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

| Part 1 | General information |
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| **Manufacturers details** | |
| Name of manufacturer | Mangalam Drugs and Organics Ltd, Unit 1 |
| Corporate address of manufacturer | Rupam Building, 3rd floor, 239, P D' Mellow Road, near GPO, Mumbai 400 001, India |
| **Inspected site** | |
| Address of inspected manufacturing site if different from that given above | Plot No 187, 2nd Phase GIDC, Vapi, Gujarat, 396 195, India<br>GPS Coordinates: 20 22 10.75N, 22 55 47.66E |
| Unit / block / workshop number | Unit 1 – Plant 1A (Block 10) and Plant1D (Block 9) |
| **Inspection details** | |
| Dates of inspection | 1 – 4 May 2018 |
| Type of inspection | Routine inspection |
| **Introduction** | |
| Brief summary of the manufacturing activities | Production and quality control of APIs |
| General information about the company and site | Mangalam Drugs & Organics Ltd is a company that is specialized in manufacturing active pharmaceutical ingredients and their intermediates. It was established in 1977 as an aromatic and specialty chemicals manufacturer and in 1996 started engaging in the manufacture of APIs and pharmaceutical intermediates. It has two manufacturing facilities, namely Unit 1 and Unit 2, located at two different sites, in Vapi, Valsad District, Gujarat State, India. Both units are of interest to WHOPQ and it is recommended that they are consecutively inspected since there is transfer of raw material and intermediates between these sites. Unit 1 site was the focus of this inspection and it consisted of a number of buildings within the compound. There were only 2 buildings in which manufacturing were performed: Block 1D (Building 9 in SMF) and Block 1A (Building 10 in SMF). Both are multi-purpose synthesis plants. Analytical and microbiological laboratories were located in buildings 02 and 03.<br><br>The following molecules were manufactured on site: |

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| | Nimesulide, Allopurinol, Bisoprolol Fumarate, Furosemide, Tenofovir Disoproxil Fumarate, Artemether, Lumefantrine, Amodiaquine Hydrochloride, Artesunate, Piperaquine Phosphate, Dihydroartemisinin, Primaquine Phosphate<br><br>Major changes since the last WHO inspection:<br>Building 7 - new raw and packaging materials, finished APIs warehouse<br>Building 13 (Block 1B)- new building hazardous solvent, liquid drum stores<br>Building 42 (Plant 1C) solvent recovery building<br>Powder processing area of Building 9 (Block 1D) renovated – new HVAC system<br>New stability and retained sample areas in a newly constructed building (02A, 03A) |
| History | The site was previously inspected by WHO twice in 2011, and once in 2014<br><br>The most recent inspection by the Gujarat Food and Drug Administration was carried out in April 2017 |
| **Brief report of inspection activities undertaken - Scope and limitations** | |
| Areas inspected | Pharmaceutical Quality System<br>Documentation<br>Facilities and Equipment<br>Utilities<br>Production<br>Quality Control<br>Packaging and labelling |
| Restrictions | N/A |
| Out of scope | APIs out of WHO scope |
| WHO APIs covered by the inspection | Lumefantrine<br>Artemether<br>Amodiaquine Hydrochloride<br>Artesunate<br>Piperaquine Phosphate<br>Dihydroartemisinin<br>Tenofovir Disoproxil Fumarate<br>Primaquine Phosphate |

| Abbreviations | Meaning |
|---|---|
| AHU | air handling unit |
| ALCOA | attributable, legible, contemporaneous, original and accurate |
| 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 |

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|---|---|
| EM | environmental monitoring |
| FAT | factory acceptance test |
| FBD | fluid bed dryer |
| 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 |
| IR | infrared spectrophotometer |
| 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 |
| NMR | nuclear magnetic resonance spectroscopy |
| NRA | national regulatory agency |
| OQ | operational qualification |
| PHA | process hazard analysis |
| PM | preventive maintenance |
| PpK | process performance index |
| PQ | performance qualification |
| PQR | product quality review |
| PQS | pharmaceutical quality system |
| QA | quality assurance |
| QC | quality control |
| QCL | quality control laboratory |
| QRM | quality risk management |
| RA | risk assessment |
| RCA | root cause analysis |
| SOP | standard operating procedure |
| TAMC | total aerobic microbial count |
| TFC | total fungi count |
| TLC | thin layer chromatography |
| URS | user requirements specifications |
| UV | ultraviolet-visible spectrophotometer |

| Part 2 | Brief summary of the findings and comments (where applicable) |
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## 1. Quality management

A formal documented system of quality assurance was established, with procedures covering all expected key quality elements being in place. QA and QC departments were independent of production. Operations were specified in written form and GMP requirements were essentially being met. Procedures were in place for notifying responsible management of regulatory inspections, serious GMP deficiencies, product defects and related actions. The procedures that were reviewed and discussed during the inspection were generally of a satisfactory standard. Product and processes were monitored and these results considered during batch release. Regular monitoring and reviews of the quality of APIs were being conducted according to documented schedules and procedures.

**Quality risk Management (QRM)**

Quality Risk Management had been introduced as a quality management tool and a procedure was in place. Quality risk assessment for Artesunate was reviewed and discussed.

**Product Quality Review (PQR)**

The procedure for Product Quality Review was spot checked. Artesunate, Primaquine and Lumefantrine PQRs were reviewed. Change Controls were reviewed. There were no complaints, returns, recalls, OOT, OOS, reprocessing or rework.

## 2. Personnel

Personnel met during the inspection appeared to have knowledge of GMP principles and showed that they received initial and continuing training, including hygiene instructions, relevant to their responsibilities. Measures were taken to prevent unauthorized people from entering production and QC areas and appeared to be effective. An organization chart was available and responsibilities for production and QC/QA were well separated. Training was conducted according to a written SOP and details were acceptable.

## 3. Buildings and facilities

Inspected workshops and facilities were maintained at an acceptable level.

Building 07 was the solids RM store, PM Store and BSR (Bonded Storage Room) Store. This was constructed in 2017 with proprietary racking with Khota stone flooring and coved joints to the walls. Relevant SOPs and photos of entry procedure were on display and a copy of the approved vendor list was available.

The manufacturing facilities were not API dedicated. Adequate ventilation, air filtration and exhaust systems were provided. Lighting in the areas visited during the inspection was considered adequate. The HVAC system provided filtered air to the Grade D cleanrooms. The flow of materials and personnel through facilities were designed to prevent mix-up and cross contamination. The company had renovated some of the existing facilities and had built several new buildings. More specifically, new buildings for warehousing finished APIs, raw and packaging materials (Building 7), for hazardous solvent and liquid drum stores (Building 13) and solvent recovery (Building 42) had been constructed. Similarly, stability and retained sample areas were hosted in a new building (02A, 03A). The powder processing area of Building 9 (Block 1D) was renovated and a new HVAC system was installed. The purified water system was acceptable.

**4. Process equipment**

Process equipment in manufacturing blocks 1A and 1D (Buildings 10 and 9) were not API dedicated. Materials of product contact were suitable. Reactor systems, and utilities, were installed to allow reflux, distillation and cooling required to make the APIs of interest. Tools and equipment were uniquely identified and status labels were generally used. Similarly measuring equipment were labelled including calibration status. In general, they were maintained according to written procedures and a plan for preventive maintenance was available.

**5. Documentation and records**

Documentation system was generally well established. Procedures on creating SOPs and on control of quality documents and records were available. The issuance, revision, superseding and withdrawal of documents were controlled. Documents related to the manufacture of intermediates and APIs were prepared, reviewed, approved and distributed according to written procedures. Specifications were established for raw materials, intermediates and APIs. BMRs were retained for each batch processed. Batches were numbered according to a written procedure of product batch number.

**6. Materials management**

There were written procedures describing the receipt, labelling, quarantine, storage, and handling of materials, as well as procedures for sampling, testing and approval or rejection of materials. Deficiencies were observed regarding the labelling of 200L drums in the solvent store and the company applied the necessary corrective actions

Material suppliers were required to be approved according to Vendor Development Procedure.

**7. Production and in-process controls**

In general, production operations followed defined procedures. Process flows (with IPCs) and routes of synthesis were available. Access to production premises was restricted to authorized personnel. Weighing and measuring devices were of suitable accuracy for the intended use. Calibration procedures and records for scales were presented. Standard weights and their certificates were available. Closed systems and dedicated pipes were used for material transfers from reactors to centrifuges. Examination of the flow of the manufacturing process and relevant equipment was in line with the BMRs examined during the inspection.

The following APIs were manufactured in Building 10 (Block 1A) and Building 9 (Block 1D)

| Block 1A | Block 1D |
|---|---|
| Nimesulide | Nimesulide |
| Lumefantrine | Lumefantrine |
| Amodiaquine HCl (stage II only) | Amodiaquine HCl |
| Piperaquine Phosphate | Piperaquine Phosphate |
| Furosemide | Furosemide |
| | Artemether |
| | Tenofovir Disoproxil Fumarate |
| | Allopurinol |
| | Bisoprolol Fumarate |
| | Artesunate |

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| | Dihydroartemisinin |
| | Primaquine Phosphate |

Process validation of Primaquine Phosphate was completed in 2016. Two batches of Primaquine crude were used to manufacture three batches of the finished API

At the time of the inspection, Lumefantrine and Artemether were manufactured in Blocks 1A and 1D respectively. Dedicated FBD filter bags and centrifuge bags were used to minimize the risk of cross-contamination.

**8. Packaging and identification labelling of APIs and intermediates**

Intermediates were handled, as required, in dedicated containers. Examples were seen of those use for Lumefantrine.

**9. Storage and distribution**

A new Raw Material, Packaging Materials and Finished APIs Warehouse (Building 7) was recently commissioned. A temperature-controlled area was available and temperature mapping had been carried out for 1 out of the 3 seasons described in the protocol. Mapping exercise for summer season was scheduled in May 2018 and for rainy season in July 2018. The results of regular monitoring were satisfactory. The sampling rooms in the warehouse were inspected.

**10. Laboratory controls**

The analytical and microbiological laboratories were inspected. The premises were generally of an acceptable standard and well equipped. Documents were organized in an appropriate manner and retrieval was achieved in a timely manner. Some raw material specifications were checked at random.

There is a dedicated area for microbiology in the QC lab. This was generally well constructed and the areas for TVC monitoring were of an adequate design and well maintained.

**11. Validation**

A Validation Mater Plan was available and it was prepared in accordance with the relevant SOP. Procedures for validation and qualification of equipment, systems, utilities, processes and analytical methods were in place.

**12. Change control and deviations**

Change control was managed according to a written SOP.

The deviation SOP included procedures for both planned and unplanned deviations. Log books for CC and deviation were available for review.

**13. Rejection and re-use of materials**

The company had in place an SOP for recovery and usage of recovered solvents. It described batch numbering system and the operations relating to recovery of solvents based on boiling points and their use in the same stage. The following solvents were recovered from different stages of manufacture; Methanol, Ethyl acetate, Monochlorobenzene, Methylene Chloride, Ethanol, Toluene, Isopropyl Alcohol and Cyclohexane. Report for recovered of methanol batch no. M001-LUF-18072 from Lumefantrine crude

stage 1 was reviewed. The SOP for recovery indicated that the specifications for recovered and fresh solvents are similar and this was spot checked and confirmed with specifications for recovered and fresh methanol batch number M001-LUF-18072.

## 14. Complaints and recalls

Product recalls were handled according to SOP "Handling of Product Recall". Handling of returned goods was controlled by SOP "Handling of returned Goods". An example was a returned batch of Lumefantrine logged in the system. It was found that the customer had changed the specification.

Complaints were handled according to the relevant SOP. Complaints regarding Tenofovir Disoproxil Fumarate were reviewed.

## 15. Contract manufacturers (including laboratories)

Some discrepancies in relation to qualification and establishment of contracts with transport companies were identified and are being reported in Part 3

| Part 3 | Conclusion – Inspection outcome |
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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, ***Mangalam Drugs and Organics Ltd, Unit 1*** located at ***Plot No 187, 2nd Phase GIDC, Vapi, Gujarat, 396 195, 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.

| Part 4 | List of GMP Guidelines referenced in the inspection report |
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1. WHO good manufacturing practices for active pharmaceutical ingredients. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth Report. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957), Annex 2.
   ***Short name: WHO TRS No. 957, Annex 2***
   http://www.who.int/medicines/publications/44threport/en/

2. WHO good manufacturing practices for pharmaceutical products: main principles. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-eight Report Geneva, World Health Organization, 2014 (WHO Technical Report Series, No. 986), Annex 2.
   ***Short name: WHO TRS No. 986, Annex 2***
   http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_986/en/

3. WHO Good Manufacturing Practices: water for pharmaceutical use. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fourth-six Report. Geneva, World Health Organization, 2012 (WHO Technical Report Series, No. 970), 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/

4. WHO guidelines for sampling of pharmaceutical products and related materials. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-ninth Report. Geneva, World Health Organization, 2005 (WHO Technical Report Series, No. 929), Annex 4
***Short name: WHO TRS No. 929, Annex 4***
http://whqlibdoc.who.int/trs/WHO_TRS_929_eng.pdf?ua=1

5. WHO guidelines on good manufacturing practices for heating, ventilation and air-conditioning systems for non-sterile pharmaceutical dosage forms. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 5
***Short name: WHO TRS No. 961, Annex 5***
http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

6. Supplementary guidelines on good manufacturing practices: validation. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fortieth Report. Geneva, World Health Organization, 2006 (WHO Technical Report Series, No. 937), Annex 4
***Short name: WHO TRS No. 937, Annex 4***
http://whqlibdoc.who.int/trs/WHO_TRS_937_eng.pdf?ua=1

7. WHO Good Practices for Pharmaceutical Quality Control Laboratories. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth Report. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957, Annex 1
***Short name: WHO TRS No. 961, 957), Annex 1***
http://www.who.int/medicines/publications/44threport/en/

8. WHO Good Practices for Pharmaceutical Products Containing Hazardous Substances. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth Report. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957), Annex 2
***Short name: WHO TRS No. 957, Annex 2***
http://www.who.int/medicines/publications/44threport/en/

9. WHO good manufacturing practices for sterile pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 6
***Short name: WHO TRS No. 961, Annex 6***
http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

10. WHO guidelines on transfer of technology in pharmaceutical manufacturing WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 7
***Short name: WHO TRS No. 961, Annex 7***
http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

11. Model guidance for the storage and transport of time-and temperature-sensitive pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 9
***Short name: WHO TRS No. 961, Annex 9***
http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

12. General guidelines for the establishment maintenance and distribution of chemical reference substances. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-First Report Geneva, World Health Organization 2007 (WHO Technical Report Series, No.943) Annex 3
***Short name: WHO TRS No. 943, Annex 3***
http://whqlibdoc.who.int/trs/WHO_TRS_943_eng.pdf?ua=1

13. WHO good practices for pharmaceutical microbiology laboratories. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 2
***Short name: WHO TRS No. 961, Annex 2***
http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

14. WHO guidelines on quality risk management. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Seventh Report Geneva, World Health Organization, 2013 (WHO Technical Report Series, No. 981), Annex 2
***Short name: WHO TRS No. 981, Annex 2***
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_981/en/

15. WHO guidelines on variation to a prequalified product. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Seventh Report Geneva, World Health Organization, 2013 (WHO Technical Report Series, No. 981), Annex 3
***Short name: WHO TRS No. 981, Annex 3***
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_981/en/

16. WHO guidelines for drafting a site master file. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 14
***Short name: WHO TRS No. 961, Annex 14***
http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

17. WHO Guidelines on good manufacturing practices: validation, Appendix 7: non-sterile process validation. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Ninth Report Geneva, World Health Organization, 2015 (WHO Technical Report Series, No. 992), Annex 3
***Short name: WHO TRS No. 992, Annex 3***
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf

18. WHO General guidance on hold-time studies WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Ninth Report Geneva, World Health Organization, 2015 (WHO Technical Report Series, No. 992), Annex 4

***Short name: WHO TRS No. 992, Annex 4***
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf

19. WHO Technical supplements to Model Guidance for storage and transport of time – and temperature – sensitive pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Ninth Report Geneva, World Health Organization, 2015 (WHO Technical Report Series, No. 992), Annex 5
***Short name: WHO TRS No. 992, Annex 5***
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf

20. WHO Recommendations for quality requirements when plant – derived artemisin is used as a starting material in the prosecution of antimalarial active pharmaceutical ingredients. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Ninth Report Geneva, World Health Organization, 2015 (WHO Technical Report Series, No. 992), Annex 6
***Short name: WHO TRS No. 992, Annex 6***
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf

21. WHO good manufacturing practices for biological products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifties Report Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 3
***Short name: WHO TRS No. 996, Annex 3***
http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex03.pdf

22. Guidance on good data and record management practices. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifties Report Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 5
***Short name: WHO TRS No. 996, Annex 5***
http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex05.pdf

23. WHO general guidance on variations to multisource pharmaceutical products. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifties Report* Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 10
***Short name: WHO TRS No. 996, Annex 10***
http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex10.pdf

24. WHO good manufacturing practices for biological products. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifties Report* Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 3
***Short name: WHO TRS No. 996, Annex 3***
http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex03.pdf