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Prequalification Team
WHO PUBLIC INSPECTION REPORT
(WHOPIR)
Active Pharmaceutical Ingredient Manufacturer

Part 1	**General information**
Manufacturers details	
Company information	
Name of manufacturer	Mangalam Drugs & Organics Ltd.
Corporate address of manufacturer	Rupam Building, 3rd floor, 239 P. D'Mello Road, Near G.P.O. Mumbai – 400 001
Inspected site	
Address of inspected manufacturing site if different from that given above	Plot No 1203 (Unit-2), III Phase G.I.D.C., Vapi – 396195 Dist. Valsad, Gujarat GPS coordinates and latitude: N 20° 22' 09.7" and E 72° 56' 35.4" *DUNS No: not available*
Unit / block / workshop number	Unit-2
Manufacturing license number	G/1315 (validity from 1/1/2017 to 31/12/2021)
Inspection details	
Dates of inspection	13-16 February 2017
Type of inspection	Initial GMP inspection
Introduction	
Brief summary of the manufacturing activities	Mangalam Unit-2 was started in 1989 and it was renovated in 2016 and new manufacturing unit or production blocks were constructed and qualified in 2016, primarily for HIV & Anti-malarial products. All 5 APIs have not been commercialized yet and awaiting WHO Pre-qualification (PQ).
General information about the company and site	Mangalam Drugs & Organics Ltd. commenced its manufacturing operations in 1977 at Vapi, Gujarat. It has since then grown into multi product manufacturing facilities at two locations and an in-house Research and Development Department.
History	The site has been regularly inspected by the state food and drug administration since 2010. This was the first WHO-PQT inspection of Mangalam Drugs and Organics Ltd., Unit-2.

Brief report of inspection activities undertaken	
Scope and limitations	
Areas inspected	Production blocks (2A, 2B and 2C) Quality control laboratory Quality management system Personnel and training Document control
Restrictions	None
Out of scope	Unit-1
WHO product numbers covered by the inspection	Lumefantrine (APIMF100) Tenofovir Disoproxil Fumarate (APIMF204) Artemether (APIMF138) Emtricitabine (WHOAPI 314) Efavirenz (WHOAPI 318)

Abbreviations

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
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)

Brief summary of the findings and comments

1. Quality management

The quality management systems were established, documented and implemented in general. The QA and QC department was independent from production. The production and quality control procedures were defined in general, different procedures (SOPs) were described in detail and were followed. In general deviations from established procedures were documented and explained.

The quality unit was responsible for testing, sampling, stability study, handling out of specification (OOS)/(OOT) out of trends results, established specification, environmental monitoring, release and reject of materials and API, issuance of certificate of analysis (CoA), out sourcing of quality control test and involved in activities related to qualification and validation.

The production unit was responsible for manufacturing of active pharmaceutical ingredients, storage of materials, packing and labelling.

The PQRs were prepared according to an SOP.

The issues related to this section have been adequately addressed by the Company, and the same shall be verified during future inspections.

2. Personnel

Personnel were qualified by education and training to perform and supervise the manufacture of APIs in general. Unit-2 organogram dated 13/1/2017 was reviewed and noted that Dr Vashi was overall in-charge for technical and operations matters. He was supported by General Manager Quality, General Manager Production and other departments who in turn reports to the managing director. The QA and production department reports separately to Dr Vashi.

The issues related to this section have been adequately addressed by the Company, and the same shall be verified during future inspections.

3. Buildings and facilities

The building, manufacturing departments and the facilities inspected (block 19: 2A plant - block 22: 2B and 2C plants, raw material and finished goods warehouse) were maintained to be acceptable in general. The flow of materials and personnel through the building or facilities were designed to prevent mix-up and cross contamination in general.

The production units were manufactured in multi-product equipment and not product dedicated.

The issues related to this section have been adequately addressed by the Company, and the same shall be verified during future inspections.

4. Process equipment

The equipment maintenance calibration and cleaning were performed according to the procedure in general.

The issues related to this section have been adequately addressed by the Company, and the same shall be verified during future inspections.

5. Documentation and records

The company had a documentation system in place consisting of organization charts, SOPs, protocols, records, reports, etc. SOPs and specifications for the product existed.

The procedure on SOP of SOPs described how SOPs should be prepared, revised and numbering system including revision number. Another procedure described as department code (QA, QC, PRD, and RD etc.), type of SOP (general, operation, cleaning and calibration) and serial number.

The procedure on control of quality documents and records was reviewed which described company's document retention policy such as minimum 3 revision for SOPs, SMF, VMP should be retained whereas some of other documents should be retained for lifetime (cleaning validation, analytical method validation, technology transfer data etc.). There was no assessment on retention of electronic documents such as HPLC and GC documents.

The issues related to this section have been adequately addressed by the Company, and the same shall be verified during future inspections.

6. Materials management

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. No rejected materials were seen in the warehouse.

The issues related to this section have been adequately addressed by the Company, and the same shall be verified during future inspections.

7. Production and in-process controls

Production processes were guided by documented procedures and instructions. Production processes including synthesis, purification, crystallization, drying, milling etc. were conducted in a non-dedicated facilities and multi-purpose equipment to manufacture the 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. Production was campaign based.

Production plant 2A (intermediate manufacturing block) was inspected covering ground floor (housed centrifuges), first floor (reactors) and second floor (reactors). This block was identified as building 19 in the site layout plan. The buildings 18, 17 and 22 were identified as pilot plant, R&D and production blocks 2B, 2C and warehouse respectively.

The issues related to this section have been adequately addressed by the Company, and the same shall be verified during future inspections.

8. Packaging and identification labelling of APIs and intermediates

Packaging and labelling operations were conducted as per the standard operating procedures. After batch release, the QC person affixed approved labels and handed over the release intimation to production. Packaging materials were checked and released according to the specifications. The containers and inside polyethylene bags used to pack finished APIs were consistent with the information in dossier.

9. Storage and distribution

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

10. Laboratory controls

The main QC laboratory was located in a separate building, block number 23 and spread over two floors. The premises, facilities and utilities were separate from production. There were dedicated rooms for activities like sample receipt and storage, wet chemistry, hot areas and instrumentation. There were adequate pieces of equipment with up to date calibration status.

The laboratory equipment HPLC (7) and GC (4) were not connected to a server. This will be implemented in due course. The analytical development laboratory (ADL) was separate from the main QC laboratory and was used for method validation and for supporting activities for R&D. The ADL was not used for routine and release testing. It was noted that contracted laboratories were used primarily for R&D purposes i.e. characterization of molecules, impurities etc. The Unit-1 lab was used for particle size monitoring.

The reference standards management was reviewed and no observation was raised.

The issues related to this section have been adequately addressed by the Company, and the same shall be verified during future inspections.

11. Validation

Process validation procedure described the procedure for establishing process and process parameters to ensure capability of performing in a reliable and consistent manner with predetermined specifications. Prospective process validation protocol for Efavirenz was reviewed and noted that three batches were taken for validation in pilot plant using an intermediate procured from China). Process validations were carried out in Pilot plant for

submission purposes for new APIs and batch size was around 10-15 kg, whereas for existing APIs, batches were taken in the production area.

The cleaning validation was done for Lumefantrine, Artemether and TDF taking three commercial scale batches in 2016. For Emtricitabine and Efavirenz, only one commercial scale batch was taken for the cleaning validation. It was claimed by the company that cleaning validation will be performed for Emtricitabine and Efavirenz taking three commercial batches. The company performs cleaning validation of each molecule without identifying worst case molecule and a 10ppm criterion was set. The maximum allowable carryover (MACO) calculation was done using minimum batch size, LD50 and therapeutic daily dose.

The issues related to this section have been adequately addressed by the Company, and the same shall be verified during future inspections.

12. Change control

The change control procedure categorized changes into critical, major and minor according to the impact on product quality and provided examples for each category. According to the procedure, change had to be closed within 90 days otherwise a justification had to be provided. By reviewing the 2017 logbook, it was noted that 17 changes were recorded and all were closed. In logbook of 2016, 153 closed changes were recorded. Most of the changes raised were regarding the revision of SOPs and specifications.

13. Rejection and re-use of materials

There was no rejection noted for the submitted APIs.

14. Complaints and recalls

Complaints procedure was reviewed. It applied to both local and export market and rated the complaints in critical, major and minor supporting each category with examples. Complaints' investigation had to be closed within 3 days if critical and 30 days if major or minor.

The recall procedure was reviewed. No recall occurred; no mock recall was ever done.

15. Contract manufacturers (including laboratories)

There was no contract manufacturing done for WHO-PQ products. It was noted that five external laboratories and Mangalam Unit-1 laboratory were used by Unit-2 for the testing of several tests.

PART 3

Conclusion

Based on the areas inspected, the people met and the documents reviewed, and considering the findings of the inspection, including the deficiencies listed in the Inspection Report, as well as corrective actions taken and planned: APIs (Lumefantrine, Artemether, Emtricitabine, Efavirenz and TDF) manufactured at **Mangalam Drugs & Organic Ltd (Unit No. 2), Plot No.1203, 3rd Phase, G.I.D.C., Vapi -396 195, Tal. - Pardi, Dist. Valsad, Gujarat, India** were 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.

PART 4

List of GMP guidelines referenced in the inspection report

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.
   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.
   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
   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
   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
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
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
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
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
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
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
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
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
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
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
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
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
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
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
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 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 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 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 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 http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex03.pdf