### Part 1

#### General information

<table>
<thead>
<tr>
<th>Manufacturers Details</th>
<th></th>
</tr>
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<tbody>
<tr>
<td><strong>Company information</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Corporate address of manufacturer</strong></td>
<td>&quot;AJANTA HOUSE&quot; Charkop, Kandivli (West) Mumbai INDIA- 400 067 Telephone Number:- +91- 22-66061000 Fax:- +91- 22-66061200/66061300</td>
</tr>
<tr>
<td><strong>Inspected site</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Address of inspected manufacturing site if different from that given above</strong></td>
<td>As above</td>
</tr>
<tr>
<td><strong>Manufacturing license number</strong></td>
<td>• G/28/1505 (Drugs specified in Schedule C, C(1) excluding those specified in schedule X) • G/25/2080 (Drugs other than those specified in Schedule C, C(1) and X) issued by Gujrat Sate Food and drugs adminstration</td>
</tr>
<tr>
<td><strong>Inspection details</strong></td>
<td></td>
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<tr>
<td><strong>Dates of inspection</strong></td>
<td>7 – 11 August 2017</td>
</tr>
<tr>
<td><strong>Introduction</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Brief summary of the manufacturing activities</strong></td>
<td>Manufacturing, packaging and testing of oral solid dosage forms (tablets, hard gelatine capsules, oral dry powder suspension) and oral jelly.</td>
</tr>
</tbody>
</table>
General information about the company and site

Ajanta Pharma Limited (hereafter 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 headquarter 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, six in India {five formulation facilities and one Active Pharmaceutical Ingredient (API) facility}, and one in Mauritius.

Dahej site was constructed in 2014 and started its operations in October 2015. Commercialization of the products being manufactured at the site started in April 2017.

History

This was first the WHO inspection.

The site has been inspected by the following authorities:

<table>
<thead>
<tr>
<th>Name</th>
<th>Dates of inspection</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDCA (Food and Drugs Control Administration) Gujarat State</td>
<td>Jul 20, 2016</td>
</tr>
<tr>
<td>CDSCO (Central Drugs Standards Control Organization)</td>
<td>Sep 08, 2016 to Sep 09, 2016</td>
</tr>
<tr>
<td>USFDA (United States Food and Drug Administration)</td>
<td>Apr 03, 2017 to Apr 07, 2017</td>
</tr>
<tr>
<td>Ministry of Health Ethiopia</td>
<td>Apr 24, 2017 to Apr 26, 2017</td>
</tr>
<tr>
<td>FDA Ghana</td>
<td>26 Jun, 2017 to 27 Jun, 2017</td>
</tr>
</tbody>
</table>

Brief report of inspection activities undertaken

See Part 2 below

Scope and limitations

Areas inspected

See Part 2 below

Restrictions

N/A

Out of scope

N/A
<table>
<thead>
<tr>
<th>WHO product numbers covered by the inspection</th>
<th>PQP Number</th>
<th>Product</th>
<th>Strength</th>
<th>Dosage Form</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MA092</td>
<td>Artemether/Lumefantrine</td>
<td>20mg/120mg</td>
<td>Tablet,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Dispersible</td>
</tr>
<tr>
<td></td>
<td>MA111</td>
<td>Artemether/Lumefantrine</td>
<td>20mg/120mg</td>
<td>Tablet</td>
</tr>
</tbody>
</table>

### Abbreviations

- **AHU**: air handling unit
- **ALCOA**: attributable, legible, contemporaneous, original and accurate
- **AQL**: acceptance quality limit
- **API**: active pharmaceutical ingredient
- **APQR**: annual product quality review
- **BDL**: below detection limit
- **BMR**: batch manufacturing record
- **BPR**: batch packaging record
- **CAPA**: corrective actions and preventive actions
- **CC**: change control
- **CFU**: colony-forming unit
- **CoA**: certificate of analysis
- **CpK**: process capability index
- **DQ**: design qualification
- **EM**: environmental monitoring
- **FAT**: factory acceptance test
- **FBD**: fluid bed dryer
- **FG**: finished goods
- **FMEA**: failure modes and effects analysis
- **FPP**: finished pharmaceutical product
- **FTA**: fault tree analysis
- **FTIR**: Fourier transform infrared spectrometer
- **GC**: gas chromatograph
- **GMP**: good manufacturing practice
- **HACCP**: hazard analysis and critical control points
- **HPLC**: high-performance liquid chromatograph
- **HVAC**: heating, ventilation and air conditioning
- **ID**: identity
- **IR**: infrared spectrophotometer
- **IPC**: in process control
- **IQ**: installation qualification
- **KF**: Karl Fisher
- **LAF**: laminar air flow
- **LIMS**: laboratory information management system
- **LoD**: limit of detection
- **LOD**: loss on drying
- **MB**: Microbiology
- **MBL**: microbiology laboratory
- **MF**: master formulae
- **MR**: management review
- **NIR**: near-infrared spectroscopy
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>NMR</td>
<td>nuclear magnetic resonance spectroscopy</td>
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<td>NRA</td>
<td>national regulatory agency</td>
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<td>OQ</td>
<td>operational qualification</td>
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<td>PHA</td>
<td>preliminary hazard analysis</td>
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<td>PM</td>
<td>preventive maintenance</td>
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<tr>
<td>PpK</td>
<td>process performance index</td>
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<tr>
<td>PQ</td>
<td>performance qualification</td>
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<tr>
<td>PQR</td>
<td>product quality review</td>
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<tr>
<td>PQS</td>
<td>pharmaceutical quality system</td>
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<td>PW</td>
<td>purified water</td>
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<tr>
<td>QA</td>
<td>quality assurance</td>
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<tr>
<td>QC</td>
<td>quality control</td>
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<tr>
<td>QCL</td>
<td>quality control laboratory</td>
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<td>QMS</td>
<td>Quality management system</td>
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<tr>
<td>ORM</td>
<td>quality risk management</td>
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<td>RA</td>
<td>risk assessment</td>
</tr>
<tr>
<td>RCA</td>
<td>root cause analysis</td>
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<tr>
<td>RH</td>
<td>relative humidity</td>
</tr>
<tr>
<td>RM</td>
<td>raw materials</td>
</tr>
<tr>
<td>RS</td>
<td>reference standard</td>
</tr>
<tr>
<td>SAP</td>
<td>system applications products for data processing</td>
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<tr>
<td>SFG</td>
<td>semi-finished goods</td>
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<tr>
<td>SOP</td>
<td>standard operating procedure</td>
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<tr>
<td>STP</td>
<td>standard test procedure</td>
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<tr>
<td>T</td>
<td>Temperature</td>
</tr>
<tr>
<td>TAMC</td>
<td>total aerobic microbial count</td>
</tr>
<tr>
<td>TFC</td>
<td>total fungal count</td>
</tr>
<tr>
<td>TLC</td>
<td>thin layer chromatography</td>
</tr>
<tr>
<td>TMC</td>
<td>total microbial count</td>
</tr>
<tr>
<td>TOC</td>
<td>Total organic carbon</td>
</tr>
<tr>
<td>URS</td>
<td>user requirements specifications</td>
</tr>
<tr>
<td>UV</td>
<td>ultraviolet-visible spectrophotometer</td>
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<tr>
<td>VMP</td>
<td>Validation Master Plan</td>
</tr>
<tr>
<td>WFI</td>
<td>water for injection</td>
</tr>
<tr>
<td>WS</td>
<td>working standard</td>
</tr>
</tbody>
</table>
Part 2  Brief summary of the findings and comments (where applicable)

Brief summary of the findings and comments

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

   Data integrity
   The document “Data integrity policy” was discussed. This document was site specific and was applicable to all cGMP data generated including, but not limited to paper and electronic data.

   Quality Risk Management (QRM)
   The SOP “Quality risk management” and its 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:
     - 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, including outsourced production and formulation as well as the upstream suppliers, equipment and facilities for drug substances and medicinal products.

   According to the SOP effectiveness of the risk management process shall be reviewed every two years.

   Risk assessment (RA) schedule April 2017 – March 2018 was presented to the inspectors.

   The RA protocol/report XX Artemether/Lumefantrine Tablet, 20mg/120mg was discussed.
General RA approach was used for all similar production and control steps and was performed in December 2016. RA covered all production steps starting from batch record issuance, receipt and storage of raw materials, sampling of raw materials, dispensing of raw materials, receipt and handling of dispensed raw materials, sifting operation, blending operation, sampling of In process materials, compression, receipt and storage of packaging materials, sampling of packaging materials, blister packaging, receipt, storage and dispatch of finished goods, quality control system, analysis of raw material / packaging material, testing of in-processes and finished products, testing of stability samples, review of analytical report, HVAC system, purified water system, compressed air, storage and dispatch of finished goods and utilities. For all these steps separate RA protocols/reports were available.

The same approach was used for Artemether/Lumefantrine Dispersible Tablet, 20mg/120mg RA. This was not discussed during the inspection.

Product Quality Review (PQR)
The SOP “Product Quality review” was discussed. According to the SOP PQR for “WHO products” should be prepared from 1st April till 31st March 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 covered all sections mentioned in the GMP.

Process capability was calculated using CpK.

<table>
<thead>
<tr>
<th>CpK result</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 ≤ CpK ≤ 1</td>
<td>Result is out of specification and unacceptable</td>
</tr>
<tr>
<td>1 ≤ CpK ≤ 1.33</td>
<td>This value indicate the need for improvements</td>
</tr>
<tr>
<td>1.33 ≤ CpK ≤ 1.67</td>
<td>This is acceptable and desired state</td>
</tr>
</tbody>
</table>

The SOP “Statistical evaluation for data analysis” was discussed. The SOP was applicable for statistical evaluation analytical and process data generated for materials, products and environmental monitoring.

Since the site was only producing validation batches of Artemether/Lumefantrine tablets and started commercial batches of other products since April 2017, the PQR for this product had limited information.

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. The SOP stated that Managing director shall attend at least one QMR meeting per calendar year. QMR were conducted every four months. Personnel unable physically to attend meeting can attend meeting via teleconference. Standard agenda was part of the SOP.
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. Copies of deviation reports were attached to the respective BMRs/BPRs. According to the SOP deviations shall be closed within 60 days, in case deviation was not closed within specified time limit, approval for another target date shall be received from CQA/QA. Deviations were trended every 6 months.

Deviation registers 1st April 2016 – 31st March 2017 were presented to the inspectors. Register and trending was maintained department wise and presented to the inspectors. Deviation register and trending for production and QC departments were discussed.

A number of deviation reports were 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)

Root cause analysis was performed by a team set up case-by-case.

Corrective actions and preventive action (CAPA)
The “Corrective action and preventive action” and CAPA register were discussed. According to the SOP CAPA should be closed within 45 days. The procedure was applicable but not limited to findings originated from external and internal audits, customer complaints, PQR, recall, returned goods, deviations, non-conformance investigations, incidents investigation, OOS and quality management review. 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.

A number of CAPAs were discussed.

The SOP “Incidence reporting”, its flow chart and registers (production and QC departments) were discussed. Registers were maintained department wise. The SOP was provided with a definition for “incidence”.

WHO public inspection report Ajanta Dahej, August 2017
This inspection report is the property of the WHO
Contact: prequalinspection@who.int
Change control (CC)
The SOP “Change control”, its 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. Changes were classified as:
- Minor
- Major

2. Good manufacturing practices for pharmaceutical products
Manufacturing processes were defined and reviewed. Qualifications and validations were discussed to be performed according to prepared protocols. Significant deviations from the initial protocol 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. Sanitation and hygiene
The company had an SOP as the basis for its approach to personal hygiene and sanitation in its production facilities. Microbial monitoring of clean room personnel was performed as part of routine batch control.

Facilities were noted to be clean and well organized during the inspection.

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).

   Process Validation (PV)
Overviews were shown of batches produced for validation purposes.

   Cleaning Validation
Cleaning validation was performed and was capable of consistently removing chemical residues, cleaning agent’s residues and microbiological contamination levels below acceptance limit from respective equipment.

When there was a change in product matrix either due to a new drug product addition or deletion of existing product, the resulting matrix was evaluated.

At least 3 consecutive complete product changeover of pre-identified worst case product were monitored in order to prove that the cleaning procedure was suitably verified.

Bracketing concept was adopted for selection of single worst case product for cleaning validation as per respective dosage forms.
Evaluation of product matrix for cleaning validation was done whenever there was introduction of new product, introduction of new processing equipment with new design and function but having larger capacity.

Hold time studies
Hold time study report for un-cleaned equipment was discussed. Holding period for un-cleaned equipment was established.

The hold time study for cleaned equipment was discussed. Holding period for cleaned equipment was established.

Hold time studies protocol and report for Artemether 20mg + Lumefantrine 120mg tablets were discussed. Objective was to establish hold time for in-process stage material. Hold time for Artemether 20 mg + Lumefantrine 120 mg (both immediate release and dispersible tablets) were established.

T mapping
The SOP “Temperature / relative humidity mapping, re-mapping and monitoring” was discussed. This SOP was applicable to storage areas, stability chambers, refrigerators, incubators, manufacturing and packaging areas and retention sample storage area. T mapping studies for storage areas where T control was required should be performed for two seasons – summer and winter. For storage areas where T and RH are required, T/RH mapping study should be performed for 3 seasons: summer, winter and monsoon. Periodic re-mapping studies intervals were defined.

T/RH mapping study report “T and RH mapping study report for raw materials warehouse” was discussed. This study was performed with full load. The empty load study was performed during the AHU qualification.

Qualification of production equipment
Production equipment qualification was performed according to the following SOPs:
- “Design qualification of equipment, instruments, utility/software systems”.
- “Factory Acceptance Test (FAT)”
- “Installation qualification”
- “Operational qualification”
- “Performance qualification and re-qualification”

Qualification of V-Blenders, Equipment IDs XX, YY, ZZ which were used during production of Artemether/Lumefantrine tablets was discussed. URS, DQ, FAT, IQ and OQ were all performed satisfactorily.

Performance qualification protocol and report XX were discussed. The results of all performance qualification verification tests were found within acceptance criteria.

AHU qualification
The annual re-qualification protocol and report were discussed for the AHU for Compression-XX. The study was well designed and concluded that the room and its AHU complied with ISO Class 8.
Compressed air qualification
The qualification documentation for the compressed air system XX was discussed. It consisted of URS, FAT, IQ, OQ and PQ reports. Monitoring was done yearly for all user points, according to a schedule. Trending was not yet done, but data were compiled for the benefit of the inspectors. These data showed that the system was well under control.

Autoclave Qualification
At the Microbiological laboratory two autoclaves were used. A vertical one was for destruction only and the horizontal double door autoclave was used for the sterilization of media. The relevant SOP and qualification study were discussed.

Computer Validation
SOP “Computer system validation” was discussed. In an Annex to this SOP a list of systems was given.

Validation of major centralized systems SAP, LIMS and the corporate training system TRIMS was done by the Head Office in Mumbai. Summary reports were available.

Other software validation reports were discussed for HPLC OpenLab Server and ThermoLab software’s. The documentation for the validation of OpenLab Server, ECM Client and Scheduler, and OpenLab Shared Service was elaborate and clear. QA had accepted the software package after the validation was done by the supplier.

ThermoLab monitoring software version 1.2 was validated. IQ, OQ and PQ reports were discussed. At the laboratory it was verified that the current version is still 1.2.

5. Complaints
The SOP “Handling of market complaints” and its flow charts were discussed. Complaints were classified as:

- Critical
- Major
- Minor

According to the SOP QA shall conduct complaints trending within 45 days of year ending. Till the date of inspection no complaints were received.

6. Product recalls
The SOP “Product recall” and its flow charts 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
According to the SOP recall effectiveness shall be evaluated every two years by mock recall. SOP did not specify for which market recall shall be performed e.g. domestic/export market. Last mock recall was performed in July 2017 for Iraq market.

Until the date of inspection there were no recalls. According to the SOP Head CQA shall intimate concerned regulatory authorities within 24 hours of the recall decision made.

7. Contract production, analysis and other activities
Manufacturing activities were not contracted out. XX laboratories were used for some chemical tests. A written contract between the contract giver and the contract acceptor which clearly established the responsibilities of each party and any technical arrangements made in connection with both parties responsibilities were clearly specified, TA specified that the contract acceptor should not pass to a third party any of the work entrusted to him or her under the contract. TA with XX and audit report were discussed.

The SOP “Contract Testing Laboratory approval” was discussed. Approval of testing laboratories was done by CQA. Re-inspection of contract testing laboratories was performed every 3 years.

List of service providers was presented to the inspectors. TAs and audit reports with XX and YY used for laundry services were discussed.

8. Self-inspection, quality audits and supplier audits and approval
The SOP “Self-inspection” was discussed. Inspection were carried out by minimum two self-inspectors, of which one shall be from QA department and other from cross functional department other than QA department. Self-inspectors should have a minimum of five years of experience in pharmaceutical industry and be fully aware about GMP requirements. According to the SOP, conflict of interest should be avoided. Observations were classified as:

- Critical
- Major
- Minor

Annual self-inspection schedule was presented to the inspectors. According to the SOP each department should be inspected at every four month interval.

Inspection was carried out using department wise check lists. Data integrity, traceability and electronic compliance topics were covered during self-inspection.

Inspection report was written by the team and CAPAs addressed by the inspected department, evaluated and approved by QA. CAPA implementation was also checked by QA.
Supplier audits and approval

The SOP “Vendor and supplier qualification” and its flow charts for:
- Vendor approval for API and excipient
- Vendor approval for packaging material
- Vendor inspection
- Supplier approval for API, PM and excipient

were discussed.

According to the SOP API and primary packaging materials vendors should be audited every 3 years. For APIs and printed packaging materials vendor’s inspections should be performed before material was procured for commercial production. Questionnaires were used for excipients and secondary packaging materials vendor approval. Questionnaires were sent out every 3 years.

Suppliers (distributors) of excipients were audited every 5 years. Vendor inspections were performed by CQA and inspection schedule was presented to the inspectors.

9. Personnel

There appeared to be an adequate number of personnel qualified to perform and supervise the manufacturing and quality control. Controls were in place to prevent unauthorized people from entering production, storage and QC areas.

The SOP “Entry and exit procedure” was discussed. This SOP was applicable to all employees and visitors entering different buildings. The SOP was also available in local language.

10. Training

Training was given to employees (staff and associates) on the basis of corporate SOP. For temporary workers the SOP “Recruitment and training of temporary workers and their medical check-up” was applied.

Employees were expected to record their own training data in Training Information Management System TRIMS.

Temporary workers received basic training. For each part of their training they need to pass a test. Training records were discussed. Health checks are the same for employees and temporary workers.

11. Personal hygiene

All personnel, prior to and during employment, had to undergo an initial health examination. Thereafter regular health examinations were carried out every year. Direct contact between the operator’s hands and starting materials, primary packaging materials and intermediate or bulk products was avoided. Smoking, eating, drinking, chewing, and keeping plants, food, drink; smoking material and personal medicines was prohibited in production, laboratory and storage areas.
12. 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. Doors giving access to gowning rooms were not interlocked.

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

Weighing areas
Dispensing of starting materials was carried out in the warehouse in three separate rooms under RLAF. Solvents were dispensed in solvents warehouse under RLAF, primary packaging materials were dispensed in packaging materials warehouse under RLAF.

Production areas
Generally production premises were designed and constructed to facilitate good sanitation. Premises were cleaned according written procedures. Entrance to the production rooms was via change rooms. Adequate storage space was provided for in-process storage and logical positioning of equipment and materials. Generally steps were taken to avoid contamination and cross contamination. Steps were taken to prevent unauthorized people from entering production areas. A fingerprint based access system was in place. Access control was granted on several levels.

The SOP “Biometric access control in plant premises”, list of authorized personnel and controlled areas were discussed.

Adequate storage space was provided for in-process storage and logical positioning of equipment and materials. Generally steps were taken to avoid contamination and cross contamination. Air pressure differentials existed of more than 5 Pascals from corridors to cubicles. Monitoring was done manually twice a day. The company was validating a BMS system with continuous monitoring that will be implemented within 6 months.

Intermediate storage rooms
Tablets were held in containers in Semi-finished storage rooms.

Packaging areas
Around 20 packaging lines were in use. Primary packaging was done in blister machines with camera detectors for missing or damaged tablets. Secondary packaging was mainly done manually. Large numbers of ejected blisters were discussed on one of the lines. According to the company these would all be reprocessed after a visual inspection. Check-weighers were installed to detect missing leaflets, blisters and incomplete over-boxes. Printing of secondary packaging material was done offline in one of three printing rooms with controlled access. Printed materials were stored in access controlled rooms. According to the procedure non-printed left-overs of materials could be returned to the warehouse. The SOP on returns was discussed.
Quality control areas
Quality control areas were separated from production areas. Microbiological laboratory (MBL) was separate and air to the MBL was supplied by separate AHU. Chemical and instrumental laboratories were designed to suit the operations to be carried out. Sufficient space was given to avoid mix ups and cross-contamination. Adequate suitable storage space was provided for storage of samples, reference standards, solvents, reagents and records.

Rodent and Pest Control
Activities were outsourced to PCI Pest Control India Pvt. Ltd in Ankleshwar on the basis of a Technical Agreement issued on 1 April 2017. SOP XX of 4 February 2017 was discussed which described the various methods of pest control. Logbooks were discussed for rodenticide checks and for other activities to control pests.

13. Equipment
Equipment was located, designed and maintained to suit the operations to be carried out. Design of equipment permitted adequate cleaning and maintenance to avoid contamination and cross-contamination.

Fixed pipework was labelled to indicate the contents and the direction of flow. Balances and other measuring equipment of an appropriate range and precision were available for production and control operations and were calibrated on a scheduled basis.

An equipment spare part e.g. punches and dies, sieves and screens were stored in a separate room, in locked cabinets. QC released food grade oil was used for lubrication of equipment parts in direct contact with product. Each piece of equipment was identified by a number and logbooks were maintained of their periodic cleaning and integrity checks.

All compression machines were equipped with one or more metal detectors. An example was discussed of the initial qualification of metal detector XX on 17 March 2015. After qualification metal detectors are subjected to preventive maintenance as per SOP XX. In all cases the standard test set is used to verify the operation of the detectors. Furthermore, during setup of production equipment and every 4 hours during production the test is repeated.

Preventive maintenance (PM) of equipment
The general SOP “Preventive maintenance schedule for equipment and utility equipment” was discussed. There were also specific SOPs for preventive maintenance of machines.

The general SOP provided the procedure for initiating, assessing, planning and implementation of preventive maintenance schedule tracking for equipment and utility equipment. QA department and Maintenance department officer were responsible for implementation of the SOP. The procedure for implementation involved: Preventive maintenance schedule tracking for equipment and utility equipment, addition of new equipment and instruments, and removal of obsolete or old, scrapped equipment and instruments. Schedule from 1st April, 2017 to 31st March, 2018 was discussed.
Utilities

Purified water (PW)
The initial Qualification of water pretreatment and purified water generation system was inspected. URS, DQ, FAT, IQ and OQ reports were discussed. PQ report was also discussed. External training was done for the operation of PWS. Training attendance records for March and April, 2015 were discussed.

SOP “Preventive maintenance of purified water system” was discussed. PM was performed in accordance with checklist.

HVAC
A total of XX AHUs provided HEPA filtered air to production cubicles and extracted dust from these. All of the equipment was situated on a technical floor. This area was inspected. Preventive maintenance for the AHU consisted of annual particle counts, annual air velocity tests and semi-annual HEPA filter integrity tests. All units contained EU7 and EU4 pre-filters which were taken out and cleaned monthly (production cubicles) or bi-monthly (non-production areas). The applicable SOP was discussed. Cleaning of the filters was done in two dedicated areas and the risk of contaminating these rooms seemed well managed.

Compressed air
The plant was inspected where compressed air was generated. Two compressors were installed to provide dry, oil-free compressed air to production equipment. At all user points terminal filters were installed. The qualification reports for the compressed air installation were discussed.

14. Materials
Materials were received, sampled and tested according to written procedures. Materials were stored under appropriate conditions established by the manufacturer in an orderly fashion. Starting materials and packaging materials were purchased from approved manufacturers and suppliers. 100 % identity tests were performed on each container of the starting materials. Two sampling rooms were provided for starting materials sampling. In addition to this separate sampling rooms were provided for solvents in solvents storage area and primary packaging material in primary packaging material storage area. Sampling was done under RLAF. The sampling procedure was generated from LIMS. Sampling was done by QC personnel, assisted by warehouse associates. The procedure includes cleaning after each sampling operation, even if the next sample is taken from a new batch of the same material.

Products under quarantine/released/rejected were appropriately segregated. Materials management was performed by SAP system:

- Receiving
- Issuance
- Dispatch

The warehouses for raw materials, primary packaging materials and for finished products were inspected. The storage space was currently adequate, but a large scale-up of batch sizes could cause a lack of space.

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Finished good warehouse had a separate, locked room for storage of returned products.

The SOP “Issuance and return of excess material” was discussed. The SOP was applicable for raw material and packaging material returned from production to warehouse.

The SOP “Receipt of packaging materials” was discussed. The SOP was applicable for receipt of all packaging materials at the Dahej site.

The SOP “Handling of returned goods” and its flow chart was discussed.

The SOP “Sampling of raw materials” was discussed. This SOP was applicable to APIs, excipients and solvents sampling. Appropriate procedures were in place to ensure the identity of the contents of each container of starting materials. Bulk containers from which samples have been drawn should be identified. For APIs 100 % identity tests were performed using Raman spectroscopy. For composite sample five or less containers were combined to perform full analysis as per STP.

The SOP “Re-testing of raw materials and packaging materials” was discussed.

The SOP “Packaging material sampling” was discussed. Sampling was performed according the AQL. Defects were classified as:
- Critical
- Major
- Minor

The SOP “Issue of raw materials” was discussed.

The SOP “Placing portable data loggers with shipments where required; retrieving the same; retrieving data from the same; and archiving it” was discussed. Data loggers were placed in all shipments. Assessment report XX for temperature during transit of XX was discussed. Such kind of reports was prepared for each consignment. Shipment was to USA by sea. T and RH were recorded every hour.

Approved suppliers
Approved suppliers lists were presented to the inspectors.

15. Documentation
Documents should be designed, prepared, reviewed and distributed with care. Documents were approved, signed and dated by the appropriate responsible persons. Documents had unambiguous contents: the title, nature and purpose were clearly stated. Documents were regularly reviewed and kept up to date. According to the procedures documents should be reviewed every 2 years.

Batch Manufacturing Records
The BMR and BPRs for dispersible tablets batch XX, the last of the validation batches, were discussed. The records are well laid out and the information is clearly legible.
16. Good practices in production
In general production operations followed defined procedures. Handling of materials and products was done in accordance with written procedures and, recorded.

Deviations were recorded and investigated in accordance with approved procedure. Operations on different products were not carried out simultaneously or in the same room. During processing, materials, bulk containers, major items of equipment, and the rooms and packaging lines being used, were labelled with an indication of the product or material being processed.

Technology Transfer
Production at the Dahej site was started up after a process of technology transfer of manufacturing processes. The applicable SOP was discussed. This SOP gave a clear flow chart of steps to be taken in case of a product transferred to a new site. The first step was to perform a risk assessment using a checklist to assess what action need to be taken to mitigate risks. Risk assessment checklist XX was reviewed. This was related to dispersible tablets.

Risk assessment was done as per requirements. Some of the activities assessed were vendor qualification, storage conditions, availability of specifications and testing procedures and determining equipment for additional training. It involved also verifying the cleaning validation matrix to see if the new product is becoming the new worst case member.

17. Good practices in quality control

General
The QC function was independent from other departments. Adequate resources were available to ensure that all QC arrangements were carried out in a timely and orderly fashion. QC personnel had access to production areas for sampling and investigations as appropriate.

The SOP “Handling of out of specification results”, its flow chart and trends April 1st 2016 – March 31st 2017 were discussed. SOP was based on MHRA guideline. According to the SOP OOSs were trended every six months.

A number of OOS investigation reports were discussed

The SOP “Handling of out of trend results” and its flow chart were discussed.

Analytical method transfer
The SOP on analytical method transfer was discussed. The finished products have 4 specifications in total. For each of these the analytical methods were checked to see which were included in the transfer operation.
Batch record review
The SOP “Review of batch records and release or reject of finished products” and SOP “Review of analytical data” were discussed. Review of batch manufacturing reports and analytical raw data was done by checklists. Head QA or designee was responsible for release of finished products; head QC or designee was responsible for release of raw materials and packaging materials.

SOP “Handling of HPLC and GC chromatography analysis in good chromatographic practice” was discussed.

The SOP “Operation of sample manager – sample workflow in laboratory information management system (LIMS) version 3.3.0E” was discussed. LIMS was used, but not limited, for:
- Sample login
- Sample registration / approval
- Sample advice sheet
- Sample allocation
- OOT / OOS alerts
- Test result submission – done by analyst, checked by QC reviewer
- Test result approval
- Work sheet printing
- Usage decision
- Lot cancellation
- OOT / OOS investigations
- Certificate of analysis (CoA)

LIMS application was demonstrated during the course of inspection. LIMS was also used for keeping registers for:
- HPLC columns
- RS and WS
- Preparation of volumetric solutions
- Calibration schedule
- Stability samples

The SOP “User creation, modification and deactivation, password and system policies and privileges of the software in the instruments” was discussed. There were four user access rights specified for Open Lab software:

Stability studies
The SOP “Stability study of finished pharmaceutical products”, stability schedule and Artemether/Lumefantrine 20mg/120mg Dispersible Tablet stability protocol/report XX were discussed. Withdrawal tolerances were specified. The tablets were kept in the following conditions:
- 40°C ± 2°C / 75% RH ± 5% RH
- 30°C ± 2°C / 75% RH ± 5% RH
T and RH in stability chambers as well as in laboratory rooms, storage rooms, incubators and refrigerators were recorded by data loggers every hour. Print outs were taken daily and readings were checked.

One batch per year was taken for on-going stability studies.

During laboratory inspection as an example Combisunate dispersible 20 / 120 tablets analytical report was reviewed. Review included cross checks of raw data, instrument log books, instrument calibration records and standards used for calibration of instruments.

Purified water (PW) analysis
The following microbiological examination tests were carried out:
- Microbial enumeration tests
- Total aerobic microbial count - NMT 100cfu/ml
- Tests for specified microorganisms (All absent/100ml)
- Bile tolerant gram negative bacteria
- E.coli
- Salmonella species
- Staphylococcus aureus
- Pseudomonas aeruginosa
- Candida albicans.

Trend analysis was performed quarterly for all user points. Trends were within specified limits.

Environmental monitoring (EM)
Every 2 weeks routine monitoring took place for viable particles (settle plates) in all rooms that were serviced by an AHU. Trend reports were issued quarterly. No excursions were found. It was recommended to include 3 or more previous quarters into the trend reports to make them more meaningful.

Reference standards
The SOP “Procurement, handling, storage and usage of reference standards (RS) and reference solution” and The SOP “Preparation and handling of working standards (WS)” were discussed. WS were qualified against Pharmacopoeia RS or an authentic in-house RS. WS were packed in amber vials for single use under RLAF. Expiry date for WS was assigned 1 year.

Retention samples
The SOP “Handling of control samples” was discussed. FPP retention samples from each batch were kept for one year after the expiry date, samples of APIs were kept one year beyond the expiry date of the corresponding finished product Retention samples were stored in movable metal compactors, inventory was available.
Back up of electronic data
According to SOP backups are made from all standalone computer systems by connecting them to a laptop with a hard drive. For that reason standalone equipment has been given an IP address, which was the same for all. Two copies of the backup on the hard drive were made onto 2 USB drives. One was kept in the office in Dahej, the other was sent to the Head Office in Mumbai.

Microbiological laboratory (MBL)
The following tests were performed in the MBL:
- Microbial limit tests
- Environmental monitoring MB tests
- Water analysis
- Hold time studies MB tests
- Cleaning validation and verification MB tests

Microbiological Testing
Media management and Growth Promotion Testing SOP was discussed. There were clear instructions on how to prepare, inoculate and incubate media for growth promoting properties and for indicative properties in case of pathogen testing. Results of these tests were recorded in registers.

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 Limited, Dahej, located at Plot no. Z/103/ A, Dahej SEZ Part II, District: - Bharuch, State: - Gujarat, INDIA-392130 was considered to be operating at acceptable level of 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.
PART 4

List of GMP guidelines used for assessing compliance

   

   Short name: WHO TRS No. 986, Annex 2


   Short name: WHO TRS No. 961, Annex 6

   http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1


   Short name: WHO TRS No. 957, Annex 2


   Short name: WHO TRS No. 970, Annex 2

   http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_970/en/


   Short name: WHO TRS No. 929, Annex 4

   http://whqlibdoc.who.int/trs/WHO_TRS_929_eng.pdf?ua=1


   Short name: WHO TRS No. 961, Annex 5

   http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1


   Short name: WHO TRS No. 937, Annex 4

   http://whqlibdoc.who.int/trs/WHO_TRS_937_eng.pdf?ua=1

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*Short name:* WHO TRS No. 957, Annex 1

*Short name:* WHO TRS No. 957, Annex 3

*Short name:* WHO TRS No. 961, Annex 7
[http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1](http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1)

*Short name:* WHO TRS No. 961, Annex 9
[http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1](http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1)

*Short name:* WHO TRS No. 943, Annex 3
[http://whqlibdoc.who.int/trs/WHO_TRS_943_eng.pdf?ua=1](http://whqlibdoc.who.int/trs/WHO_TRS_943_eng.pdf?ua=1)

*Short name:* WHO TRS No. 961, Annex 2
[http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1](http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1)

*Short name:* WHO TRS No. 981, Annex 2
   Short name: WHO TRS No. 981, Annex 3
   http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_981/en/

   Short name: WHO TRS No. 961, Annex 14
   http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

   Short name: WHO TRS No. 992, Annex 3

   Short name: WHO TRS No. 992, Annex 4

   Short name: WHO TRS No. 992, Annex 5

   Short name: WHO TRS No. 992, Annex 6
   *Short name: WHO TRS No. 996, Annex 3*

   *Short name: WHO TRS No. 996, Annex 5*

   *Short name: WHO TRS No. 996, Annex 10*