

**WHO PUBLIC INSPECTION REPORT  
(WHOPIR)**

**Finished Product Manufacturer**

**Part 1: General information about the inspection**

Name of manufacturer	<b>Maphar Laboratories</b>
Physical address	Km 10 route Côtière 111, Q.I. Zenata, Ain Sebaâ, 20250 Casablanca, Morocco
Postal address	As above
Telephone number	+ 212 522 67 80 00 + 212 522 67 80 28
Fax number	+ 212 522 67 80 50
Summary of all the activities performed by the manufacturer (e.g. manufacturing, packing).  Indicate dosage forms and type of products (e.g. tablets; penicillin or cephalosporin containing products)	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
Scope of inspection	General and Product Specific GMP inspection with data verification.
Date of inspection	8 - 11 February, 2010
Programme	Prequalification of Medicines Programme

## **Part 2: Summary**

The manufacturing site of Maphar SA, (Zenata site), located in Casablanca, Morocco was inspected by a WHO prequalification inspection team on the above mentioned days.

### ***General information about the company and the site. History of WHO or regulatory agencies' inspections***

For general information see previous report. The Zenata site was also inspected by WHO in January 2008, however not all GMP topics were covered during the previous inspection.

Production scale of the prequalified products has increased remarkably over the last two years.

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

The focus of this inspection was to verify production and quality control activities and to assess compliance with WHO GMP.

The areas inspected included the following:

- Receiving areas (raw materials and packaging materials)
- Storage areas for starting and packaging materials
- Sampling and dispensing areas
- Production areas related to the product such as sieving area, compaction area, blending, compression, and packaging areas
- Quality control laboratory (chemical, stability testing, microbiological laboratory)
- Quality assurance and documentation
- HVAC
- Purified water system
- Compressed air

Documents reviewed included (but not limited to):

- Quality Risk Management
- Schematic drawings of AHUs
- Qualification protocol/report and data for AHU No 3
- Schematic drawings of PW system
- Schematic drawings of compressed air system
- Batch records
- Deviations
- Complaints
- Annual Product Review
- Training plans and records
- Self inspection and schedule
- Various SOPs
- Calibration and qualification procedures and records

- Stability testing

### ***2.1. Quality Assurance (QA)***

A quality assurance system was implemented and maintained

The Quality Assurance (QA) department and Quality Control (QC) department were independent from production. Production and control operations were clearly specified in writing. Necessary controls on starting materials, intermediate products and bulk products, in-process controls, calibrations, and validations were carried out.

#### Change Control

Formal system for change control was described in a written procedure. All documentation related to changes was managed electronically. Change control flow chart was available for inspection. A number of change control reports were reviewed and found to be broadly satisfactory.

#### Deviation management

Deviations were classified into three categories: critical, major and minor. Flow chart was available. Deviation forms were attached to Batch Manufacturing Instructions (BMI) and Batch Packaging Instructions (BPI). A number of deviation records were reviewed and found to be satisfactory.

#### Product Quality Review

Product Quality reviews (PQR) were prepared in accordance with the revised SOP. Revision had been carried out after the latest WHO inspection.

#### Quality risk management (ORM)

A quality risk management procedure had been approved and revised. Till the date of inspection, QRM procedure had been applied for some procedures.

### ***2.2. Good manufacturing Practices for Pharmaceutical products***

Good manufacturing practices were implemented and generally maintained.

Necessary resources were provided, including qualified and trained personnel, adequate premises and space, suitable equipment and services, appropriate materials, containers and labels, approved procedures and instructions, suitable storage, adequate personnel, laboratories and equipment for in-process controls.

Manufacturing steps were recorded in batch manufacturing and packaging records; records were made during manufacture.

Instructions and procedures were generally written in clear and unambiguous language. Qualification and validation were performed.

### ***2.3 Sanitation and Hygiene***

The topic was not specifically covered during the inspection; no notable concerns were identified during the inspection. The hygiene measures in place were generally found to be sufficient to assure the prevention of contamination of the premises and product.

#### ***2.4 Qualification and Validation***

The key elements of the qualification and validation program were defined and documented in several Validation Master Plans (VMP). Re-validation or re-qualification periods were specified.

##### Process validation

A process validation reports were reviewed. Reviewed process validation reports were found to be satisfactory.

##### Holding time studies of cleaned equipment

MB analysis was performed to establish clean equipment holding time.

##### HVAC re-qualification

Specific AHU requalification report was checked and found to be satisfactory.

#### ***2.5. Complaints***

Dealing with complaints was specified in a written SOP, flow chart was available. A person responsible for handling of complaints was designated. Attention was given to counterfeiting. If a product defect was discovered or suspected in a batch, consideration was given to whether other batches should be checked in order to determine whether these were affected. If required, recall should be initiated. Complaints were classified into four classes, definitions and examples for all classes were given in the SOP.

Complaint trending was carried out every three months. Trends were reviewed and the system was found to be satisfactory.

#### ***2.6 Product Recalls***

The system to recall the products from the market was in place. The authorized person responsible for the execution and coordination of recalls was designated and was the Responsible Pharmacist. Recalls were classified into three levels.

In case there are no recalls, a dummy recall should be carried out annually.

#### ***2.7 Contract production and analysis***

Manufacturing activities were not contracted out.

Contract cleaners were used for the cleaning of premises and surroundings. Contract was available.

Pest control was contracted out. Contract was available.

### ***2.8 Self inspection and Quality Audits***

Self inspection was carried out once per year according to a written SOP and audit schedule. Audit report was written and corrective actions (CA) proposed. Implementation of CA was checked by the QA.

#### **Supplier audit and approval**

Vendor approval procedure was reviewed and found to be satisfactory.

Audits were system audits. Audit report was drawn up and CA was evaluated by the QA.

### ***2.9 Personnel***

In general, the personnel met during the inspection were experienced, skilled and conscientious.

The following job descriptions were reviewed and written job delegations were available:

- Quality Director
- Responsible Pharmacist
- Head of QC
- Head of Production

### ***2.10 Training***

A number of training records, including training on risk management were reviewed. Trainings were generally evaluated using questionnaires with given answers and open questions. General training program and specific training programs of departments for 2010 was presented. Contract cleaners' training record was available.

### ***2.11 Personal Hygiene***

Personnel Hygiene SOP was reviewed and found to be satisfactory. No notable concerns were identified during the inspection of the production areas and the level of hygiene observed was considered satisfactory. Direct contact was avoided between operators' hands and starting materials, primary packaging materials and intermediate or bulk product.

All changing rooms were provided with photographs which described the gowning procedures.

### ***2.12 Premises***

The buildings and facilities used for manufacture and quality control were located, designed, and constructed to facilitate proper cleaning, maintenance and production operations. Premises were designed to ensure the logical flow of materials and personnel. Production areas had adequate space around equipment and acceptable material flow to prevent mix-ups and contamination, with separate entrances for personnel and materials. Premises used for the manufacture of finished products were suitably designed and constructed to facilitate good sanitation. Premises were carefully

maintained and cleaned, cleaning was recorded. Premises were protected against the entry of insects, birds or animals. Pest control procedure was in place.

#### Storage areas

Receiving and dispatch areas had measures to protect materials and products from adverse weather conditions. Storage areas were of sufficient capacity to allow orderly storage of various materials and products with proper separation and segregation. Sampling was carried out in two separate areas designed for the purpose. Weighing of starting materials was carried out in three separate units designed for the purpose.

#### Production areas

Production areas were laid out in a way to provide logical flow and required cleanliness level. Walls, floors and ceilings were smooth and free from cracks and open joints. Production areas were effectively ventilated.

#### Quality control (QC) areas

Quality control laboratories were separated from production areas. Sufficient space was given to avoid mix-ups and cross-contamination. Sufficient space was provided for samples, reference standards, solvents, reagents and document archiving.

Preventive maintenance program for 2010 was presented for the facilities.

### ***2.13 Equipment***

Process equipment was installed and maintained in a manner that minimized the risk of error and contamination. Balances and other measuring equipment with appropriate range and precision were available for production and control operations and were calibrated on a scheduled basis. Standard weights used for in-house checking of balances were sent to outside calibration.

Calibration due date labels was attached to the equipment.

Production equipment was cleaned on a scheduled basis.

Laboratory equipment and instruments were suited to the testing procedures undertaken.

Annual schedule for calibration was kept in MS Excel, monthly schedules were printed out. Preventive maintenance program was in place. On spot checks the schedules had been followed.

The following calibrations related to the PW system were checked and found satisfactory:

- Flow meter
- Conductometer
- TOC meter

### ***2.14 Materials***

Materials were stored in high bay racks; smaller quantities were stored in separate room(s). Materials were received, quarantined, located and released by the computer system.

Upon receipt, materials were checked against purchase orders. Starting materials were sampled 100% for identity tests and labeled with "sampled" labels.

Temperature was monitored continuously. Temperature mapping was carried out.

There were separate sampling units for starting materials and primary packaging materials. Entrance to the sampling units was via airlocks, separate for personnel and materials. Sampling was done under RLAF. RLAF was operating continuously. Line clearance was carried out by the warehouse operator. Disposable sampling tools were used. Samples were taken only from the top of the drums.

Entrance to the dispensing rooms was via airlocks, separate for personnel and materials. RLAF was operating continuously. Line clearance was carried out by the warehouse operator. Dispensing was done by a person belonging to the warehouse; each dispensed material and its weight was independently checked by another warehouse operator. Balances were checked daily.

### ***2.15 Documentation***

In general, the documentation system was established and maintained, documents were approved, signed and dated by appropriate responsible persons, regularly reviewed and kept up to date. Alterations made to documents were signed and dated. Specifications and testing procedures were available.

Batch related documents were kept for 10 years.

### ***2.16 Good practices in production***

Handling of materials and products was done in accordance with written procedures and was recorded, checks on yields and reconciliation of quantities were carried out. During processing, materials, bulk containers, equipment, rooms and packaging lines being used were labeled. Access to production premises was restricted. In-process controls were performed by operators within the production area.

Temperature and relative humidity in the changing rooms and production rooms were controlled.

The general design of the facilities was appropriate and premises were well maintained.

Processes were generally under good control. Blending, granulation, compaction, compression, primary and secondary packaging areas were visited. Food grade lubricants

were used for punches and dies. Cleaning procedure for punches was in place. Punches were numbered and rotation was ensured.

PW was used for final rinsing of the equipment. Equipment was dried using filtered compressed air or left to dry on ambient conditions.

IPQC room was provided with equipment for controlling compression parameters such as disintegration and friability. Tablet weight, thickness and hardness were controlled in the compression room airlock.

Primary and secondary packaging

Primary and secondary packaging process was inspected and found to be satisfactory.

**2.17 Good practice in Quality Control**

Good Practice in Quality Control were generally implemented and maintained. Adequate facilities, personnel and approved procedures were available. Records of analysis were checked. CoA was signed by the head of QC laboratory.

An analyst training file was reviewed.

OOS and Out of Trend (OOT) results were investigated in accordance with a written SOP which included a flow chart.

Reference substances:

Pharmacopoeial and primary reference standards and working standards were stored under appropriate storage conditions (fridges, freezer, and room temp.).

Required primary standards (Int. Ph) were available.

Finished products' retention samples were properly stored in a separate storage room which was temperature mapped. Temperature was monitored and recorded two times per day.

Microbiology

The laboratory conducted water and environment monitoring, starting material, finished product and stability testing.

The SOP for preparation of media, growth promotion testing and media preparation records were reviewed and appeared to be satisfactory. There was a separate autoclave for media sterilization and for destruction. Autoclave validation using thermocouples was carried out and the results were satisfactory. Autoclave was re-validated every year.

Sub culturing SOP was reviewed and found to be satisfactory. 5 passages were allowed. Master cultures and subcultures were properly stored.

Purified water and environmental monitoring trends were reviewed and found to be satisfactory.

#### *Stability studies*

Stability chambers were equipped with alarms which were connected to the QC and security. Temperature characterization studies for walk-in chamber were reviewed and found to be satisfactory.

#### **Utilities**

HVAC system, Purified water system and compressed air system were inspected briefly and seemed to be under good control.

### **Part 3: Conclusion**

Based on the facilities inspected, the personnel met and the documents reviewed, and considering the inspection observations listed in the inspection report, Maphar Laboratories located Km 10 route Côtière 111, Q.I. Zenata, Ain Sebaâ, 20250 Casablanca, Morocco, was considered to be operating at an acceptable level of compliance with WHO GMP.

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.