

WHO PUBLIC INSPECTION REPORT Finished Product Manufacturer
**WHO PUBLIC INSPECTION REPORT
(WHOPIR)**
Finished Product Manufacturer
Part 1: General information

Name of Manufacturer	Ajanta Pharma Limited
Unit number	NA
Production Block	NA
Physical address	B-4/5/6, MIDC Industrial Area, Paithan Aurangabad, Maharashtra State, INDIA
Contact address	Mr Mani Kuriakose mani.kuriakose@ajantapharma.com
Date of inspection	17, 18, 19 and 20 June 2013
Type of inspection	Routine inspection
Dosage forms(s) included in the inspection	Artemether/Lumefantrine 20/120mg Tablet (MA052) Artemether/Lumefantrine 20/120mg Dispersible Tablet (MA092) Artesunate/Amodiaquine 25/67.5mg Tablet (MA095) Artesunate/Amodiaquine 50/135mg Tablet (MA096) Artesunate/Amodiaquine 100/270mg Tablet (MA097)
WHO product categories covered by the inspection	MA052 (Prequalified) MA092 (Prequalified) MA095 (Under assessment) MA096 (Under assessment) MA097 (Under assessment)
Summary of the activities performed by the manufacturer	Manufacturer and packer of oral solid dosage forms - tablets, hard capsules, granules and powders.

Part 2: Summary

General information about the company and site

Ajanta Pharma Limited (hereafter Ajanta) was incorporated in 1973. Ajanta has three finished pharmaceutical product sites in India (Chikalthana, Chitegaon and Paithan) one in Mauritius and other one in Turkmenistan. Also, Ajanta has an API site in Waluj, Aurangabad, India.

The manufacturing site in Paithan was commissioned in 1983 on a 71,531 square meters plot with a constructed area of 22,748 square meters. Ajanta Paithan site manufactures non-sterile solid dosage forms (tablets coated and uncoated, capsules and powders).

The site is relatively large, employing 220 regular staff plus around 200 casual workers. The site is engaged in the manufacture of a large number of non-sterile solid dosage forms to a variety of international and Indian domestic markets.

History of WHO and/or regulatory agency inspections

This is a routine GMP inspection on Ajanta Paithan. The last inspection was conducted on 27-30 June 2011 with the UK MHRA.

The manufacturing site had been inspected by the USFDA in September 2012 for 9 of the general products submitted for approval. One 483 pertaining to the control of the worksheet generated by LIMS was raised, and a compliance letter was issued after the response.

Focus of the inspection

The inspection focused on the production and control of Artemether/Lumefantrine 20/120mg tablet (MA052), Artemether/Lumefantrine 20/120mg dispersible tablet (MA092), Artesunate/Amodiaquine 25/67.5mg tablet (MA095), Artesunate/Amodiaquine 50/135mg tablet (MA096) and Artesunate/Amodiaquine 100/270mg tablets (MA097). The inspection covered all the sections of the WHO GMP text, including premises, equipment, documentation, materials, validation, sanitation and hygiene, production, quality control and utilities.

In addition, an investigation was also carried out following the receipt of a complaint from the Global Fund regarding the low assay content found in MA052.

Inspected Areas

- Quality Assurance
- Sanitization and hygiene
- Qualification and validation
- Complaints

- Recalls
- Self-inspection
- Personnel
- Training
- Personal hygiene
- Premises
- Equipment
- Materials
- Documentation
- Production
- Quality control

2.1 QUALITY ASSURANCE

The quality management system at site was broadly satisfactory and had systems in place to ensure the quality of products manufactured. There was an adequately designed and correctly implemented system of quality assurance incorporating GMP and quality control. It was documented and its effectiveness was monitored through self-inspections. All parts of the quality assurance system were adequately staffed with competent personnel, and there were suitable and sufficient premises, equipment, and facilities.

The issues raised were adequately addressed and will be verified during future inspections.

2.2 GOOD MANUFACTURING PRACTICES (GMPs) FOR PHARMACEUTICAL PRODUCTS

Products were consistently produced and controlled to the quality standards appropriate to their intended use and as required. Systems were in place to reduce the risk of cross-contamination and mix-ups.

The manufacturing processes for the reviewed products were defined and systematically reviewed, and shown to be capable of consistently manufacturing pharmaceutical products of the required quality that comply with their specifications.

The issues raised were adequately addressed and will be verified during future inspections.

2.3 SANITATION AND HYGIENE

A satisfactory level of sanitation and hygiene was practised on site. The scope of sanitation and hygiene 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. Potential sources of contamination were eliminated through the programme of sanitation and hygiene.

2.4 QUALIFICATION AND VALIDATION

The site had identified what qualification and validation work was required to prove that the critical aspects of their operations were controlled. In general, this area was found to be satisfactory.

2.5 COMPLAINTS

An SOP on the handling of complaints was available which essentially covered the classification, timelines, review of these complaints at the Management Review meeting and trending etc. A complaint register was maintained on a yearly. A complaint was reviewed and noted that adequate investigation was performed by the site and responded accordingly.

2.6 PRODUCT RECALLS

An SOP on product recall was available which adequately described different levels of class (wholesale, retail and consumer level) including classification into Class I, II and III. As per the procedure, mock recall should be performed every 2 year if no recall was initiated. The latest mock recall from the export market covering African countries was performed in 2013. In general, mock recall was found satisfactory.

2.7 CONTRACT PRODUCTION AND ANALYSIS

The company contract out some analytical tests to outside laboratories, however, the number of contract tests is limited to those requiring specialist instrumentation such as Atomic adsorption spectroscopy and X-ray diffraction. Technical agreement and audit reports for one of the laboratories were inspected and were found to be satisfactory.

It was noted that the company does not contract manufacture any of the product for any other company. Some of the products produced by Ajanta were sold under different company name.

2.8 SELF INSPECTION AND QUALITY AUDIT

The procedure on self-inspection was available which stipulate that self-inspection shall be carried out every 4 month or when investigation. The observations noted from the self-inspection were classified into critical, major and minor. The schedule for the self-inspection for 2012 and 2013 (April, August and December) was reviewed and found satisfactory. The self-inspections for year 2012 were accomplished according to the schedule.

The issues raised were adequately addressed and will be verified during future inspections.

2.9 PERSONNEL

There were sufficient qualified personnel to carry out all the tasks for which the manufacturer was responsible. The company employed around 200 temporary workers mainly for the non-critical operations (housekeeping, shifting of materials etc and quality control).

2.10 TRAINING

Employee training was conducted as per procedure according to the following training categories: induction, on the job, on-going in house and external. Casual workers helpers were instructed to follow operator and supervisor directions. According to procedure casual workers received general GMP training and on the job verbal training at the time of joining the company however no critical operations or equipment handling tasks could be assigned to these workers.

The issues raised were adequately addressed and will be verified during future inspections.

2.11 PERSONAL HYGIENE

An adequate level of personal hygiene was observed by all those concerned with manufacturing processes. Direct contact was avoided between the operator's hands and starting materials, primary packaging materials and intermediate or bulk product. Personnel were wearing clean body coverings appropriate to the duties they performed, including appropriate hair covering. Used clothes were stored in separate closed containers until properly laundered. Laundry was outsourced.

Smoking, eating, drinking, chewing, and keeping plants, food, drink, smoking material and personal medicines was not be permitted in production or in any other areas where they might adversely influence product quality.

Personal hygiene procedures included the use of protective clothing for all persons entering production areas including employees and visitors.

2.12 PREMISES

A site inspection was undertaken which covered all manufacturing, storage and QC areas. The facilities are described in detail in the Site Master File.

Two dispensing areas were used for dispensing and weighing material. Personnel accessed the dispensing area via gowning room using electronic access control. Material was passed into the dispensing room using an airlock. No wooden pallets were used for storing material throughout the site.

Primary packaging materials were sampled according to an ANSI/AQL plan. Testing of PVC/PVDC and other packaging materials was performed in a dedicated IPC

laboratory equipped to perform the following test: visual appearance, bursting strength, pin hole test, rub test, thickness (gauge and micrometer). There was a dedicated area for sampling primary packaging material with separate entry for material and personnel. Materials were sampled in 100 000 class area under LAF. Primary packaging materials entered the primary area (from secondary area) via interlock pass box.

The primary manufacturing areas consisted of standard granulation, drying, compression, encapsulation and coating areas which were suitably controlled segregated and maintained. Separate air handling systems were in use for each manufacturing cubicle, which contained terminal HEPA filters. The air in these rooms was classified on an annual basis. The company turned off Air handlers in areas not in use. The policy in relation to this activity was inspected, and found to contain suitable controls over this practice (for example retaining air-handling in areas where product was stored, and allowing suitable clean-up of areas prior to bringing them back into use).

The packaging at site consisted of a newly constructed secondary packaging hall with 8 lines, which were well segregated. The packaging methodology itself was very basic.

Purified water was generated using a double Reverse Osmosis system from the municipal supply. Water was stored in a stainless steel tank which fed a 316L steel distribution loop, sanitised by heat on a weekly basis. In general, the system was maintained and controlled adequately except the replacement of RO membrane and monitoring of spray valve. .

2.13 EQUIPMENT

Equipment was located, designed, constructed, adapted, qualified and maintained to suit the operations to be carried out. The layout and design of equipment also aimed to minimize the risk of errors and permitted effective cleaning and maintenance in order to avoid cross-contamination, build-up of dust or dirt, and, in general, any adverse effect on the quality of products.

2.14 MATERIALS

The receipt, storage and distribution of materials were performed in two buildings within the Paithan site. In the building in which warehousing and manufacturing take place there is a clear separation with restricted entries between primary (manufacturing and primary packaging) and secondary (secondary, tertiary packaging and storage) areas. The second building was used for receipt, storage and distribution of packaging material and finished products along with a testing facility for packaging material.

Material and personnel had dedicated access to the warehouse. Personnel gowning included wearing dedicated shoes beyond the change rooms. Material entered the

building from the receiving dock through a de-duster area. The rodent controls were located outside the building; flytraps were installed in areas that opened to the outside. Δp limits between de-dusting area and receiving dock was 0.5-1.5 mmH₂O.

2.15 DOCUMENTATION

A documentation system was in place to guide production and control of products. These included: Site Master File (SMF); Validation Master Plan (VMP); standard operating procedures (SOPs); Batch Manufacturing and Packaging Instructions and records; specifications of starting materials, packaging materials, packaging components and finished products; standard testing procedures, analytical records and certificates of analysis; qualification and validation protocols, schedules and reports; training schedules and records. There were corresponding records in form of reports, forms, checklists, logbooks, registers maintained as evidence of compliance with the procedures and specifications.

2.16 GOOD PRACTICES IN PRODUCTION

The site was essentially a multi-product facility which handled a large number of APIs. The production facility was broadly divided into primary manufacturing area (manufacturing and primary packaging) and secondary area (secondary packaging, warehouse and FG store). There were three storage condition set up for various storage and production areas (25±5°C, 20±5°C / 35-65%RH and cold store 2-8°C for RM storage area).

The workmen working in various production areas were identified by unique colour uniform (light blue for operator, tan for housekeeping staff, dark blue for maintenance and white apron for the staff including QA/QC). The laundry was outsourced and was changed every day for the workmen working in the core processing area including product changeover. The canteen facility was provided outside of the manufacturing facility.

The issues raised were adequately addressed and will be verified during future inspections.

2.17 GOOD PRACTICES IN QUALITY CONTROL

The quality control testing was performed in the following areas: wet chemistry, instrumentation room, stability testing area and microbiology laboratory. QC samples and data were managed by LIMS. Documentation, retention sample and stability chamber rooms were also located in the same building. Note: laboratory facilities were in process of expansion to be completed within two months from the time of inspection.

The issues raised were adequately addressed and will be verified during future inspections.

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, *Ajanta Pharma Limited, Paithan, Aurangabad, India* 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.