

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

Name of Manufacturer	Maphar Laboratories Ltd.
Unit number (e.g. Unit III)	Zenata site
Production Block (e.g. PB01)	N/A
Physical address	Km 10 route Côtière 111, Q.I. Zenata, Aïn Sebaâ, 20250 Casablanca, Morocco
Contact person (senior person representing the company and to whom the report will be sent) and email address.	Dr. Alain Richard, alain.richard@sanofi.com, Industrial Affairs Head Mrs. Kawthar Tahiri, kawthar.tahiri@sanofi.com, Quality Manager Mrs. Valerie Faillat-Proux, valerie.faillat-proux@sanofi.com, Regulatory Affairs Director
Date of inspection	21 to 24 January 2013
Type of inspection (e.g. routine, follow-up)	Routine, investigation
Dosage forms(s) included in the inspection (e.g. coated tablets, hard gelatine capsules)	Prequalified products: MA056 Artesunate/Amodiaquine 25/67.5mg MA057 Artesunate/Amodiaquine 50/135mg MA058 Artesunate/Amodiaquine 100/270mg
WHO product numbers covered by the inspection (e.g. HA001)	MA56, MA57, MA58
Summary of the activities performed by the manufacturer (e.g. production, quality control, packaging)	Manufacturer and packer of oral solid dosage forms - tablets, hard capsules, granules and sachets, oral liquids and external liquids, semi-solid dosage forms - suppositories, ointments and creams and secondary packer of sterile liquid forms

Part 2: Summary

General information about the company and site

Maphar is a company manufacturing products for Sanofi-Aventis, under the direction of Sanofi-Aventis. It possessed 3 sites near Casablanca, but one of these sites, the Cypres site, had recently been closed. The Zenata site was the object of this inspection and was responsible for the manufacturing and testing of solid, semi-solid and liquid dosage forms. Another joint Sanofi/Maphar site, spot-checked during this inspection (located at Sanofi - Route de Rabat RP1), was recently rebuilt and configured to enable finished product storage and distribution.

The Zenata site is one of the two manufacturing sites for Coarsucam/ASAQ® tablets. The Artesunate API is manufactured and supplied internally by sanofi Gaessio in Italy and the amodiaquine API is manufactured and supplied by Ipca Ratlam and Ipca Indore in India.

According to the company presentation given during the opening meeting, there was just over 250 staff in production, of which 21% are in the quality unit.

The following changes were brought to the Zenata site after the last WHO inspection (performed in 2010):

- In May 2012, a new Director of Quality was appointed. Other staff changes included changes in management from one division to another in the areas of Quality Control (QC) and Qualification-validation-metrology for staff who already had an adequate level of experience for work in their new divisions.
- In 2010, a new water loop was installed for the external solution workshop.
- In 2012, a blistering machine, a labelling machines and sieve analysis equipment, high-performance liquid chromatography (HPLC) and gas chromatography (GC) equipment were added. A new solids form area was created. A new tablet press was in process of being validated and qualified for the manufacturing of artesunate/amodiaquine tablets.

History of WHO and/or regulatory agency inspections

The Maphar Zenata site was last inspected by the WHO from March 28-29, 2011. It was also inspected by the WHO in February 8-11, 2010 and in January 2008.

Inspections by Nigerian, Tanzanian, and Ugandan national medicines regulatory authorities have been performed.

Sanofi audits for safety and quality are performed every 2 years. The site has been ISO 14001 and OHSAS 18001 certified in 2011. The site undergoes regular customer audits (once every 2 months on average).

Focus of the inspection

The inspection focused on the production and control of Artesunate/Amodiaquine tablets (MA056 Artesunate/Amodiaquine 25/67.5mg, MA057 Artesunate/Amodiaquine 50/135mg, MA058 Artesunate/Amodiaquine 100/270mg). These will be re-ferred to as “ASAQ” 25, 50 or 100 respectively in the rest of this report. The inspection covered all the sections of the WHO GMP text, including premises, equipment, documentation, materials, validation, sanitation and hygiene, production, quality control and utilities. This inspection also served to follow-up on the corrective and preventive actions taken further to the recall and out of specification batches that were reported, starting January 2011.

Inspected Areas

Day 1

After introductions and a company presentation, inspectors proceeded to the review of the following documents:

- Product quality review (PQR) for 2012 for the 100/270 mg strength.
- Process validation reports for 2012 for the 100/270 mg strength.
- Deviations list for ASAQ and standard operating procedure (SOP).
- Trending for assay and content uniformity for 2012-2013.
- Change control reports.

Day 2

After giving a summary of the deficiencies and areas inspected during day 1, inspectors reviewed:

- Optimization of the tablet press and compactor granulator.
- Trends and results obtained using the new method vs. the old method, partial validation by comparative statistical analysis.
- Deviations.
- Out-of-trends (OOTs).
- Supplier qualification.
- Complaints and market recalls.
- Optimization project for the tablet press.
- Change of compacting pressure.
- Change in the regulation settings for the compactor.
- Change in the target average tablet weight.
- 3-in-1 procedure and statistical report (statistical report for Coarsucam comparing old method to new method).
- Procedure of management of procedures (version 7).
- Analyst’s laboratory logbooks.
- Most recent specifications and test methods for WHO.
- Review of Batch Production Records and revisions for selected batches of the product.
- OOT and deviation reports.
- Recalls procedure SOP.

- SOP on Management of complaints under the Access to Medicines programme.
- Complaints SOP, dated 15 June 2012.
- Correction for the date of qualification of the mixer (equipment 1) (this was an issue raised by inspectors which was shown to have been ultimately corrected by the company).
- Supplier approval and qualification documentation for active ingredients and for excipients, dated 17 and 4 December 2012 respectively.
- Visit of the starting material warehouse.
- Inventory.
- Monitoring of temperature/humidity, pest control.
- -Sampling and approved supplier list.
- The day was ended with the visit of warehousing areas for starting materials.

Day 3

After giving a summary of the deficiencies seen and areas inspected during day 1, inspectors inspected production and the quality control laboratory in parallel.

The following was also reviewed:

- Supplier qualification/disqualification.
- Flow diagrams for production.
- Stability programme for 2013 and stability chambers.
- Management and qualification of reference standards.

The day was ended with a visit of the distribution centre common to Maphar and Sanofi Aventis, located at Route de Rabat (R.P. 1) Ain Sebaa – 20 250 Casablanca - Morocco. The old distribution centre was rebuilt and the production part was demolished in 2011. New storage and preparation areas (secondary repackaging for the local market only) were recently built.

Day 4

After a review of the maintenance schedule and reports, the inspection of quality control was continued.

This included a review of:

- Microbiology
- NIR and FTIR spectroscopy instruments and database and the observation of an analyst performing a NIR test on raw materials pending analysis.
- Electronic HPLC data.
- HPLC system configuration parameters.
- Password control and security.
- System and project audit trails.
- Furthermore, details of the HVAC system and other GMP relevant utilities, the qualification of equipment and cleaning validation were inspected.
- Remaining documents (reviewed in the conference room), including a review of training.

2.1 QUALITY ASSURANCE

The quality management system was generally well established and an adequate organizational structure, standard operating procedures and related resources. Quality assurance was independent from production and adequately fulfilled its functions in the most part. Managerial responsibilities were well defined and specified in signed job descriptions.

Quality Risk Management (QRM)

A general SOP was available for quality risk management at the site. The basis for the document was the ICH Q9 guideline and Sanofi's Global Quality directive. Examples were not reviewed as there were none available for ASAQ tablets.

Product quality reviews (PQRs)

The PQR for 2012 was reviewed for the 100/270 mg strength. As 90 days is allowed between the end of the calendar year, the PQRs for the 50/135 mg and 25/67.5 mg strengths were not yet available.

The PQR for the 100/270 mg strength was performed for batches manufactured between January 2012 and December 2012 and covered all codes.

Out-of-trends (OOTs)

The handling of Out of trends was reviewed. Issues were raised and are in the process of being resolved.

Note: Other areas of the QA system (deviations, change controls and OOSs) were also reviewed.

2.2 GOOD MANUFACTURING PRACTICES (GMPs) FOR PHARMACEUTICAL PRODUCTS

Good manufacturing practices were adequately implemented in general. The necessary resources were provided. Manufacturing processes were defined and reviewed. Qualification and validation was performed. Operators were trained to adequately carry out the prescribed procedures, and generally adequate records were made during manufacture.

2.3 SANITATION AND HYGIENE

Adequate procedures and facilities were established for sanitation and hygiene. The premises and equipment seen were clean. Gowning and changing procedures were appropriate and displayed in the necessary areas. This area was found to be acceptable overall.

2.4 QUALIFICATION AND VALIDATION

Process validation

Process validation and revalidation was reviewed and was considered to be acceptable overall. .

Qualification of equipment

The qualification master plan was reviewed. It contained requirements for DQ, IQ, OQ, and PQ. The requalification period was required to be annually for the HVAC, the purified water (PW) and compressed air systems. Other relevant equipment will be revalidated every 5 years.

The overview of requalification for 2012 and planning for 2013 was reviewed. Qualification reports were reviewed in detail for equipment used in the manufacturing of ASAQ tablets.

Requalification HVAC

See 2.12

Cleaning validation

The cleaning validation approach and cleaning validation documentation was reviewed for equipment used during the production of ASAQ tablets. The qualification protocol from June 2010 was reviewed as well.

The final report was completed in January 2013. All parameters were fulfilled during the validation study. The cleaning methods were declared to be validated.

2.5 COMPLAINTS

The complaints SOP dated 15 June 2012, was reviewed and was found to be acceptable in general. Retention samples were verified in every case. According to the procedure, history was also verified to ensure that the complaint was not recurrent and this was followed through the key performance indicators (KPIs). The complaints were registered and managed through an electronic system called “QSC”.

The SOP on Management of complaints under the Access to Medicines programme, 31 January 2011, was also reviewed. There was a 24 hours target for the complaint info to be transmitted to the Global PTC Business Team Department and this was to be done by the designated person of Regulatory Affairs.

According to the procedure, risk classification was done by Corporate Risk Management. The site was responsible to do the investigation ultimately although this was managed by Corporate. An adhoc quality board would be reunited on a regular basis to discuss the action plan and findings. This was stated in the Maphar SOP.

A product alert team is also built in parallel to manage the impact of the issue on public health and on the company and on the risk of product shortage.

2.6 PRODUCT RECALLS

The current Maphar procedure on recalls was reviewed. The difference between products for local distribution and product sent for international distribution to distribution warehouses (e.g., Unicef, MSF) was explained. It was explained that for a recall process, the authorities have to be informed but if Sanofi does not know where the product has been distributed, it will not be possible to adequately perform the recall.

The different stakeholders were defined as:

- Customer
- Payers
- Authorities
- National Programs in the fight against malaria.

The product codes could be used but are not effective in all cases. Information from the distributors needs to be obtained because there are cases where a product with a code for a specific country is actually sent to another country.

2.7 CONTRACT PRODUCTION AND ANALYSIS

This area was not inspected due to time constraints.

2.8 SELF INSPECTION AND QUALITY AUDIT

This area was not inspected due to time constraints.

2.9 PERSONNEL

In general, the personnel met during the inspection were experienced, skilled and conscientious. Written and signed job descriptions and job delegations were available.

2.10 TRAINING

Training was managed by QA via an Access database defining the different trainings to which personnel have participated. Training plans and records seen were considered to be acceptable in general.

2.11 PERSONAL HYGIENE

No concerns were identified during the inspection of the production areas and the level of hygiene observed was considered to be satisfactory. Adequate protective gowning was in use for all staff in production.

2.12 PREMISES

Premises were in a good state of maintenance and repair.

Storage areas

Storage areas were found in good condition. Receiving areas were built to protect materials and products from adverse weather conditions. Storage areas were of sufficient capacity to allow storage of various materials and products with proper separation and segregation.

Temperature and humidity was monitored continuously. Temperature mapping was carried out. Calibrated sensors (rotronic, annual calibration) were installed.

Sampling was carried out in two separate areas designed for the purpose. Sampling areas were protected by reverse laminar airflow (RLAF) units and dedicated for APIs and other materials.

Appropriate airlocks for transfer of materials and personnel were in place. Correct function of personnel airlock and differential pressure at filters installed in the RLAF units was checked and documented on a daily basis.

Production areas

Areas used for production were found in good condition. All workshops relevant for the production of ASAQ tablets were inspected in detail (see 2.16).

HVAC system

AHUs supplying air to production were inspected.

AHU's and related installations were found to be in good condition overall. Labelling and control of differential pressure at relevant filters was in place. Suitable installations were used to prevent backflow during power cuts.

Requalification of HVAC

An annual requalification programme was in place. The last report for the compression /compaction area dated 8 June 2012 was reviewed. The extent of revalidation was in conformance to the relevant SOP.

Issues being raised regarding the direction of airflow were addressed in the company CAPAs.

Microbial monitoring of production area

The annual review for 2012 was reviewed and considered acceptable overall.

2.13 EQUIPMENT

The state of repair and maintenance of equipment was generally satisfactory.

2.14 MATERIALS

Warehousing

The process for the reception of raw materials, packaging materials and bulk products was reviewed and found to be satisfactory.

Materials were stored in a high-bay warehouse. Location in the high-bay warehouse, release and management of goods receipts and outgoing goods was determined using the computerized systems in place.

Labelling of bins / pack units was complete. A bar code system was implemented.

Printed packaging materials were stored in the same area as other materials.

The inventory was performed annually. Quantities were checked for all materials as per the valid SOP.

Inventory was done in the responsibility of warehouse manager and accounting department. If discrepancies were found, investigations were done and afterwards the quantities were corrected in the computerised system.

Instructions regarding the reporting of discrepancies to the relevant persons in the GMP field were missed. These should be added to turn the required attention to printed packaging materials.

Storage area for rejected materials

Rejected materials were stored in separated and locked part of the high-bay warehouse. Before performing the destruction, the approval of the Ministry of Health has to be sought.

Supplier approval and qualification/disqualification

The approved supplier lists for active ingredients and excipients were reviewed along with the process used for the addition of a new supplier. Supplier management was considered to be acceptable overall.

Control of materials was considered to be adequate in general.

Water

The SOP for production and distribution of purified water (dated 10 June 2007), actual drawing, and system description were reviewed along with the purified water system which was considered to adequately designed and maintained.

Compressed air

Purification of compressed air was evaluated for the production area. Relevant filters and absorption dryer were in place. The relevant SOP was available and gave a limit of -20°C for atmospheric dewpoint. The air compressor logbook showed values in the range of -40°C.

Nitrogen

Nitrogen cylinders used for production were inspected. Certificates of analyses were reviewed.

2.15 DOCUMENTATION

The documentation system was well established and maintained. Documents were approved, signed and dated by appropriate responsible persons, regularly reviewed and kept up to date. Overall, document control was found to be acceptable in general.

2.16 GOOD PRACTICES IN PRODUCTION

All handling of materials and product was generally done in accordance with written procedures or instructions and adequate records were maintained, as supported by BMRs and BPRs.

There were adequate provisions for in process checks and calculations of yield at various states of production.

Practices in production were considered to be satisfactory in general.

2.17 GOOD PRACTICES IN QUALITY CONTROL

Microbiology

- Reference strains and subculture management was found to be adequate overall.
- Media preparations and tests were recorded and performed in an appropriate manner.

The biosafety cabinet which was used to perform subculture of strains was Class 1 with a surrounding class 2 area. Environmental monitoring with petri dish was done every day.

- pH tests were done using a pH meter which was appropriately calibrated.
- Autoclave cycles were entered in a controlled logbook and included cycle number and full printouts of temperature and pressure readings

-Qualification of the autoclave: qualification documents were reviewed And were found to constitute adequate evidence that the autoclave had been appropriately qualified.

Reference standards

They were managed in a LIMS system, following the appropriate SOP. For amodiaquine: the secondary reference standard was verified to have been tested for purity against the official reference standard (Ph. Int distributed by EDQM) in duplicate with 3 repeats.

Stability studies

The stability programme for 2013 was shown and was considered to be acceptable overall.

Part 3: Conclusion

Based on the areas inspected, the people met and the documents reviewed, and considering the findings of the inspection, including the observations listed in the Inspection Report, as well as the corrective actions taken and planned, *Maphar Laboratories* Km 10 route Côtière 111, Q.I. Zenata, Aïn Sebaâ, 20250 Casablanca, Morocco, 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.