

**Prequalification Team Inspection services
WHO PUBLIC INSPECTION REPORT
(WHOPIR)
Finished Product Manufacturer**

Part 1: General information about the inspection

Name of manufacturer	M/s Ajanta Pharma Limited
Physical address – production departments	Ajanta Pharma Ltd, B-4/5/6 MIDC Industrial Area, Aurangabad, Paithan District, Maharashtra, 431 18, India
Postal address	As above
Dosage form included in the inspection	Tablets
WHO product numbers covered by the inspection	Prequalified products : <ul style="list-style-type: none"> • Artemether/Lumefantrine Tablet, Dispersible 20mg/120mg (MA092) • Amodiaquine (hydrochloride)/Artesunate Tablet 67.5mg/25mg (MA095) • Amodiaquine (hydrochloride)/Artesunate Tablet 135mg/50mg (MA096) • Amodiaquine (hydrochloride)/Artesunate Tablet 270mg/100mg (MA097) • Artemether/Lumefantrine Tablet 20mg/120mg (MA111)
Type of inspection	Routine inspection
Date of inspection:	25 – 28 April 2016
Summary of the activities performed by the manufacturer	Manufacturing, packaging, quality control, stability testing, storage and distribution of: <ul style="list-style-type: none"> • Tablets (coated and un-coated) • Capsules • Oral powders

Part 2: Summary

General information about the company and site

Ajanta Pharma Limited (here after referred as “Ajanta”) was incorporated in 1973. Ajanta is involved in manufacturing and marketing of the pharmaceutical products in India and overseas. Ajanta’s global head quarter and corporate office is located at Kandivli, Mumbai. Ajanta employs over 5,600 personnel worldwide (including India) including sales, marketing, Research and Development (R&D), manufacturing, quality, regulatory, human resources, accounts, finance, secretarial, legal, administration and various other functions. In India, Ajanta has several branded generic products with therapeutic focus on cardiology, ophthalmology, dermatology, musculoskeletal and Over-the-counter (OTC) segments. Ajanta’s products are developed at the Research and Development (R&D) center located at Kandivli, Mumbai, India.

Globally, Ajanta has seven manufacturing facilities, five in India {Four formulation facilities and one Active Pharmaceutical Ingredient (API) facility}, one in Mauritius and one in Turkmenistan.

The drug licensing authority, Food and Drug Administration of Maharashtra, India has granted the manufacturing licenses AD/018 in form 25 and AD/024 in form 28 to manufacture pharmaceutical products at Paithan site.

Toxic or hazardous products, β -Lactams, cytotoxic drugs, hormones and steroids were not being manufactured at the site.

History of WHO or regulatory agencies inspections

The site was last inspected by WHO in June 2013. The site has also been inspected by the various regulatory authorities.

Focus of the inspection

The inspection covered sections of the WHO GMP for non-sterile products text, including quality assurance, premises, equipment, documentation, validation, production, and manufacture.

Inspected Areas

- Quality Assurance
- Qualification and validation
- Complaints
- Recalls
- Contracts
- Premises
- Equipment
- Documentation
- Production
- Quality control

3.1 PHARMACEUTICAL QUALITY SYSTEM (PQS)

Principle

In general PQS was implemented. Production and control operations were specified in written form and GMP requirements were generally followed. Product and processes were monitored and the results taken into account in batch release and regular reviews of the quality of pharmaceutical products were conducted. Periodic management reviews were performed.

In-house Quality Management Software (QMS) was used for:

- CAPA management
- Change control management
- Deviation management
- Market complaints management

Quality Risk Management (QRM)

The SOP “Quality risk management” and register were discussed. The SOP explained risk identification, risk analysis, risk evaluation, risk control, risk communication and risk review. Tools used for the risk management were specified:

- Failure Mode effect analysis (FMEA – 5 scoring system) – applied for:
 - to prioritize risks and monitor the effectiveness of risk control activities
 - to equipment and analyze manufacturing operation and its effect on product or process
- Hazard analysis and critical control points (HACCP) – applied to identify and manage risk associated with physical, chemical and biological hazards
- Hazard operability analysis (HAZOP) - applied to manufacturing process, , equipment and facilities for medicinal products.

The RA report No XX Artemether/Lumefantrine Tablet, Dispersible 20mg/120mg was discussed. RA covered all production steps starting receipt and storage of raw materials, quality control, storage and dispatch of finished goods and utilities.

Product Quality Review (PQR)

The SOP “Product Quality review” was discussed. According to the SOP PQR should be prepared for all batches manufactured in one year beginning from 1st April till 31st March of next year and published before 30th June of next year. Data was trended using control charts or process capability studies. All products of same strengths, formulation and manufacturing process but different batch sizes were included in the same PQR.

The SOP “Statistical evaluation for data analysis” was discussed. According to the SOP interpretation of process capability was following:

Cpk result	Interpretation
<1.00	Process is not capable
1.00 – 1.33	Product is barely manufacturable
1.34 – 3.00	Process is good
>3.00	Process is excellent

Management review (MR)

The SOP “Quality management review (QMR)” and QMR report form were discussed. QMR team was comprised of the heads of all departments. QMR were conducted once in 4 months.

Deviations

The SOP “Handling of deviations”, deviation report form and register were discussed. The report form specified two types of deviations: planned and unplanned. Deviations were reviewed and approved by corporate QA, closed by the site QA. Deviation register was presented to the inspectors. Register was maintained department wise and presented to the inspectors.

A number of deviation reports were discussed.

Change control (CC)

The SOP “Change control”, flow chart and change control form were discussed. Changes were reviewed and approved by corporate QA, closed by the site QA. CC register was presented to the inspectors. Register was maintained department wise.

CC No XX was discussed.

Corrective actions and preventive actions (CAPA)

The SOP “Corrective action and preventive action” and CAPA register were discussed. CAPAs were classified as:

- Critical
- Major
- Minor

CAPAs post effectiveness was reviewed by Corporate Quality Assurance (CQA) or Quality Assurance (QA). CAPA register was maintained department wise.

CAPA form No XX was discussed.

Root cause analysis (RCA)

The SOP “Root cause analysis” was discussed. The RCA was used for investigation of deviations, complaints, out of specification (OOS) test results, out of trends (OOT), inspection findings, non-conformance and incidents. The following tools were used for RCA:

- 5 Why analysis
- Ishikawa diagram
- Failure Mode effect analysis (FMEA)

3.2 GOOD MANUFACTURING PRACTICES (GMPs) FOR PHARMACEUTICAL PRODUCTS

Manufacturing processes were defined and reviewed. Qualifications and validations were performed. Necessary resources were provided and records were made during manufacture. Significant deviations were recorded and investigated, root causes were determined and corrective and preventive action were implemented. A system was available to recall any batch of product from sale or supply and complaints about marketed products were examined.

3.3 SANITATION AND HYGIENE

The company had a standard operating procedure as the basis for its approach to personal hygiene and sanitation in its production facilities. Environmental monitoring was regularly performed.

3.4 QUALIFICATION AND VALIDATION

Validation Master Plan (VMP)

The key elements of a qualification and validation program were defined and documented in the Validation Master Plan (VMP). VMP review period was two years. Separate computer system validation plan was under preparation.

Qualification reports for compression machines XX were discussed.

3.5 COMPLAINTS

The SOP “Handling of market complaints”, flow charts, trends and register (January 2015 – April 2016) were discussed. Complaints were classified as:

- Critical
- Major
- Minor

Complaints trending was carried out yearly.

A number of complaints were discussed.

3.6 PRODUCT RECALLS

The SOP “Product recall”, flow charts and register (January 2015 – April 2016) were discussed. Recalls were classified as:

- Class I
- Class II
- Class III

According to the SOP there were three levels of recalls:

- Wholesaler level
- Retail level
- Consumer level

In case there were no recalls within 2 years, then mock recall should be executed.

3.7 CONTRACT PRODUCTION AND ANALYSIS

Production activities were not contracted out. Six contract laboratories were used for some tests. Agreement with the contract testing laboratory “YY” was discussed.

3.8 PERSONNEL

General

The manufacturer had an adequate number of personnel with the necessary qualifications and practical experience. Personnel were aware of the principles of GMP and received initial and continuing training, including hygiene instructions, relevant to their needs. Steps were taken to prevent unauthorized people from entering production, storage and QC areas.

Training

The SOP “Recruiting and training of temporary and their medical checks up” was discussed. Temporary workers had to undergo general cGMP and induction training before induction into various departments. According to the SOP temporary workers should undergo at least the following trainings:

- Personnel health and Hygiene
- Entry / exit procedures
- Safety
- Uniform usage and its handling
- General instructions
- Job related training

Training modules were available in local language.

Training effectiveness was evaluated by questionnaires with pre-given multiple choice answers.

3.9 PREMISES

General

Changing rooms were designed as airlocks and used to provide physical separation of the different stages of changing. Changing rooms were flushed with filtered air.

Ancillary areas

Rest and refreshment rooms were separate from manufacturing and control areas.

Weighing areas

Dispensing of raw materials was carried out in warehouse in two LAF booths. The SOP “Issue of raw materials” was discussed. Dispensing sequence was specified: excipients → API → flavor → color.

Production areas

The premises were laid out in such a way as to allow the production to take place in areas connected in a mostly logical order, corresponding to the sequence of the operations and to the requisite cleanliness levels.

Quality control areas

Sufficient space was given to avoid mix ups and cross-contamination. Adequate storage space was provided for samples, reference standards, solvents, reagents and records. Microbiological laboratory was not physically separated from the QC laboratory. It was noted that extension to the existing laboratories will be done in the nearest future.

3.10 EQUIPMENT

General

Equipment was located, designed, constructed, adapted and maintained to suit the operations to be carried out and permitted effective cleaning and maintenance.

Preventive maintenance (PM)

The SOP “Preventive maintenance schedule for equipment and machines in pharma plant and utility” and PM schedule were discussed. Equipment dedicated check lists were used to record PM.

Purified Water (PW)

Purified water was produced by reverse osmosis. Conductivity and pH were monitored on-line in two places: after Reverse Osmosis and at the return loop. Water in the loop was in continuous circulation; Total Organic Carbon, Temperature and velocity were monitored also on line at the return loop. Sand filter and softener were backwashed every day manually. PW system daily record log book and differential water pressure and filter cleaning record log book were presented to the inspectors. PW system was sanitized once per week by hot water.

The “Operation of purified water system” was discussed.

PW trends for December 2015 to March 2016 were discussed. All results were less than specified alert limit 50.

PW system was well maintained.

3.11 MATERIALS

General

Incoming starting materials and finished products were quarantined after receipt until they were released for use or distribution.

Starting materials

Starting materials were purchased from approved suppliers. Approved suppliers lists for starting materials (active and inactive) and packaging materials was presented to the inspectors.

Rejected, recovered, reprocessed and reworked materials

The SOP “Reprocessing/reworking of batch” was discussed.

3.12 DOCUMENTATION

In general documents were designed, prepared, reviewed and distributed with care. Documents were approved, signed and dated by the appropriate responsible persons. Documents were regularly reviewed and kept up to date. Records were made or completed when any action was taken.

Standard operating procedures (SOP) and records

Generally various SOPs and records of actions taken were available for all activities carried out on site. Records were kept for major and critical equipment.

3.13 GOOD PRACTICES IN PRODUCTION

General

In general production operations followed defined procedures. Deviations from procedures were recorded and investigated. Checks on yields and reconciliation of quantities were carried out. Materials, bulk containers, major items of equipment, rooms and packaging lines being used, were labelled to identify the product or material being processed and the batch number. Access to production premises was restricted to authorized personnel. In-process controls were carried out in IPC laboratory.

Before processing operations was started, steps were taken to ensure that the work area and equipment are clean and free from any starting materials, products, product residues, labels or documents not required for the current operation. Necessary in-process controls and environmental controls were carried out and recorded.

3.14 GOOD PRACTICES IN QUALITY CONTROL

General

The QC function was independent of other departments. Adequate resources were available to ensure that all the QC arrangements are effectively and reliably carried out. QC personnel had access to production areas for sampling and investigation as appropriate.

Out of specification results (OOS)

The SOP “Handling of out of specification results” and flow charts were discussed.

A number of OOS investigation reports were discussed.

Part 4: 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 M/s Ajanta Pharma Limited, located at Ajanta Pharma Ltd, B-4/5/6 MIDC Industrial Area, Aurangabad, Paithan District, Maharashtra, 431 148, India was considered to be operating at an acceptable level of compliance with WHO good manufacturing Practices for pharmaceutical products.

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.