

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

Name of Manufacturer	Mylan Laboratories Limited
Unit number	Unit 1
Production Block	Block 1, 2, 4, 7, 8
Physical address	Mylan Laboratories Ltd. Survey No. 10 Gaddapotharam, IDA, Kazipally Medak (Distr.) Pin: 502319 Andhra Pradesh, INDIA
Contact person and email address.	Mr Pallab De Sr.V.P, Corporate Quality Assurance e-mail: pallab.de@mylan.in
Date of inspection	23 to 26 April 2012
Type of inspection	Routine Inspection
Active Pharmaceutical Ingredient(s) included in the inspection	Artemether (APIMF 153) Artesunate (APIMF 161) Dihydroartemisinin (APIMF 178) Pyronaridine Tetrphosphate (APIMF 190)
Summary of the activities performed by the manufacturer	Production and quality control of APIs

Part 2: Summary

General information about the company and site

Mylan Laboratories Ltd. is a company that is specialized in the manufacturing of active pharmaceutical ingredients and their intermediates. It is now part of Mylan Laboratories Inc., Indiana, USA, and was acquired in 2007 as former Matrix Laboratories and renamed in 2011. Mylan Laboratories Ltd has 9 manufacturing facilities located at different sites all over India and one site in China, The headquarter in India is at Hyderabad. Unit 1 site at Kazipally was the focus of this inspection. It had 8 production blocks. It is located about 60 km from Hyderabad Airport.

43 products were manufactured at this site; these included the following products with APMIF certificate: Artemether, Artesunate, Dihydroartemisinin, Lamivudine, Lopinavir, Neverapine, Pyronaridine Tetraphosphate, Tenofovir Disoproxil Fumarate, and Zidovudine.

The number of persons working at Mylan Laboratories Unit 1 was about 539, of which 249 were involved in production, 59 in Quality Control, and 22 in Quality Assurance. 58 people were working in Process Development, 14 in the warehouse and 63 in Engineering Department. Total number of personnel within Mylan Laboratories Ltd. India was about 8000.

History of WHO and/or regulatory agency inspections

This was the third WHO inspection of this site. Previous inspections took place in 2011 and 2006. The site had been inspected by USFDA in 2011, 2009, and in 2007; however the product scope was different from this inspection.

Focus of the inspection

The inspection covered most of the sections of WHO GMP for Active Pharmaceutical Ingredients, including Quality Management; Personnel; Buildings and Facilities; Process Equipment; Documentation and Records; Materials Management; Production and In-Process Controls; Packaging and Identification Labelling of APIs and Intermediates; Storage and Distribution; Laboratory Controls; Validation; Change Control; Rejection and Reuse of Materials.

Areas inspected

Introductory Meeting

- Introductions
- Scope of inspection
- Overview of activities at site
- Organization chart
- Job description
- Inspection of the Quality Management System
- Product Quality Reviews (PQR)
- Change Control
- Deviations

- Complaints
- Recalls
- Out of Specification investigations
- Self-inspections

Inspection of Production Operations & Facilities

- Warehousing and storage
- Sampling
- Production operations
- In-process sampling and controls

Packaging operations

- Packaging materials
- Packaging and labelling operations

Quality Control

- QC Labs
- Sampler management
- Testing of APIs
- Reference substance and working standards
- Retention Samples
- Stability chambers
- Stability results for selected products
- Microbiology lab

Utilities

- Purified Water
- Building Management Systems

Validation

- Process validation
- Validation Master plan, protocols
- Facility & equipment qualification
- Cleaning validation

Materials Management

- Supplier approval
- Sampling, testing & raw material release

Review of batch documents

- Batch record review
- Batch Release systems

Review of procedures from facility tour

- Production / cleaning procedures
- Calibration procedures & Programmes
- Staff training programme & records

Post inspection summary meeting

2.1. QUALITY MANAGEMENT

Quality management systems were established, documented and implemented in general.

The QA/QC department was independent from production.

The production and quality control procedures were defined in general, different procedures (SOPs) were described and were followed.

The SOP for PQRs and PQRs for the following APIs were inspected

In order to verify compliance with the principles of GMP for APIs, regular internal audits were being conducted on six month schedule for all departments. Non-compliance reports were recorded. Corrective actions were taken accordingly and reviewed by QA.

Quality Risk Management had been introduced as a QM-tool and was regulated by SOP. Risk assessments were documented.

2.2 PERSONNEL

Personnel were qualified by education and training to perform and supervise the manufacture of APIs in general. SOP on Training (CQA/GMP/018/04) regulating training topics / modules, training schedules (FM026/CQAGMP/018/02) and test sheets were reviewed. Attendance of a person at his assigned trainings was traceable. Additionally casual workers were employed.

An organization chart was available. Key personnel responsibilities were specified in job descriptions.

The described responsibilities were reviewed for the following key personnel:

1. Quality Assurance Manager
2. Quality Control Manager
3. Production Manager
4. Manager Warehouse
5. Site head

2.3 BUILDINGS AND FACILITIES

The workshops and the facilities inspected were well maintained and the level of cleanliness was acceptable in general. The flow of materials and personnel through the blocks were designed to prevent mix-up and cross contamination in general.

The production units for the four products in focus of this inspection were not dedicated. All units were used as multi-product facilities. There was no production for the inspected APIs during the inspection.

Utilities

The utilities, the general pipework as well as the air handling units in the clean rooms were designed and maintained to be acceptable in general. Pipelines and product flow were identified. Drawings of the utility systems were available and some of these were examined.

The clean rooms were classified as grade D. The AHUs were equipped with a sequence of inlet filters of 10 µ, 5 µ, 1 µ, and 0.3 µ; the HEAP filters were corresponding to class H13. SOP on environmental monitoring was reviewed.

Water

Purified water was used as a solvent in the process and in the last stages of the four processes. All production blocks were equipped with the purified water system.

The water to feed the purified water system was sourced from a well and transferred by street tankers into underground reservoirs on site. The system consisted of sand filter, activated carbon filter, cation and mixed bed ion exchange etc.

The purified water circulation was continuous in two sub loops equipped with a UV lamp each. UV intensity, pH and conductivity were monitored inline each loop (see Part 5 for observations.)

Containment

The company claimed that there were no other highly sensitizing materials either produced or handled at this site, nor any other APIs of high pharmacological activity, such as steroids or cytotoxins.

2.4 PROCESS EQUIPMENT

The equipment maintenance and cleaning were performed to an acceptable level. A SOP on preventive maintenance covered maintenance schedules of all equipment and referred to formats for dedicated schedule lists for each type of equipment. This SOP on preventive maintenance was reviewed.

Cleaning procedures and records were available for inspection. The time frame for cleaning of equipment and its subsequent release for use in the manufacture of the API were specified in the Production Batch Record and in the equipment cleaning procedure.

Calibration

Calibration of devices (temperature, pressure etc.) was conducted according to the established program, and performed by the engineering department following fixed schedules. Balances and scales were checked daily, calibration was done monthly by the Production Dept. and once a year by a governmental group. SOP on calibration was reviewed.

Computerized Systems

The Material Management Module by SAP was introduced in 2011 to follow material purchase and reception as well as material manufacturing, finishing, storage, and shipping. The previous batch numbering system and use of suffixes was replaced.

The analytical status of each batch of raw material or batch manufactured was documented, traceable and controlled with each material movement. Accounting of stock was associated with raw material assignment (dispensing) to each production batch and amount of material manufactured. Storage location in each of the warehouses was also controlled by SAP MM.

No computer systems were used in the production processes.

2.5 DOCUMENTATION AND RECORDS

Documentation System and Specifications

The company had a documentation system in place consisting of organization charts, SOPs, protocols, records, reports, etc. Specifications existed for each API.

The SOP on control of documents and several other SOPs were reviewed pertaining to the activities associated with the product processing, cleaning of equipment, etc. The Master Manufacturing Formula of the inspected APIs was reviewed.

The Master Batch Production Record for Artemether was reviewed.

Equipment Cleaning and Use Record

Equipment cleaning and use records were generally in place. Cleaning of rooms and equipment was conducted at defined time intervals. Batch to batch cleaning was done according to documented procedures and filed with the respective batch record. Flexible pieces of equipment, i.e. hose pipes and container were handled and cleaned separately. Hose pipes and filter cloths were discharged at the end of production campaign.

Records of Raw Materials, Intermediates, API Labelling and Packaging Materials

Records including an approved vendors list were available from the SAP MM files. API labels were controlled and printed by SAP MM on request.

Laboratory Control Records

SOPs and analytical control records were available and were presented for inspection.

2.6 MATERIALS MANAGEMENT

General Controls

There were written procedures describing the receipt, labelling, quarantine, storage, and handling of materials, as well as the procedures for sampling, testing and approval or rejection of materials. SOP on vendor approval (CQA/GMP/042/02) was reviewed (see Part 5 for observations.)

The storage conditions and operation in the warehouse such as temperature in the cold storage and finished APIs storage room was under control.

Rejected materials were seen in the warehouse, but there was a separated and locked area for such material.

2.7. PRODUCTION AND IN-PROCESS CONTROLS

Production processes were guided by documented procedures and instructions. Production processes including synthesis, purification, crystallization, drying, milling, packaging etc. were conducted in non-dedicated facilities and multi-purpose equipment to manufacture the four APIs in focus of this inspection. Clean areas were available for the final steps of the API's manufacture, such as isolation, drying, milling, sifting, and packaging. There were in-process controls conducted at appropriate stages of the synthesis to monitor performance of the process and quality of the intermediates and APIs.

There were several production blocks at the Unit-1 site. All these facilities were used in a multipurpose manner.

2.8 PACKAGING AND IDENTIFICATION LABELLING of APIs AND INTERMEDIATES

Packaging and labelling operations were conducted as per standard operating procedures. After batch release the QC person affixed approved labels and handed over the release intimation to production.

General

Packaging materials were checked and released according to specifications. The containers and inside PE bags used to pack finished APIs were consistent with the information in dossier.

Packaging and Labelling Operations

The labelling operations were designed to prevent mix-ups as only one product was handled in the labelling room at any one time.

2.9 STORAGE AND DISTRIBUTION

The company had appropriate and separate storage warehouses and areas for starting materials, packaging materials, solvents, intermediates, and finished APIs.

Cleaning of warehouse areas was regulated by SOP. The qualification of the temperature distribution in the cold storage and final product room was reviewed. An observation was made.

2.10 LABORATORY CONTROLS

General Controls

The main QC laboratory was situated at a separate building. The premises, facilities and utilities were separate from production. There were dedicated rooms for activities like wet chemistry and instrumentation. There were adequate pieces of equipment with up to date calibration status. Records of sample receipt and allocation of analysis were inspected.

Reference Standards

Primary reference, working reference standards and register were reviewed and found to be acceptable.

Testing of Intermediate and APIs

The SOP for sampling and testing of intermediates and APIs, STP and Batch Analysis Record of a selected batch were reviewed. The SOP on HPLC operations was reviewed.

The access right to the HPLC testing programme were checked and found acceptable in general.

Microbiological Testing

The microbiological laboratory was situated in the neighbouring Unit II. The SOP for media preparation and records were checked. Data of microbiological testing of water was reviewed and found to be acceptable.

Stability monitoring of APIs

The long term and accelerated stability study were performed as per conditions submitted in the dossier. An SOP on stability testing was available for inspection.

Retention Samples

The retention samples of the inspected antimalarial APIs and their starting material Artemisinin were kept in the cold storage as required.

Records

OOS SOP and log book for 2010 and 2011 were reviewed. Investigations had been performed. Deviation log books were also inspected.

2.11 VALIDATION

The company had policy, procedures, protocols and reports for validation and qualification of processes, procedures, equipment, utilities etc.

Validation Master Plan regulated all qualification and validation activities. Process Validation Protocol for Artesunate and the validation report was reviewed.

The four APIs in focus of this inspection were taken over from R&D to production and processes were validated in 2009 and in 2010. Reprocessing and recovery of solvents had been elaborated. There was limited production history and experience with these products.

Three validation batch records and validation documents were reviewed.

The validation master batch records have been reviewed, including some R&D batches. Beside these validation batches only few commercial size batches were produced.

Qualification

Qualification was done according to SOP. Major pieces of equipment were qualified as per the written installation and operational qualification protocols before taking them for product processing. In general qualification reports were available. Revalidation was scheduled every 5 years.

Qualifications of reactor and HVAC for one Block were reviewed along the sequence of User Requirement, DQ, IQ, OQ, and PQ.

Cleaning Validation

The company had procedures, protocols and reports for the cleaning validation of major pieces of equipment described in the Cleaning process for equipment and their verification. MACO was calculated according to the 10 ppm rule for all products. Details for cleaning, sampling, and testing were reviewed. Cleaning records were reviewed for selected reactor.

2.12 CHANGE CONTROL

There was a procedure for change control and for handling and investigation of deviation. The change control register and records were maintained. The procedures to initiate the change control, temperature change control and planned deviation were discussed.

2.13 REJECTION AND RE-USE OF MATERIALS

Recovery of solvents and materials at different stages of synthesis was conducted on site according to the product process. This was reflected in the respective batch records and validated with one batch only so far. Re-use of recovered product from mother liquors including further purification was used in some steps.

2.14 COMPLAINTS AND RECALLS

Standard operating procedures were available to handle complaints and recalls. The SOP on handling of market complaints and the SOP on handling of product recall were reviewed.

There were no customer complaints or recalls as none of the materials of the four APIs in focus of this inspection had been sold.

2.15 CONTRACT MANUFACTURERS (INCLUDING LABORATORIES)

According to the company, there were no contracted manufacturing activities. The particle size test was contracted out. The contracts for HVAC qualification and calibration activities, as well as the testing of water delivered against drinking water specification and on pesticides were reviewed. The contracts exhibited a comparable structure.

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, APIs manufactured at Mylan Laboratories Limited, Unit-1, Survey No. 10, Gaddapotharam, Kazipally Industrial Area, Medak District – 502319, Andhra Pradesh India was considered to be manufactured in compliance with WHO GMP for Active Pharmaceutical Ingredients.

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.