



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

**PART 1: GENERAL INFORMATION**

|                                                         |                                                                                                                                                                    |
|---------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Name of Manufacturer                                    | Oxalis Labs                                                                                                                                                        |
| Production Block                                        | General Block                                                                                                                                                      |
| Physical address                                        | Oxalis Labs, Vill. Theda, P.O.lodhimajra , Baddi, Distt. Solan, India                                                                                              |
| Date of inspection                                      | 27 - 30 April 2015                                                                                                                                                 |
| Type of inspection                                      | Initial inspection (new site)                                                                                                                                      |
| Dosage forms(s) included in the inspection              | Solid Dosage Form (Tablet)                                                                                                                                         |
| WHO product numbers covered by the inspection           | <b>Product under assessment:</b><br>Anti-malarial (MA)                                                                                                             |
| Summary of the activities performed by the manufacturer | Manufacturing, packaging, quality control, stability testing and release of metered doses inhalers (MDI), external preparations, soft gelatin capsules and tablets |

**PART 2: SUMMARY**

***General information about the company and site***

The site Oxalis Labs, Vill Theda, P.O.lodhimajra, Baddi, Distt. Solan, India is located in an industrial area and is surrounded by industrial units that are of non-chemical nature.

The site has two production blocks:

- General Block
- MDI Block

The site started operations in September 2012. Oxalis Labs is contract manufacturing facility for Macleods Pharmaceuticals. All products manufactured in Oxalis Labs are for Macleods Pharmaceuticals. Macleod's corporate office is located in Mumbai.

No hormones, steroids, cephalosporin's, beta-lactams or cytotoxic were manufactured at the site.

### ***History of WHO and/or regulatory agency inspections***

The site was not previously inspected by a WHO Prequalification team.

The site was inspected by Health and Family Welfare Department, Himachal Pradesh, India on 19 March 2015.

### ***Focus of the inspection***

The inspection focused on the production and control of Oral Solid Dosage form product under assessment

### ***Inspected Areas***

Elements of various systems were inspected, and included:

- Pharmaceutical quality system
- Sanitization and hygiene
- Qualification and validation
- Complaints
- Recalls
- Supplier qualification
- Personnel
- Training
- Personal hygiene
- Premises
- Equipment
- Materials
- Documentation
- Production
- Quality control

## **PART 3: INSPECTION OUTCOME**

### **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. Managerial responsibilities were specified in job-descriptions. 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.

### Quality Risk Management (QRM)

The SOP “Quality Risk Management” described two QRM methods: Hazard Analysis & Critical Control Points (HACCP) and Failure mode and effects analysis (FMEA).

An overall evaluation of the risk involved throughout the entire manufacturing process was performed using the HACCP method.

### Product Quality Review (PQR)

The SOP “Product Quality Review” was reviewed. All batches manufactured during the calendar year should be considered for the PQR. PQR for the previous year should be completed by the end of March. When no batch or less than 3 batches were manufactured; review of data of the product should be carried out.

The PQR Summary of conclusions highlighted the overall quality trend and areas for improvement.

### Change Control (CC)

The SOP “Change control” was used to control the changes proposed that may have an impact on product quality. A manual record keeping system was in place.

Changes affecting the facility and the equipment were recorded on different forms. Changes were categorized as:

- Major
- Moderate
- Minor

A guideline was provided in the SOP for the classification of changes. Quality assurance (QA) decided on the classification of the change and on the members of the change control committee.

CC registers for 2014 and 2015 and specific CC reports were also reviewed.

### Deviations

The SOP “Handling of Deviations” was reviewed. Records were processed manually; no computerized system was used for deviation management.

The company classified the deviations as:

- Major
- Minor and
- Critical
- Planned
- Unplanned

Deviation registers for 2014 and specific deviation reports were also reviewed.

#### Non-conformance reports (NCR)

The SOP “Handling of Non-conformance” was used to record non-conformances on the shop floor and make decisions along with In-process Quality Assurance (IPQA) regarding the actions to be taken.

IPQA initiated the NCR report, head of department (production) signed for the approval of proposed corrective actions.

#### Corrective Actions and Preventive Actions (CAPA)

SOP “Corrective action and Preventive action” procedure was followed during CAPA management.

According to the SOP, CAPA projects could originate from the following sources: incidents, deviations, CC, NCR, out of specifications (OOS) and others. Post implementation actions were reviewed prior to CAPA project closure.

CAPA register and specific CAPA reports were reviewed during the inspection.

### **3.2 GOOD MANUFACTURING PRACTICES (GMPs) FOR PHARMACEUTICAL PRODUCTS**

In general good manufacturing practices were implemented. The necessary resources generally were provided. Manufacturing processes were clearly defined and systematically reviewed. Qualification and validation were performed. Instructions and procedures were written in clear and unambiguous language. Records were made during manufacture and significant deviations were recorded and investigated. Records covering manufacture and distribution were retained and system was available to recall any batch of product from sale or supply.

### **3.3 SANITATION AND HYGIENE**

Premises and equipment were maintained at acceptable level of cleanliness. The scope of sanitation and hygiene covered personnel, premises, equipment and apparatus, production materials and containers, products for cleaning and disinfection.

### **3.4 QUALIFICATION AND VALIDATION**

The key elements of a qualification and validation program were defined and documented in the Validation Master Plan (VMP). VMP was checked. VMP was approved by Macleods Pharmaceuticals Corporate QA. VMP also specified preventive maintenance schedule for equipment.

Re-qualification criterion after major changes was specified for equipment / instrument / utilities, facilities / areas.

Periodic re-qualification intervals were set up.

Operational qualification and performance qualification protocol/report for blender mixer granulator (BMG) was spot checked.

Blister primary packaging machine, equipment re-qualification protocol/report was checked. Re-qualification was carried out in March 2013.

#### Cleaning validation

The acceptance criterion was based on visually clean criteria, 10 PPM / dose criteria. The smallest value derived from the above criteria was considered as the acceptance criteria for the product based on worst-case.

The SOP “Procedure to perform cleaning validation study” was reviewed. Cleaning validation was based on worst case product approach. Bracketing was used for grouping of products manufactured in identical equipment chain. Two types of cleaning were used:

- Type A – batch-to batch change
- Type B – product-to product change.

Sampling methods used for cleaning validation were:

- Swab sampling
- Rinse sampling

Rinse sampling and swab sampling techniques were defined in the SOP. Swab samples were taken from 25 cm<sup>2</sup>. Swab recovery studies were carried out for Stainless Steel (SS), Teflon and glass surfaces.

HPLC and UV methods were used for cleaning validation of Artemether & Lumefantrine tablets. Worst case products were selected based on solubility.

Rapid Mixer Granulator and multi-mill cleaning validation reports were checked.

SOP Operation and cleaning of multi-mill was reviewed.

#### Clean equipment hold time studies

A specific clean equipment hold time protocol/report was checked.

Swab sampling technique was used. Total bacteria counts (TBC) and total fungal counts (TFC) were counted at the specific time intervals:

#### Excel sheets validation

Excel sheets were used in Quality control (QC) laboratory to enter data for calculations. According to the VMP Excel sheets re-validation should be carried out every two years. In case new calculation formulas were applied (for example new Standard Tests Method,

etc.) - the Excel sheet was subject to re-validation.

#### Computerized systems - revalidation

Programmable logical control (PLC) systems should be re-validated every 5 years.

### **3.5 COMPLAINTS**

Complaints and other information concerning potentially defective products were reviewed according to written SOP and the corrective actions were taken.

The SOP “Handling of customer complaints” was reviewed. Head QA and Corporate QA (CQA) were responsible for complaint investigation. Complaint impact assessment was performed by Head QA/designee. Complaints were classified as:

- Critical
- Major
- Minor

According to the SOP detailed risk assessment (RA) should be performed for critical complaint and root cause of the complaint should be found out. After identifying root cause CAPA should be proposed. Decisions and measures taken as a result of a complaint should be recorded and referenced to the corresponding batch records. If a product defect was discovered or suspected in a batch, consideration was given to whether other batches should be checked in order to determine whether they are also affected. Based on the SOP, in case the complaint batch failed to meet predetermined approved specifications, it must be recalled.

A specific complaints investigation reports were reviewed.

### **3.6 PRODUCT RECALLS**

Till the date of inspection there was no recalls initiated. There was a system in place to recall products from the market. The SOP “Product recall” was reviewed. SOP specified:

- Voluntary recall
- Forced recall

Recalls were classified as:

- Class I – defective/dangerous/potentially life threatening medicines that could result into serious health risk/adverse events or even death. According to the SOP Class I recall should be initiated within 24 hours after receipt.
- Class II – medicines that possible could cause temporary or medically reversible adverse health problem or mistreatment. According to the SOP Class II recall should be initiated within 48 hours after receipt.
- Class III – medicines that are defective and are unlikely to cause adverse health reaction etc. According to the SOP Class III recall should be initiated within 5 working days after receipt.

According to the SOP competent authorities of all countries to which a given product had been distributed were informed. The effectiveness of the arrangements for recalls were tested and evaluated from time to time.

To check the effectiveness of the recall procedure mock recall should be performed every two years  $\pm$  3 months. Till the date of inspection one mock recall (Class III) for domestic market was performed on 6.08.2014.

### **3.7 CONTRACT PRODUCTION AND ANALYSIS**

Technical agreement (TA) between Macleods Pharmaceuticals Limited and Oxalis labs was reviewed. TA specified Quality agreement for Pharmaceutical products and division of responsibilities.

Technical agreements were created and approved according to the corporate (Macleods) guidelines. Requirements of both parties (contract giver and contract acceptor) were specified. Technical agreements were reviewed once in two years.

During the inspection the technical agreement between Macleods Pharmaceuticals Limited, Corporate (Mumbai) and Macleods Pharmaceutical Limited (Sarigam, Gujarat) was reviewed.

### **3.8 SELF INSPECTION AND QUALITY AUDIT**

The SOP “Self-inspection” was reviewed. Self-inspection was carried out by cross functional team which consisted of personnel from different departments. Inspectors were trained in-house.

The following items were included in the self-inspection:

#### **QA**

- Personnel and administration
- Production
- Stores
- QC
- Environmental Health and Safety
- Engineering
- IT

Self-inspection was carried out using department based check lists.

#### Self-inspection team

Self-inspection team was approved by the Head QA

#### Frequency of self-inspection

Self-inspection was carried out twice per year according to the annual schedule. Self-inspection schedule for 2015 was presented to the inspectors.

#### Self-inspection report

A “Self-inspection report and its compliance” was written at the completion of a self-inspection. The report included:

- Observations and observations category (critical, major and minor)
- CAPA taken
- Target completion date
- Responsibility
- Follow-up status of CAPA
- Remarks

#### Follow-up action

Self-inspection team who performed the inspection was responsible for follow up actions. Inspection team leader and Head QA were responsible to make decision if follow up inspection was required.

#### Suppliers audit and approval

Vendors were qualified and approved according to corporate (Macleods Pharmaceuticals) guidelines. This procedure was transposed to Oxalis Laboratories Labs as per SOP “Vendor Qualification and Approval”. The procedure applied to all vendors/brokers of raw materials and packaging materials.

Suppliers were divided in two groups:

- Directly supplying materials without storage at their facility
- Holding materials in their warehouse as per recommended storage conditions.

Selection of suppliers was based on facility and questionnaire. First questionnaire was sent to the vendor followed by auditing. Auditing was performed using a checklist included in the SOP. There was no ranking of suppliers.

Requalification was performed at a frequency of once in three years. Macleods Pharmaceuticals CQA decided on steps to be taken during re-assessment such as re-audit. Some of the criteria considered during re-assessment were: supply history, complaint, regulatory approvals etc.

### **3.9 PERSONNEL**

#### General

In general, there were sufficient qualified personnel to carry out the tasks for which the manufacturer was responsible. Individual responsibilities were clearly defined and recorded as written descriptions. Personnel were aware of the principles of GMP received initial and continuing training, including hygiene instructions.

### The site Organogram

The Organogram presented was approved and dated, QA Assistant General Manager and QC Senior Manager reported to the Executive Vice President Corporate QA & Regulatory Affairs (RA) Macleods Pharmaceutical.

Separate Organograms were presented for QC and QA.

### Key personnel

The head of production department and quality department were independent of each other. In general key personnel was qualified and experienced.

The following Job responsibilities were reviewed:

- QA Assistant General Manager
- Senior Manager QC
- Assistant Manager production General block

## **3.10 TRAINING**

The SOP “Training of personnel” was reviewed. The following training was provided:

- Induction training
- On-job training
- Annual training
- Advanced training

The procedure how to perform training was explained in the “Training manual”. Training manual specified 16 training modules:

- GMP
- Documentation
- Process control
- Cross contamination
- Warehousing
- Utilities
- Officer role
- Risk analysis
- Basic microbiology
- Environment Health & Safety Procedures
- Coating
- Adverse drug reaction
- Explosion hazard during powder processing
- Granulation
- Compression
- Packing

Global training covered Training modules plus additional training, for example: documentation and data control, personal hygiene etc. Mainly training was given by trainers; however the following training topics were “self-reading” training:

- Basic microbiology
- Procedure for personnel hygiene
- On site emergency plan
- Selection of personal protective equipment
- Safety work permit
- Rounding of analytical results

Training schedules for 2014 and 2015 were presented to the inspectors and spot checked. All training modules listed above were covered annually.

For officers and positions above officer level, training effectiveness was evaluated through written multiple choice questionnaires; operators’ training effectiveness was evaluated orally and practically. It was explained that verbal training for operators was given mainly in local language.

The SOP “Contract labor policy for entry & exit in the factory premises” was spot checked. The following training was given to the labor workers:

- Do’s and don’ts in production areas.
- GMP

Both training modules were available in local language. Training records were presented to the inspectors. Training records were retained in QA.

The SOP “Analyst qualification” was reviewed. The procedure was applicable for newly recruited analysts. Analyst’s qualification was carried out for specific tests. An analyst qualification records for working with HPLC were spot checked.

QC department Analyst Qualification matrix and specimen signature lists were available and presented to the inspector.

### **3.11 PERSONAL HYGIENE**

The SOP “Procedure for personnel hygiene” was spot checked. If any employee was suffering from infectious disease like conjunctivitis or severe cold, person was not allowed to work. Direct contact was avoided between the operator’s hands and starting materials, primary packaging materials and intermediate or bulk product. Smoking, eating, drinking, chewing, and keeping plants, food, drink, smoking material and personal medicines were not permitted in production, laboratory and storage areas.

The SOP “Procedure for Medical Check-up” was checked. Annual health check-up was

carried out for each employee by a qualified medical practitioner and records were retained.

### **3.12 PREMISES**

#### General

In general premises were located, designed, constructed, adapted and maintained to suit the operations to be carried out. Premises used for the manufacture of finished products were suitably designed and constructed to facilitate good sanitation. Premises were designed and equipped so as to afford maximum protection against the entry of insects, birds or other animals.

#### Ancillary areas

Rest and refreshment rooms were separate from manufacturing and control areas. Facilities for changing and storing clothes and for washing and toilet purposes were easily accessible and appropriate for the number of users.

#### Storage areas

Storage areas were of sufficient capacity to allow orderly storage of the various categories of materials and products. Receiving and dispatch bays were separated and protected materials and products from the weather. Receiving areas were designed and equipped to allow containers of incoming materials to be cleaned.

#### Weighing areas

The weighing of starting materials was carried out in two separate weighing areas.

#### Production areas

Premises were laid out in such a way as to allow the production to take place in areas connected in a logical order corresponding to the sequence of the operations and to the requisite cleanliness levels and allowed logical positioning of equipment and materials. In general where starting and primary packaging materials and intermediate or bulk products were exposed to the environment, interior surfaces were smooth and free from cracks and open joints, did not shed particulate matter, and permitted easy and effective cleaning. Production areas should be effectively ventilated.

#### Quality control areas

QC laboratories were separated from production areas and designed to suit the operations to be carried out in them. There were suitable storage space for samples, reference standards solvents, reagents and records.

### **3.13 EQUIPMENT**

Equipment was located, designed, constructed, adapted and maintained to suit the operations to be carried out. Balances and other measuring equipment with appropriate range and precision were available for production and control operations and were

calibrated on a scheduled basis. Calibration due-date labels were attached to the equipment. Current drawings of critical equipment and support systems were maintained.

Calibrated standard weights used for in-house verification of balances were available. The calibration certificate for the set of standard weights was presented to the inspectors.

#### Preventive maintenance (PM)

The SOP “Preventive maintenance policy” was checked. SOP was applicable for all equipment in production area, utility area, AHU, duct collection system, Exhaust unit, air preparation units, Laminar Air Flow & Reverse Laminar Air Flow and water tanks. According to the SOP annual maintenance should be prepared for all critical equipment. Frequency for annual PM was defined and PM was carried out as per PM SOP for particular equipment.

The SOP “Preventive Maintenance of Compression Machines was checked. PM was done according to the checklist dedicated to the equipment. Spot checks showed that PM schedule for compression machines was followed.

The SOP “Operation and calibration of Shimadzu HPLC system with Chromeleon software” was checked. HPLC calibration was done in-house, every 6 months. Spot checks showed calibration schedule for 2014 was followed.

PM of the Shimadzu HPLC was done by service provider. Annual maintenance contract (AMC) with serviced provider was spot checked.

Calibration planner for instruments (2014 and 2015) was spot checked. Spot checks showed that calibration schedules were followed.

### **3.14 MATERIALS**

#### General

In general materials used for operations such as cleaning, lubrication of equipment did not come into direct contact with the product and was of a food grade. Incoming materials and finished products were quarantined after receipt or processing, until they were released for use or distribution. Materials and products were stored under the appropriate conditions and in orderly fashion to permit batch segregation and stock rotation by a first-expire, first-out rule.

#### Purified Water (PW)

PW system was installed at the end of 2012 and started producing PW in January 2013. Separate PW system was provided for the Tablet block. Water source was bore well.

PW in loop was in continuous circulation, T was maintained less than 25 °C. T and PW flow rate was controlled at the return.

PW tank air filter was replaced every 6 months. Filter CoA was available. PW tank and loop sanitization was carried out weekly. Whole PW generation system was sanitized every 15 days.

Ultra Violet (UV) lamp was replaced after 7200 hours; UV lamp intensity was monitored on line. Conductivity and Total Organic Carbon (TOC) were also monitored on line. PW system equipment was labeled and labels contained required information (see section compressed air and nitrogen).

Air filter replacement and PW system sanitization records were spot checked.

PW system installation documentation was presented to the inspectors. For performance qualification 3 stage approach was used:

- 1<sup>st</sup> phase was for 21 days; samples were taken and analyzed from all sampling points. Raw water, soft water and PW was tested in accordance to established specifications;
- 2<sup>nd</sup> phase was for 30 days; samples were taken and analyzed from all sampling points. Established specifications parameters were verified after completion of the stage. Routine sampling plan was established;
- 3<sup>rd</sup> phase was for one year; reduced sampling, covering all sampling points in 7 days. Samples from return loop were collected and analyzed daily.

PW trends for all 3 phases were checked for the specific sampling points.

Alert and actions limits were established In general PW system was well maintained. Water used in the manufacture of pharmaceutical products was suitable for its intended use.

The SOP “Sampling, testing and release of water” was spot checked.

#### Materials management

Materials management (Raw materials, excipients and packaging materials) was controlled by Enterprise Resource Planning (ERP) system. It was said that the system initially was validated in 2010 and re-validated in 2015. ERP validation protocols/reports were not checked during the inspection. Access rights to release the product from quarantine to production were given to QC personnel. Warehouse staff was able to manage only inventory control of the materials.

Material code transfer procedure was used on site. In case of code transfer ERP system automatically transferred product to quarantine status. Subsequently sampling was carried out and after QC release code transfer was approved.

### Starting materials

Starting materials were purchased from approved suppliers. For each consignment the containers were checked for integrity of package and seal and for correspondence between the order, the delivery note, and the supplier's labels. The "Raw materials verification sheet" was used to check incoming materials. Damage to containers and any other problem that might adversely affect the quality of a material were recorded and reported to the QC department and investigated. In case one delivery of material was made up of different batches, each batch was considered as separate for sampling, testing and release and Analytical Report Protocol (ARP) No. Procedures were in place to ensure the identity of the contents of each container of starting material. Sampling of raw materials was carried out in separate sampling booths. One sampling booth was dedicated for primary packaging materials sampling. Maximum of samples in composite sample was defined – not more than (NMT) 5. Dispensing was carried out in two areas.

Temperature (T) & Relative Humidity (RH) mapping protocol and report for approved Raw materials store, general block was reviewed. According to the VMP T&RH mapping studies should be performed in each season: summer, winter and rainy season. Studies were carried out for 10 consecutive days.

### Packaging materials

Printed packaging materials were stored in secure conditions to exclude the possibility of unauthorized access. Each delivery or batch of printed or primary packaging material was given a specific reference number.

### Intermediate and bulk products

Intermediate and bulk products were kept under appropriate conditions.

### Finished products

Finished products were held in quarantine until their final release. The status of finished products stored in this warehouse was controlled by ERP only, therefore no status labels were attached to shipper boxes.

After release finished products were transported to the central warehouse in Ambala.

### Recalled products and Returned goods

Segregation was provided for the storage of rejected, recalled, or returned materials or products.

### Rejected, recovered, reprocessed and reworked materials

The SOP "Reprocessing, recovery and reworking" was spot checked. According to the SOP no reprocessing or reworking of non-conforming intermediate or finished product was permitted.

#### Reagents and culture media

Records were available and maintained for the receipt and preparation of reagents and culture media. Positive and negative controls were applied to verify the suitability of culture media each time they were prepared and used. Growth promotion tests on the media were performed when a fresh stock was received and each time when media was prepared

Reagents made up in the laboratory were prepared according to written procedures and appropriately labelled. The labels were signed and dated by the person preparing the reagent.

#### Reference standards

Working standards were kept under controlled conditions. Working standards were used for all types of analysis.

Lumefantrine working standard was available; traceability was demonstrated to USP primary reference standard lot F0H108.

#### Waste materials

Not covered during this inspection

### **3.15 DOCUMENTATION**

#### General

In general documents were designed, prepared, reviewed and distributed with care. In general, documents were approved, signed and dated by the appropriate responsible persons. Documents were regularly reviewed and kept up to date. Alterations made to documents were signed and dated.

The documentation system at Oxalis was mainly based on Macleods Pharmaceuticals Corporate guidelines and procedures. At Plant level SOP on SOP described how to prepare Batch Production Records, specifications and standard test procedures. At Corporate level guidance documents were in place for the preparation of Master documents, Standard Tests Procedures and Specifications.

The SOP "Document and data control" was checked. Original sets of documents were retained in QA. This SOP was applicable to SOPs, Specifications, Analytical Data Sheets, General Tests Procedures, Batch Manufacturing and Batch Packaging Records, Protocols etc. According to the SOP on SOPs, Specifications, Analytical Data Sheets, General Tests Procedures, Batch Manufacturing and Batch Packaging Records should be reviewed every two years. Documents related to the production and quality control should be retained until the expiry date of product + 1 year. Documents such as qualification and validation protocols/reports, methods of analysis etc. were retained permanently.

#### Labels

Labels applied to containers, equipment or premises were clear and unambiguous.

#### Specifications and testing procedures

Testing procedures were validated. Approved, signed and dated specifications and testing procedures were maintained by QA department.

#### Specifications for starting and packaging materials

Approved, signed and dated specifications for starting and packaging materials were maintained by QA department.

#### Specifications for intermediate and bulk products

Specifications for intermediate and bulk products were available.

#### Specifications for finished products

Specification for Artemether/Lumefantrine tablets 20 mg/120 mg was reviewed.

#### Master formulae

Authorized master formula was available.

#### Packaging instructions

Authorized packaging instructions were available.

#### Batch processing records

A batch processing record was available for Artemether/Lumefantrine tablets 20 mg/120 mg. Before any processing begins, checks were made that the equipment and work station are clear of previous products (line clearance), documents, or materials not required for the planned process, and that the equipment is clean and suitable for use. Line clearance was recorded.

#### Batch packaging records

A batch packaging record was available for Artemether/Lumefantrine tablets 20 mg/120 mg. Before any packaging operation begins, checks were made that the equipment and work station are clear of previous products (line clearance), documents or materials not required for the planned packaging operations, and that equipment is clean and suitable for use. Line clearance was recorded.

#### Standard operating procedures 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.

#### Batch numbering system

The SOP "Allotment of batch number was reviewed.

### **3.16 GOOD PRACTICES IN PRODUCTION**

Till the date of inspection one submission batch for filing to the WHO had been manufactured and released. During the inspection one batch (batch size 110000 tablets) manufacturing process was completed, second batch was under compression and third batch was under blending. These batches were part of process validation for the 110000 tablets batch size.

#### 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. Operations on different products were not carried out simultaneously or consecutively in the same room or area. 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 performed by IPQA within the production area.

#### Prevention of cross-contamination and bacterial contamination during production

Precautions were taken to prevent the generation and dissemination of dust by provided airlocks, pressure differentials, and air supply and extraction systems. In general contamination and cross-contamination of starting material or of a product by another materials or product were avoided. Production areas were subject to periodic environmental monitoring.

Pressure in production corridors was positive to the production rooms. Pressure difference was maintained 15 PA. During inspection a specific air handling unit (AHU) serving Granulation room, was inspected.

HVAC system was installed in 2012 and was in operation since January 2013. The air was filtered via the following filters cascade:

- EU 4 (10 micron)
- EU 4 & EU 6 (5 micron)
- EU 7 (3 micron)
- HEPA EU 13 – (8 HEPA filters were installed in the ceiling of the room).

Pressure differentials between different filters were not monitored. Pressure differential magnehelic gauges were under installation during the inspection. Filters cleaning records were spot checked.

AHU starting and switching off sequence was specified in the SOP “Operation of AHU”.

Alarm system was not provided for the HVAC system. However it was noted that CC was initiated to install alarm system and pressure differential magnehelic gauges between the filters.

Four rooms were provided for filters cleaning:

- De-dusting room. Compressed air was used to remove the dust
- Washing room. Filters were cleaned using soft water and compressed air was used to remove remains of water
- Drying room. Filters were placed on perforated shelves, during drying room temperature was maintained 45 °C.
- Clean filter storage room. In this room also spare filters were stored.

After cleaning filters were checked visually for damage.

HVAC initial qualification was not checked during the inspection. Re-qualification was carried out yearly.

A specific AHU re-qualification report was checked. The tests performed were identical to initial qualification.

Calibration certificates were available and checked for the following equipment:

- Anemometer
- Photometer
- Manual pressure differential gauge
- Sling psychrometer
- Particle counter

AHU qualification was carried out following ISO 14644. In general HVAC system was well maintained.

The SOP “Environmental monitoring (EM) of classified area” was spot checked. Settle plates and active air sampling was used for EM. Alert and action limits were specified.

EM by settle plates was carried on once in a week for each location and fort nightly for active air sampling. EM trends for Granulation room from were checked. Till the date of inspection alert limits had not been reached.

#### Processing operations

Before processing operations were 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. Time limits for storage of equipment after cleaning and before use were stated and based on validation data. Significant deviations from the expected yields were recorded and investigated.

Measuring, weighing, recording, and control equipment and instruments were serviced and calibrated at specified intervals and records maintained.

Separate bins contained the dispensed material for individual batches. Dispensed liquids (i.e. isopropyl alcohol) were stored according to batch numbers on separate metallic pallets.

On line metal detectors were installed for all compression machines. Metal detector challenge tests using ferrous, non-ferrous and SS particles were carried out at the start of the compression, every 4 hours and at the end of the production.

Punches and dies were stored in locked SS cabinets. Dedicated set of punches and dies was used for Artemether/Lumefantrine 20mg/120mg tablet. Punches and dies drawings were available and dimensions were checked upon receipt. Punches and dies rotation was ensured. Food grade lubricant was used. CoA of the lubricant was presented to the inspectors. Diamond paste was used for dies and punches polishing. Punches and dies inspection set calibration status and calibration certificates were checked during inspection.

#### Packaging operations

Before packaging operations begun, steps were taken to ensure that the work area, packaging lines, printing machines and other equipment are clean and free from any products, materials or documents used previously and which are not required for the current operation. The line clearance was performed according to an appropriate procedure and checklist and recorded.

Primary packaging lines were connected to the secondary packaging lines. One primary/secondary packaging line was used for Al/PVC blister packaging. Primary packaging line did not have any on-line checks (for example pharma code, empty “pockets” etc.).

Stereos were stored in the locked cabinets. Blisters integrity tests were carried out every hour and recorded in the BMR.

#### Compressed air

There were 3 air compressors: one of these was standby.

Compressed air quality was analyzed every 6 months. The following tests were carried out:

- TBC&TFC

- Water vapor
- Oil mist

#### Nitrogen

Nitrogen was generated on site from compressed air, 0.2 micron filters were installed at all points of use.

Nitrogen quality was analyzed every 6 months. The following tests were carried out:

- TBC&TFC
- Water vapor
- Oil mist

All equipment was labelled, labels contained the following information:

- Equipment name
- Equipment ID
- Activity
- Done on
- Due on
- Done by
- Checked by

### **3.17 GOOD PRACTICES IN QUALITY CONTROL**

#### General

The QC function was independent from other departments. QC personnel had access to production areas for sampling and investigations if required. QC laboratories (raw materials (RM) testing, finished goods testing, stability laboratory and microbiology laboratory) were located on the second floor of the general tablet manufacturing block.

Samples to be analyzed were taken by:

- QC for raw materials and packaging materials
- QA for in-process and finished products

Uniformity of dosage units testing documents for specific batch was verified. Tests were carried out on two HPLC systems. Ten samples were prepared for each active ingredient (Artemether and Lumefantrine) originating from composites taken from the bulk product. Results were well within specifications.

HPLC column storage and record keeping was verified in the Raw Material testing laboratory.

#### Control of starting materials and intermediate, bulk and finished products

Samples of starting materials, packaging materials, intermediate products, bulk products and finished products were taken by approved methods. Sufficient samples of starting

materials and products were retained to permit future examination of the product.

The SOP “Sampling, testing, rejection and release of raw materials” was reviewed. According to the SOP excipients and APIs 100% sampling was done for ID tests. Composite sample of maximum of 5 containers were used for:

- Assay
- Loss on drying (LOD)/water tests

Final composite sample was formed from each composite sample. Full analysis was performed on final composite sample.

The SOP “Sampling, testing, rejection and release of packaging materials” was reviewed. AQL was used for sampling of packaging materials. Inspection level II and normal sampling level was applied. Defects were defined as:

- Critical
- Major
- Minor

#### Out-of-specification

The SOP “Handling of out of specification” as well as the OOS register were reviewed.

#### Test requirements - starting and packaging materials

Before releasing a starting or packaging material for use, the QC manager ensured that the materials have been tested for conformity with specifications for identity, strength, purity and other quality parameters. An identity test was conducted on a sample from each container of starting materials.

#### Test requirements - in-process control

In-process control records were maintained and formed a part of the batch records.

#### Test requirements - finished products

For each batch of medicines, there was an appropriate laboratory determination of satisfactory conformity to its finished product specification prior to release. Products failing to meet the established specifications or any other relevant quality criteria were rejected.

#### Electronic data management

Back-up of electronic data was created on servers and tapes.

Tapes were made 3 times per week. Two copies were retained at Oxalis Laboratories (at Baddi location) and one in the corporate offices.

The ERP system was handled by corporate QA (Macleods) no related procedures were created and/or approved at Oxalis Laboratories.

Data integrity related SOPs reviewed during the inspection were the following:

- User management of computer system
- User management for Chromeleon Chromatographic
- Good Chromatography Practices

#### Batch record review

QC analytical records were reviewed as part of the approval process of batch release.

#### Retention samples

Retention samples from each batch of finished product were kept for at least one year after the expiry date. Finished products were kept in their final packaging and stored under the recommended conditions. Samples of active starting materials were retained for at least one year beyond the expiry date of the corresponding finished product.

Retention samples were stored in chronological order at temperature NMT 25°C (current reading: 22°C) and 55%RH (current reading: 51%RH). Artemether and Lumefantrine Tablet (20 mg+120 mg) Lot No 14TAI0001A retention samples were stored in location B40. Incoming record (240 tablets) and reconciliation after yearly verification (24 tablets) were presented to the inspectors.

#### Stability studies

A written program for ongoing stability determination was developed and implemented.

The following conditions were provided in individual stability chambers:

- Temperature: 25°C $\pm$ 2°C and Relative Humidity: 60% $\pm$ 5%
- Temperature: 40°C $\pm$ 2°C and Relative Humidity: 75% $\pm$ 5%
- Temperature: 30°C $\pm$ 2°C and Relative Humidity: 65% $\pm$ 5%
- Temperature: 30°C $\pm$ 2°C and Relative Humidity: 75% $\pm$ 5%

There was a central data collection system that collected data on hourly bases. This information was printed daily and it was available at the time of inspection. Printouts were verified for the month of Dec. 2014 (for chamber with Temperature: 25°C $\pm$ 2°C and Relative Humidity: 60% $\pm$ 5%).

In the event of a temperature excursion audio and visual alarm notified QC laboratory personnel and security gate.

#### Microbiological laboratory

The microbiological laboratory had a separate AHU from the manufacturing plant.

Main activities performed in the microbiology laboratory were:

- Microbial Limit Tests of water and finished products
- Environmental monitoring

- Preparation of media

There was a dedicated area for garment washing and drying. Glassware was washed and decontaminated in a separate room with a dedicated autoclave. Disposables were double bagged (after decontamination) and sent to incineration. Plates were washed, dried in the oven and sterilized in double door autoclave.

Bowie Dick test was performed daily and recorded. Autoclave qualification was performed once in six months.

There was a separate incubator for the storage of biological indicators. This cabinet was empty at the time of the inspection.

Environmental monitoring samples were kept at 20-25°C for 3 days; after the reading of the initial results samples were moved to 30-35°C for 2 days.

### **3.18 TRANSFER OF TECHNOLOGY (ToT)**

ToT was done from Macleods Pharmaceuticals Daman site. “Report for technology transfer for Artemether + Lumefantrine 20mg+120 Mg Tablets” was reviewed.

The SOP “Technology transfer” was reviewed.

The “Risk assessment report by HACCP analysis” for product Artemether + Lumefantrine Tablets was checked

#### Process validation

Artemether and Lumefantrine Tablets (20 mg+120 mg), validation report was checked.

Validation task force included: QA, Manufacturing, QC and Microbiology, Engineering, Formulation and Development.

Equipment record included: dispensing area, production area, granulation area, compression area, tablet inspection area and primary packaging.

Environmental monitoring limits were set to temperature: 22°C+/-3°C and relative humidity: NMT 50%RH 50 ± 5% RH.

Raw material test record reference and uncoated tablet finished product test reference were also part of the validation report.

Analytical method transfer and validation was also checked.

#### Analytical method validation

The Guideline for Analytical method validation was reviewed. It was a corporate guideline applied to the validation of pharmacopoeial and in-house methods.

The SOP “Cleaning validation of Swab/Rinse sample” was also reviewed; it contained the verification of tests methods as follows:

- Recovery
- Limit of detection
- Linearity
- Precision
- Solution stability
- Interference of the swab

Traces of Lumefantrine in Swab/Rinse sample method was spot checked.

#### **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, Oxalis Labs (General Block), located at Vill. Theda, P.O. lodhimajra, Baddi, Distt. Solan, India, was considered to be operating at an acceptable level of compliance with WHO GMP guidelines.

All the non-compliances observed during the inspection that were listed in the full report as well as those reflected in the WHOPIR, were addressed by the manufacturer, to a satisfactory level, prior to the publication of the WHOPIR

This WHOPIR will remain valid for 3 years, provided that the outcome of any inspection conducted during this period is positive.