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Prequalification Team Inspection services
WHO PUBLIC INSPECTION REPORT
(WHOPIR)
Finished Product Manufacturer

Part 1	**General information**
Manufacturers details	
Company information	
Name of manufacturer	Maphar Laboratories
Corporate address of manufacturer	Km 10, Route de Rabat, Ain Sebaa, Zenata industrial area Casablanca, Morocco GPS coordinates: 33.633552; -7502859
Inspected site	
Address of inspected manufacturing site if different from that given above	Maphar, route de Rabat. RP/1 AIN Sebaa 20250 Casablanca Maroc
Unit / block / workshop number	NA
Manufacturing license number, (delete if not applicable)	No. 93/16 DMP/23
Inspection details	
Dates of inspection	8 - 11 November 2016
Type of inspection	Routine GMP inspection
Introduction	
Brief summary of the manufacturing activities	Manufacture of finished pharmaceutical products, intermediate or bulk, packaging, laboratory testing, batch certification and batch release, storage. The manufacturing site of Maphar is located in Zenata industrial estate. The plant was originally established in 1951. The site produces various dosage forms such as oral solid (tablets, capsules and granules), liquids (oral and for external use) and semisolids (suppositories, ointments and creams).

	The total surface area of Zenata manufacturing site is 25,670 m^2 whereas building surface is 12,900 m^2. The manufacturing facility is designed to produce 70 million boxes per year, and it has a storage capacity of 7000 pallets. The site produces 199 formulas, 2000 batches per year, uses 142 APIs, 315 raw materials and 1280 packaging materials. From the presentation, it was also noted that Zenata manufacturing site has 323 headcounts.
General information about the company and site	According to the opening meeting presentation and review of the site master file: Maphar is a Sanofi company which has 102 manufacturing sites in 41 countries. In Morocco, Maphar has one manufacturing site based in Zenata industrial estate of Casablanca whereas there is a distribution centre located in Ain Sebaa, Casablanca. The Ain Sebaa distribution centre (capacity of 14100 pallets and 5 cold rooms with a capacity of 130 pallets) is responsible to store finished product Artesunate/Amodiaquine tablets (ASAQ) before being dispatched for distribution. The finished product of ASAQ was not distributed directly from Morocco; instead it was transferred to France for onward distribution.
History	The last WHO Prequalification inspection on Zenata manufacturing site was conducted in January 2013. In addition, the site was inspected by Ministry of Health (MoH), Morocco in May 2013, Tanzania Food and Drugs Administration (TFDA) in February 2015, Sierra Leone MoH in April 2015 and Nigerian NAFDAC in July 2015.
Brief report of inspection activities undertaken	
Scope and limitations	
Areas inspected	Areas related to ASAQ manufacturing and testing were inspected.
Restrictions	None
Out of scope	Due to the time constrains, some of the sections were not covered.
WHO product numbers covered by the inspection	MA056: Artesunate/Amodiaquine (as Hydrochloride) 25mg/67.5mg tablets MA057: Artesunate/Amodiaquine (as Hydrochloride) 50mg/135mg tablets MA058: Artesunate/Amodiaquine (as Hydrochloride) 100mg/270mg tablets

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. Pharmaceutical quality system

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. The site uses several computer based applications:

- Phoenix for the management of change controls, deviations and CAPA
- LIMS for the laboratory data management
- Geode for documents management
- SAP for material management
- TAC for continuous temperature/relative humidity monitoring (distribution centre)

The procedures related to product quality review, quality risk management, deviations, change controls and corrective actions and preventive actions were reviewed.

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

2. Good manufacturing practices for pharmaceutical products

In the manufacturing areas, the material and personnel flows were adequately separated, and during the inspection, personnel wore adequate clothes related to the activities to be performed. Qualifications and validations were discussed to be performed according to prepared protocols. Significant deviations from the initial protocol were recorded and investigated, root causes were determined and corrective and preventive action were implemented. A system was available to recall any batch of product from sale or supply and complaints about marketed products were examined.

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

3. Sanitation and hygiene

The company had a SOP as the basis for its approach to personal hygiene and sanitation in its production facilities. Areas were found to be cleaned and well maintained.

4. Qualification and validation

The key elements of a qualification and validation program were defined and documented in the Validation Master Plan (VMP). This section was not inspected due to time constraints.

5. Complaints

The SOP "Handling of market complaints" and its flow charts were discussed. By reviewing the APQR, in 2015 no complaints were received for ASAQ.

6. Product recalls

The SOP "Product recall" and its flow charts were discussed. By reviewing the APQR, in 2015 no recall was performed for ASAQ.

7. Contract production, analysis and other activities

It was claimed that the manufacturing activities for "WHO" products were not contracted out. The contract laboratories were used by Maphar for certain tests.

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

8. Self-inspection, quality audits and suppliers' audits and approval

Self-inspections were performed routinely according to the self-inspection procedure and schedule.

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

9. Personnel

The manufacturer seemed to have had an adequate number of personnel in manufacturing areas.

For responsible staffs, the duties were recorded in written job descriptions.

Measures were taken to prevent unauthorized people from entering production, storage and QC areas.

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

10. Training

Training was given to employees on the basis of the SOP. By interviewing, personnel appeared to have practical experience.

11. Personal hygiene

During the inspection visit, it was noted that the people wore suitable garments and had a correct behavior in the manufacturing and testing areas.

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

12. Premises

Exposed surfaces were smooth, impervious and unbroken. Changing rooms were designed as airlocks and used to provide physical separation of the different stages of changing. Changing rooms were flushed with filtered air. Airlock doors were interlocked. Premises were cleaned and disinfected according to written procedures.

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

Storage areas were of sufficient capacity. Receiving and dispatch bays protected materials and products from the weather. Segregation was provided for the storage of rejected, recalled, or returned materials or products.

Separate sampling areas were provided for sampling of APIs, inactive materials, primary and secondary packaging materials. APIs, inactive materials and primary materials were sampled under laminar airflow (LAF).

Dispensing for APIs/inactive materials and primary packaging materials was carried out in dispensing rooms under LAF. Dispensing was carried out by warehouse officer and checked by the production officer. Materials were dispensed in poly bags and stored in stainless steel containers / cages.

The layouts of the facilities were available and discussed.

The premises were laid out in such a way as to allow the production to take place in areas connected in a mostly logical order, corresponding to the sequence of the operations and to the requisite cleanliness levels. The working and in-process storage space did permit the orderly and logical positioning of equipment and materials so as to minimize the risk of confusion between different pharmaceutical products or their components, to avoid cross-contamination, and to minimize the risk of omission or wrong application of any of the manufacturing or control steps. Interior surfaces (walls, floors and ceilings) were found to be smooth and free from cracks and open joints. They did permit easy and effective cleaning and disinfection. Production areas were ventilated, with air-control facilities (including filtration of air to prevent contamination and cross-contamination, as well as control of temperature and, where necessary, relative humidity) appropriate to the products handled, to the operations undertaken and to the external environment.

Sufficient space was given to avoid mix ups and cross-contamination. Adequate storage space was provided for samples, reference standards, solvents, reagents and records.

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

13. Equipment

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

Fixed pipework was clearly labelled to indicate the contents and the direction of flow.

Both dedicated and shared equipment were used for ASAQ manufacture.

The environmental conditions in the production areas were controlled by HVAC system bearing HEPA filters in manufacturing areas. In order to avoid cross contamination the access in the manufacturing cubicle was allowed by airlock/SAS which was maintained in overpressure with respect to the cubicle and main corridor. The main manufacturing corridor; each cubicle had a dedicated AHU.

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

14. Materials

Incoming starting materials and finished products were quarantined after receipt until they were released for use. Starting materials were purchased from approved suppliers. Approved suppliers lists for starting materials (active and inactive) and packaging materials were available in the SAP system as well as a hard copy. For each consignment, the containers were checked for integrity of package and seal. Damage to containers and any other problem that might adversely affect the quality of a material recorded and reported to the QA department. Check-lists were used for materials receipt. Received goods were compared with purchase order.

The vendors of starting materials were selected, qualified and monitored according to SOPs.

Finished products were stored in a separate warehouse / distribution centre named as Ain Sebaa located 5KM far from Zenata production site. The distribution centre was also inspected by the inspectors on the last day of the inspection.

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

15. Documentation

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

16. Good practices in production

In general production operations followed defined procedures. Deviations from procedures were recorded and investigated. Checks on yields and reconciliation of quantities were carried out. 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 the production operator which was not verified by another production or QA operator. It was also noted that in-process controls were not performed by QA personnel within the production area without any justification.

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. As a common corridor was serving several processing cubicles, it would be useful to conduct a risk assessment and propose additional procedural controls where required.

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.

Separate airlocks were provided for material and personal entrance to the granulation rooms, though granulation rooms were not used for ASAQ. For other manufacturing cubicles, an airlock/SAS was always available to guarantee a bubble air zone.

Metal detectors were installed to all compression and capsuling machines. Metal detectors were challenged using Fe (0.35 mm), non-Fe (0.3 mm) and SS (0.5 mm) test kits at the beginning, at the end of the production run and every two hours.

Before packaging operations begun, steps were taken to ensure that the work area, packaging line, printing machine and other equipment were clean and free from any products, materials or documents used previously. The line clearance was performed and recorded in the BPRs.

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

17. Good practices in quality control

The QC function was independent of other departments. Adequate resources were available to ensure that all the QC arrangements were effectively and reliably carried out. The QC personnel had access to production areas for sampling and investigation as appropriate.

The chromatographic software's were managed through different software whereas some of the HPLC systems were connected with network, while most of the HPLC systems were running on standalone equipment.

The microbiology laboratory was not inspected due to time constraint.

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

PART 3
Conclusion

Based on the areas inspected, the people met and the documents reviewed, and considering the findings of the inspection, including the observations listed in the Inspection Report, ***Maphar Laboratories*** **located at** ***Km 10, Route de Rabat, Ain Sebaa, Zenata industrial area, Casablanca, Morocco*** was considered to be operating at an acceptable level of compliance with WHO good manufacturing Practices for pharmaceutical products.

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

1. 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/

2. 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/

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