8 SELF INSPECTION AND QUALITY AUDIT

SOP and flow chart of the self inspection process were presented. In 2013, 13 self inspections were planned and performed. This year, 11 self inspections are planned. There is a regular training of established auditors and every year, new auditors are trained.

Supplier's audits and approval

Management of Material Supplier SOP and approved vendor list were reviewed. The two APIs Lumefantrine and Artemether used for Coartem tablets were audited by the corporate audit group. The quality agreement with the APIs supplier was reviewed and discussed during the inspections.

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. The people met during inspection were competent and had good understanding of the GMP requirements.

2.10 TRAINING

It was not covered by this inspection.

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.

Manufacturing areas and the QC laboratory were generally of a good standard. An environmental monitoring programme was in place and was followed. Environmental monitoring (surfaces and air) was carried out on the regular base. Alert and action limits were established.

The production building was extended in 2013. Premises were protected from entry by insects, birds and animals.

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 for inspection.

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 materials used for production of Coartem tablets were sampled for identity test purpose. The company performed once a year of full testing for Artemether and Lumefantrine APIs according to the company's procedure.

Purified Water system

The water loop was extended since the previous inspection but the rooms on focus are not concerned. The Coartem area is fed by a separate loop. The control and monitoring procedure remained the same since last inspection. The Microbiological trends for 2012 and 2013 were assessed. No alert limit was obtained.

2.15 DOCUMENTATION

In general, the documentation system was established and maintained.

Documents were designed, prepared, reviewed and distributed as per SOP on Document control and management and SOP on Preparation, approval and distribution. The management of electronic data generated by computer system was discussed with the company during inspection.

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 SMF descriptions. Access to production areas was restricted to authorized personnel.

Coartem tablets were not being manufactured at the time of the inspection. There were no other activities in most of the areas used for this product.

Production operations were done following clearly defined procedures. Master BMR and BPR, as well as Coartem batch document were reviewed. The manufacturing process has not been changed since last inspection.

The bulk tablets for Artemether/Lumefantrine 20/120mg dispersible tablets were manufactured by other Novartis site and only the packaging operation was performed on the site.

The return goods SOP was reviewed, this activity is under Quality assurance evaluation. It does not allow cold chain products to be back in the saleable stock. This is to address a deficiency of previous report.

The rework and reprocessing SOP was presented. No finding.

2.17GOOD PRACTICES 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 reference substance, retention sample and stability chamber areas were inspected and considered operation at an acceptable level.

Chemistry Laboratory

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

All volumetric glassware was in good condition; all reagents were properly labelled and referenced to a method of preparation. General laboratory equipment was properly maintained and calibrated. The cleaning procedure of glassware was inspected.

The specifications and testing report of APIs of Lumefantrine and Artemether were reviewed.

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.

The HPLC testing procedure was reviewed and the section of manual integration was discussed.

Microbiology

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

The microbiology laboratory has no changes since last inspection.

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 Co., Ltd., located in No. 31 Yong'an Road, Changping District, Beijing 102200. P. R. China was considered to be operating at an acceptable level of compliance with WHO GMP 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.