

Prequalification of Medicines Programme
WHO PUBLIC INSPECTION REPORT
Finished Product Manufacturer

Part 1: General information

Name of Manufacturer	Ajanta Pharma Ltd
Unit number	Paithan
Production Block	N/A
Physical address	b-4/5/6, MIDC Industrial Area Paithan District 431128. Aurangabad Maharashtra India
Date of inspection	31 August to 3 September 2009
Type of inspection	Routine
Dosage forms(s) included in the inspection	Non coated tablets
WHO product numbers covered by the inspection	MA052 (Artemether plus Lumefantrene 20/120mg)
Summary of the activities performed by the manufacturer	Production and quality control

Part 2: Summary

General information about the company and site

Ajanta Pharma Ltd (hereafter referred to as APL), manufactured ORS powder, capsules and tablets at this site. In another site in Chickhalthana (also in Aurangabad) beta-lactam containing products were manufactured. The site is medium size and the company performed all activities of manufacture on site.

History of WHO and/or regulatory agency inspections

The site was inspected twice before by a WHO inspection team, in 2007 and January 2009. The above mentioned product was prequalified in late 2008. The site was also previously inspected by various DRAs.

Focus of the inspection

The inspection focused on the production and control of non coated tablets with specific focus on artemether / lumefantrine tablets. As a result of the findings in the previous inspection, considerable focus was placed on the inspection and verification of data relating to process validation and stability.

Inspected Areas

On the first day, after arrival, the company representatives introduced themselves. Business cards were exchanged. The inspectors introduced themselves and this was followed by the company presentation. The inspectors explained the focus of the inspection and the proposed plan for the day. A list of documents was given to the company and the documents were requested for review. The documents presented were then inspected including:

- Approved suppliers lists (old and new)
- Specifications for APIs and FPP
- Batch Manufacturing record (Master)
- SOP and records for Product Quality Review (PQR), complaints, deviations, change control, OOS results
- Interim Product Quality Review report for 2009
- List of batches manufactured in 2009 as well as customers these were supplied to
- Process flow chart
- Process validation protocol and report
- Batch Manufacturing Records for various batches (revalidation, validation after change, batches selected from PQR)
- SOP for archiving of documents

The following was inspected, verified and discussed:

Issue	Remark
Wet granulation and dry granulation	The company informed the inspectors that they were no longer going to manufacture the dry granulation process product on site
Material and product codes	These were noted and it was verified that the correct API (code and manufacturer) was used in batches, and reflected in the BMRs
Inventory Control System	The company explained that there was no means of code transfer for materials
Approved supplier list	Codes, materials, manufacturers and suppliers were inspected and vendor approval was discussed
Score line on tablet	The prequalified product has no score line
PQR	A year is calculated from April to March
Stability testing program	First three production batches and the first batch per year is placed on stability
Rework and reprocessing	The company does have an SOP but there had been no reworks or reprocessing in 2009
PQR and Interim PQR	IPQR was prepared for the purpose of the inspection. This was reviewed by the inspectors. Tabulated in process control test results were verified against the BMRs and source document (excel sheet).
Process validation	Three batches were subjected to validation as part of the revalidation procedure following the last inspection. An additional three batches were subjected to process validation when there were changes in equipment and changed from 2 sub lots of lumefantrene granulation to a single lot. The validation protocol and report (revalidation) was inspected. Raw data was verified e.g. samples for content uniformity (final blend) in three batches for the two substances, focusing on sample locations and sample analysis. The chromatograms were inspected, and concentrations were calculated. On the second day, the electronic files were inspected.

On the second day, the inspectors started by giving feedback on the observations of the previous day. This was followed by assessment of process validation and a brief inspection of parts of the QC laboratory was undertaken. A site inspection was started in the warehouse. Documents were inspected.

Issue	Remark
Process validation	For the assessment of the process validation report of the blending process, the results of the report were assessed versus the printed chromatograms and the Excel sheet calculations and results in the Quality Control Department. An assessment of these results was also performed versus the electronic data for the batches, overlay of chromatograms, the acquisition of data and its modification and the audit trail.
	The assay results for the active substance Artemeter (batch n° 1007/08) and lumefantrine (batch n° 0084/09) were assessed versus the chromatograms issued. According to the dossier, the assay methods were different for active substance and for finished products.
	The impact of the level of the load in the hopper on the compression process was also assessed for the manufactured batches (P0479C & P0499C).
	The manufacturing site used an internal software (Inventory Control System (ICS)) developed to balance the receiving and the issuance of starting materials and packaging materials.
	In the receiving area, containers were de-dusted, then labelled and logged into the ICS system before being labelling as quarantined. Sampling was then performed and the containers were labelled as under test before being released and stored as accepted starting materials. The manufacturer dispensed each starting material into a double polybag for different batches; the cleaning was performed between the dispensing of two different starting materials. Dedicated utensils were used.
	Storage capacity of the manufacturing site was assessed and clarifications were given on the location of products on pallets and the logical flow of products.

On the third day, the inspectors started by giving feedback on the observations of the previous day. This was followed by reviewing the SOP for complaints, complaints register, and complaint investigation reports. Then the packaging materials stores were inspected. After lunch, the production areas were inspected including granulation areas, compression areas, tools storage (punches and dies, FBD bags), the wash bay and a quick visit to the newly constructed area. Relevant documents were reviewed in some areas.

Issue	Remark
Complaints	<p>SOP, register, investigation reports, trends: The SOP detailed the procedure for handling, investigation, reporting, and corrective action. The complaints register was reviewed and the complaint received from WHO was reviewed. The batch records were reviewed by the inspectors.</p> <p>The review showed that a thorough investigation was done by the company, but that the complainant had purchased the non-qualified product, the complaint referred to pack sizes not produced by the company, and that no samples / photos were available for the products complained about.</p> <p>The SOP did not clearly specify reporting of complaints of a serious type to national authorities. This was corrected through corrective actions taken after the inspection.</p>
Training records	Training records for some operators in production were reviewed. This included initial and ongoing training records, assessment records and training certificates.
Competency	Competency list of production staff and authorization to perform tasks was discussed.
SOP for roles and responsibilities	Dispensing and FBD operator responsibilities (job descriptions) were requested as well as evidence of training and authorization to perform tasks after training and assessment.
XRD	The diffractogram of a batch of Lumefantrene was inspected as well as evidence of the working standard having been sent to the contract laboratory.
Log books	The use log books for equipment in granulation I (RMG, Mill, FBD and sifter) were inspected.
BMR	The BMR for Apmol 500 under process was inspected including for line clearances and set up for compression, and in process tests.
HVAC	The SOP for start up and shut down of AHUs was reviewed, as well as some records for pressure differentials for various areas.

On day four, the inspectors started by giving feedback on the observations of the previous day. This was followed by a review of the layout of the new area, area classifications, air pressure cascade, specifications for temperature and relative humidity and related controls. The lists indicating the various AHUs for different areas were reviewed. Several documents were requested and inspected.

A site inspection was done before lunch (granulation areas and washing area), and after lunch, additional documents were inspected. The service area was also visited to inspect elements of the HVAC system.

Issue	Remark
Qualification of AHU 27 and granulation area	Selected elements in the qualification were reviewed including air changes, installed filter leakage testing, and particulate monitoring (at rest). Data and certificates were inspected.
Air balancing	Air balancing records were reviewed (old and new area) - with AHUs on and off in different areas, AHU start up and shut down
Change control for the PW system and qualification and validation	Qualification and validation of the extended water loop and installation of the new water tank were inspected.
Production areas	Brief inspection of the areas where air flow direction was verified, and MOC of the PW loop was checked. The wash bay was inspected including the SOP for cleaning and CIP of In process bins.
Service area and HVAC	AHU 27 was inspected and the AHU for compression 3 (with dust collecting system).
Review of other documents	Trending of water sample results Stability protocol for Artefan 20/120 (6 batches) SOP for sampling and sampling plan for packaging material Reconciliation of packaging material (production)

2.1 QUALITY ASSURANCE

The company quality assurance system consisted of a quality policy, SOPs and other related documents and systems that were reviewed during the inspection. These were implemented, controlled and monitored through a site QA system as well as a corporate quality assurance responsibility.

2.2 GOOD MANUFACTURING PRACTICES (GMPs) FOR PHARMACEUTICAL PRODUCTS

The company implemented various systems to ensure compliance with GMP.

2.3 QUALIFICATION AND VALIDATION

The company had performed qualification and validation in various areas. However - the qualification of the extended PW loop lacked some details. This was corrected through corrective actions taken after the inspection.

2.4 COMPLAINTS

The SOP for complaints was reviewed and amended since the previous inspection, and was generally acceptable.

2.5 PRODUCT RECALLS

Not inspected.

2.6 CONTRACT PRODUCTION AND ANALYSIS

Not inspected.

2.7 SELF INSPECTION AND QUALITY AUDIT

Not inspected

2.8 PERSONNEL

Personnel that were interviewed on site were able to provide answers to the questions raised. Authorization of supervisors to perform tasks was not clearly defined. This was corrected through corrective actions taken after the inspection.

2.9 TRAINING

Training records were reviewed, and in general were considered to be acceptable.

2.10 PERSONAL HYGIENE

Garments and general hygiene was observed as acceptable.

2.11 PREMISES

The building was medium size and consisted mainly of bricks with plastered walls. Since the last inspection, the new extended area for production was completed and operational. The new area was spacious and of good design and finishing. Personnel and material flow was acceptable. Additional plans were mentioned for further expansion of dispensing, storage and packaging areas. The HVAC system was in general acceptable in terms of its design.

2.12 EQUIPMENT

The equipment used for the production of tablets was in general acceptable - excluding the cleanliness of some equipment where residues were observed on the equipment even after cleaning had been done.

2.13 MATERIALS

Materials were generally handled in accordance with GMP recommendations (receiving, cleaning, quarantine, sampling, release etc). However, the sampling and storage of packaging materials still required attention and the FIFO system appeared not to be always followed. Re-test date policy and control required attention. This was corrected through corrective actions taken after the inspection.

2.14 DOCUMENTATION

Documentation existed and consisted of SOPs, manuals, protocols, reports, specifications etc. These were in most cases acceptable.

2.15 GOOD PRACTICES IN PRODUCTION

Acceptable.

2.16 GOOD PRACTICES IN QUALITY CONTROL

The activities and practices in the QC laboratory were not inspected in detail. Focus was placed on selected activities in relation to control and reliability of data.

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 - Ajanta Pharma Ltd, b-4/5/6, MIDC Industrial Area Paithan District, 431128. Aurangabad, Maharashtra, India - was considered to be operating at an acceptable level of compliance with WHO GMP guidelines for the manufacture of non coated tablets.