



## WHO PUBLIC INSPECTION REPORT

### (WHOPIR)

#### Finished Product Manufacturer

#### Part 1: General information

Name of Manufacturer	The Jordanian Pharmaceuticals Manufacturing Company (JPM Co.) P.L.C.
Unit number	n/a
Production Block	n/a
Physical address	Al-Razi Site: P.O.Box 151, Um Al-Amad 16197 Jordan Tel (+9626)4290744 Fax (+9626)4290752
Contact person and email address.	Ms. Lina Nabulsi, Technical Director Email: Lnabulsi@jpm.com.jo; linabulsi@gmail.com Tel: 962 6 4290744 Ext 205 Mob: 962 79 5541081
Date of inspection	17-20 May 2015
Type of inspection	Initial
Dosage forms(s) included in the inspection	Tablets
WHO product categories covered by the inspection	TB products
Summary of the activities performed by the manufacturer	Production, packaging, quality control testing and release of finished pharmaceutical products.

#### PART 2: SUMMARY

##### *General information about the company and site*

The Jordanian Pharmaceuticals Manufacturing Company (JPM) was founded in 1978. It was licensed for manufacturing and marketing of medicinal products by the Jordan Food and Drug Agency. The company develops and produces pharmaceutical products of oral solid, liquid and semi-solid dosage forms. JPM is also a technology provider, one of its major activities is to out-license its products to other manufacturing companies in the Arab world, Africa, and Eastern Europe.

No penicillins, cephalosporins, hormones or toxic products are manufactured at the site.

The company is research-based and part of the staff is qualified with “sponsored education” (worldwide). It counted 467 staff members.

An overview of the company's activities in pharmaceutical research and development, publications and also innovative contributions to USP monographs was given during the opening meeting.

An effective presence in developing markets was one of the key company policy targets.

The Al-Razi site consisted of one main building which accommodated warehouses, production, laboratories and administration offices, another small building which accommodated the utilities and maintenance workshop, and a third one containing the cafeteria and the clinic.

The total area of construction was 15,000 m<sup>2</sup>, while the total production area was 5,700 m<sup>2</sup>. The raw materials warehouse was 1870 m<sup>2</sup> and the packaging materials/finished products warehouses were 1085 m<sup>2</sup>. The annual production capacity of the plant was 500 million tablets, 77 million capsules, six million bottles (liquid products) and four million tubes of creams and ointments.

The manufacturing building contained areas for the production of tablets, capsules, suppositories, creams, ointments and oral liquids. It also housed quality control and microbiology laboratories, research and development laboratories, packaging areas, warehouses, administrative areas such as the departments of Purchasing, Finance and Staff Affairs. The main building was arranged in different floors: ground floor, first floor, second floor and the roof.

The manufacturing building has been positioned on site to make the best use of the slope. Starting materials were received at the high level while the finished products were dispatched at the lowest level. The raw materials store is at the south.

#### ***History of WHO and/or regulatory agency inspections***

This was the first WHO inspection of this site. The history of authority and company inspections was available (e.g. 2012: Sudan, Uganda, Iraq; 2013: South Africa; 2014: Sandoz, Yemen, Saudi Arabia, Jordan).

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

The inspection focused on the production and control of anti-TB products (TB292 Moxifloxacin 400 mg tablets). 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.

#### ***Inspected Areas***

- Quality Assurance (QA)
- Sanitization and hygiene
- Qualification and validation
- Complaints
- Recalls
- Self-inspection
- Personnel
- Training

- Personal hygiene
- Premises
- Equipment
- Materials
- Documentation
- Production
- Quality control

## **PART 3: INSPECTION OUTCOME**

### **3.1 PHARMACEUTICAL QUALITY SYSTEM (PQS)**

#### **Quality risk management**

The standard operating procedure (SOP) entitled “Quality Risk Management (QRM) Policy”, authorized on 19.04.2015, was reviewed. The evaluation report for “Reducing Number of Air Sampling Point Tested for Manufacturing Controlled Area & Microbiology Lab” was also reviewed as one example of the QRM system.

QRM was required to apply to change control, deviation, complaints, qualification and validation.

#### **Product quality review (PQR)**

The SOP entitled “Product quality review for products produced for all solid dosage forms”, was reviewed. There was no PQR written for products when less than ten batches were manufactured, in general, but data was collected and summarized in reports.

Since there had not been any production of Moxifloxacin as of yet, an example was shown for another product (Oximal 15 mg tablet). The PQRs covered active material suppliers, inactive ingredient suppliers, changes, deviations, stability monitoring results, out of specifications (OOS), complaints/returns/recalls, marketing authorizations, technical agreements, equipment and utility qualification, and all other necessary sections.

#### **Out-of-specifications (OOS)**

Several examples of OOS were reviewed alongside the relevant SOP. When quality issues were raised, appropriate regulatory filings were made. This area was acceptable overall after corrective and preventive actions.

#### **Change controls**

There were several documents describing the handling of changes:

- SOP Change Control / General: This SOP was valid for changes in areas related to quality system at JPM. The change control logbook was available.

Three examples were checked and found to be well documented, namely:

- Change entitled “Introduction CAPA system”: the change control form was evaluated by QA and logged at 29 April 2015. The change control process was not finished prior to the inspection because of the need to update other

documents which will be linked to the corrective and preventive action (CAPA) system (e.g. non-conformances, complaints).

- Change of high performance liquid chromatography (HPLC) system (Data integrity, backup, security): Each user would be assigned his own username/password. Audit trails were activated for both methods and sequences, backup system was to be updated and data would be saved in files at the servers in which the users did not have the permission to change or delete any data. Implementation was finished in December 2014 and verified by QA on 15 January 2015.

The SOP entitled “Change Control/Production Manufacturing Formula and Processing Instruction” was reviewed. This document set a procedure followed for the controlling of planned changes, steps of rework/reprocess procedure applied to manufacturing formula and processing instructions. Other changes were handled by different procedures (changes in starting material manufacturers, changes in starting materials and finished product specifications and methods of analysis). Different logbooks were in place. There were four changes in starting material manufacturers documented for 2015 and eight for 2014. The manufacturer change report for Sodium Alendronate was reviewed as an example and was generally considered acceptable.

With regards to regulatory approvals: the SOP entitled “Follow-up post approval changes and variations”, authorized on 17.04.2014, was reviewed.

### **Deviations**

The SOP entitled “Handling of non-conformance cases” was reviewed. Since there was no SOP specifically covering deviations, this SOP partially covered this topic. It described the procedure for the handling of non-conformance cases of intermediate, bulk and finished products / starting materials / packaging materials or deviation from approved procedure. Non-conformance reports and log book were defined. Examples were reviewed (e.g. valid OOS results, cross-contamination, improper storage conditions, and failure to adhere to an approved procedure).

### **CAPA system**

The CAPA SOP (Handling of corrective and preventive action) was reviewed and considered acceptable overall.

## **3.2 GOOD MANUFACTURING PRACTICES (GMPs) FOR PHARMACEUTICAL PRODUCTS**

In general good manufacturing practices were implemented. The necessary resources were generally provided. The procedures and manufacturing instruction were established. Qualifications and validations were performed, adequate premises and equipment were available for production, in-process controls and storage, and operators were trained.

## **3.3 SANITATION AND HYGIENE**

This area was generally considered acceptable, from what was seen during the inspection of production and from microbiological/environmental monitoring test results.

### **3.4 QUALIFICATION AND VALIDATION**

#### **Validation master plan (VMP)**

«Validation Master Plan/Al-Razi Site», authorized on 04.03.2014, was reviewed. Risk assessment was required to determine the scope of qualification and validation.

#### **Equipment qualification**

The re-qualification protocol for Gally Tumble Blender, authorized on 23.09.2014 and Installation and the Operation Re-qualification Protocol for Fette Tablet Compression Machine Model P2100 (S.N:06738), authorized on 07.05.2015 were reviewed. The existing “Equipment Qualification Status Report/2015”, was reviewed. The report showed that all equipment were qualified according to the VMP. It was approved by the Validation Team Head and QA Manager, but without the date of approval.

TFC-520 Roller compactor (Serial No. RC-200 45614) was installed in 09.2008 and qualification was finished on 22.02.2009. Installation qualification, operational qualification and performance qualification (IQ, OP and PQ) protocols and the qualification summary report were reviewed. Noracin Tablets were selected for process validation. Design qualification (DQ) and risk assessment were not part of qualification. Calibration information for the instruments used for testing during OQ was not included in the report, it was resolved in CAPA.

Qualification of HVAC system: Qualification and requalification documents were reviewed.

Qualification for the compressed air system was done in 2010. Qualification for the dryer Atlas Copco, FD410 was finalised on 13 October 2010.

Process validation was reviewed for the change in the manufacturing process from slugging to compaction granulation (Vector roller compactor – TFC-520) for a very large number of products. The validation protocol was reviewed. It stated that validation would be performed on three consecutive batches of dry granulation product. The company was reminded of the necessity to file the appropriate regulatory filings with the WHO, should such changes be made to WHO prequalified products. Capacity to file such regulatory changes was confirmed by a brief inspection of the regulatory affairs department.

The logbooks for the Vector roller compaction equipment was reviewed for 2014-2015.

#### **Method validation**

Method validation for Moxifloxacin was reviewed and included the necessary elements for specificity, linearity and range, accuracy, precision, stability and robustness. The raw data was verified.

#### **Cleaning validation**

The “Cleaning Validation Master Plan”, authorized on 7.05.2015 was reviewed. The cleaning validation protocol entitled «Execution of Cleaning Validation/Verification for Solid and Liquid Lines (Chemical Testing)», authorized

on 13.09.2012 was reviewed. It was a general protocol for all equipment. Cleaning SOPs for all equipment and containers were not listed in the protocol.

The “Points of Visual Inspection and Sampling of Cleaned Equipment (for Solid Dosage Forms)/Chemical tests”, authorized on 11.03.2015, was reviewed.

IBC 600L was used for multiple products, including Moxifloxacin tablets, Valsartan/Hydrochlorothiazide tablets, but there was no product list for this piece of equipment, this was resolved in CAPA.

Cleaning of the Blender Serial No. G876-B01/IBC Containers No. (1-7), was reviewed.

### **3.5 COMPLAINTS**

Complaints and other information concerning potentially defective products were reviewed according to the written SOP and appropriate corrective actions were generally taken. The SOP entitled “Handling of customer complaints” was reviewed. Head QA was responsible for complaint investigation. Complaint impact assessment was performed by the Head QA/designee. In accordance with the SOP, complaints were classified and decisions and measures taken as a result of a complaint should be recorded and referenced to the corresponding batch records. 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 they were also affected. According to this SOP, all the complaints must be closed in thirty days or the long term corrective actions be stated the time plan. Trend analysis of complaints was performed on a yearly basis as part of an annual report. There were nine complaints received in 2014 and none in 2015 until the inspection. There were no complaints related to Moxifloxacin.

### **3.6 PRODUCT RECALLS**

There had been no recall in ten years. There were two SOPs about recall, entitled “Product recalls initiation”, and “Recalls conduction”. Recalls were classified as per the following.

-Class I: there is a reasonable probability that the use of a product will cause serious adverse health consequences or death.

-Class II: The use of a product may cause temporary or medically reversible adverse health consequences, or where probability of serious adverse health consequences is remote.

-Class III: The use of a product is not likely to cause adverse health consequences.

According to the SOPs, there were three depths of recalls: wholesale level, retail level (pharmacies) and consumer level.

A meeting would be scheduled and after the meeting, the decision to recall would be made and the QA manager filled in the recall declaration form.

Recall effectiveness checks usually started immediately after the recall announcement, but the period between the two activities depends on the recall urgency. Mock recalls had not been conducted as of yet. This was resolved in the company CAPAs.

### **3.7 CONTRACT PRODUCTION AND ANALYSIS**

The manufacture of ibuprofen soft gelatine capsules was contracted to an outside party. No other activities were contracted out, hence this area was not inspected in detail.

### **3.8 SELF INSPECTION AND QUALITY AUDIT**

#### **Items for self-inspection**

The on SOP “Preparation, conduction and follow up of self-inspection” was reviewed. Items for self-inspection included:

- Personnel Hygiene
- Personnel Training
- Health Monitoring
- Adherence to standard procedures
- Facility maintenance and physical status of equipment
- Correct labelling and good documentation practices
- General housekeeping
- Compliance of the adopted systems and practices with GMP requirements and continuous improvement issues.

#### **Self-inspection team**

The self-inspection team consisted of the Head QA, one member of QA and one member of personnel selected from another department.

#### **Frequency of self-inspection**

- Annual inspection was performed yearly.
- Frequent-inspection was done at least monthly.
- Non routine inspection, upon need.

#### **Suppliers audits and approval**

See Section 3.14 Materials.

### **3.9 PERSONNEL**

#### **General**

In general, there were sufficient qualified personnel to carry out the tasks for which the manufacturer was responsible. Individual responsibilities, however, should be more were not very clearly defined and recorded in some instances.

Personnel were aware of the principles of GMP received initial and continuing training, including hygiene instructions.

#### **Organization chart**

Organizational structure was reviewed.. Currently, Quality Control Manager and Quality Assurance Manager reported to Technical Director directly. As per the Organization Structure shown, Research & Development Manager and Manufacturing Executive Manager, which were under Operation Director, reported to the Technical Director as well.

## **Key Personnel**

Job descriptions for key personnel were reviewed.

- Technical Director
- Head Manufacturing Executive Manager
- Quality Assurance Manager
- Quality Control Manager
- QA Compliance Team Head
- QA Compliance Specialist

There were no job descriptions for General Director and two Deputy General Directors. This issue was resolved in the company CAPAs.

### **3.10 TRAINING**

The system document “JPM Training System” was reviewed. This document gave a complex description of the electronic training management system in place.

Training records were reviewed. Training for the new SOP “Handling of corrective and preventive action” was done from 12 until 14 May 2015. Training records for newly issued documents were available.

Training records related to the documents relevant for every employee were kept in the electronic training systems. The Supervisor in charge was responsible to check the completeness of the training for every employee.

An additional programme for session training on general topics (e.g. GMP, personnel hygiene) was in place. A checklist for the evaluation of the training success and training evaluation forms for new employees were available. For instance:

- Evaluation form for Compliance officer, topic: batch record review, conclusion: person was capable of reviewing batch records.

### **3.11 PERSONAL HYGIENE**

The various changing areas inspected were clean, gowns used by personnel, were clean and free of product residue. The SOP entitled “General instructions” was reviewed. According to the SOP, all staff prior to and during employment should undergo health examinations. Hygiene is one of the training programs to all the staff. Personnel should be instructed to wash their hands before entering production areas. Any person shown at any time to have an apparent illness or open lesions will not be allowed to come in the production area.

Annual health check-up was carried out for each employee by a qualified medical practitioner and records were retained.

### **3.12 PREMISES**

#### **General**

In general, buildings and facilities used in the manufacture of tablets were located, designed, and constructed to facilitate cleaning, maintenance and operations as appropriate to the type and stage of manufacture. Buildings and facilities had adequate space for the orderly placement of equipment and materials. Laboratory areas and operations were separated from production areas.



### **Ancillary areas**

Rest rooms were separate from manufacturing and control areas. Toilets were located outside of the production area. Utilities and the maintenance workshop were located in another independent small building.

### **Storage areas**

Two separate warehouse areas were used at the JPM site. The first area was used for raw materials. The second area was used for packaging materials and finished products. High-rack facilities were installed for all types of materials. Cleaning status of areas and materials was very good.

Starting materials were kept in the Raw Materials Store, which was adjacent to the south of the manufacturing building at the highest level. Packaging materials and finished products were stored in the Packaging Material Store and Finished Product Warehouse separately, which were connected to the north of the manufacturing building at the ground level. Separate areas were available for finished products and packaging materials. Additional security was implemented for printed packaging materials (separate locked room).

Receiving and dispatch bays protected materials and products from the weather. The receiving bay was roofed over. A material airlock was installed behind, to allow controlled transfer to the storage area.

Segregation was provided for the storage of rejected, recalled, or returned materials or products and printed materials. The temperature was monitored by an environmental monitoring system.

A sampling room with a laminar flow unit was installed in a separate room in the Raw Materials Store. Entrance to the sampling rooms was via change rooms for personnel and separate entries were used for materials.

Storage conditions were set at <25°C for raw materials and <30°C for finished products. Humidity was set at <60% (this was specified in the SOP “Follow up of storage conditions in the warehouse”, authorized on 15.05.2015).

Monitoring was done with the building management system (BMS). Additionally, weekly printouts of the data from the temperature logger installed in the warehouse were available.

### **Weighing areas**

The weighing area (D15) was located at the first floor in the manufacturing building and was part of production area.

Materials from the warehouse were transferred through a suitable airlock.

A laminar flow unit equipped with HEPA filters and dust extraction was installed to prevent contamination of the surroundings.

### **Production areas**

Schematic drawings of the production department were available and used for the inspection of production.

Areas used for production were found in good condition. All workshops relevant to the production of Moxifloxacin tablets were inspected.

Manufacturing took place on two main levels in addition to an intermediate level which was used for powder discharge to compression and filling machines, making use of gravity.

In general, the production area was laid out to allow production steps to take place in a logical order. The surfaces were smooth and free from cracks. Equipment and materials were orderly positioned to minimize the risk of confusion between different pharmaceutical products or their components. Temperature, relative humidity and pressure differentials were continuously monitored and controlled (BMS).

A clean corridor concept was in place (overpressure in the production corridor) to avoid cross-contamination in between different production areas.

The primary production area (including primary packaging) was suitably separated from the other areas. Personnel and materials had to pass change rooms via their respective airlocks.

Areas where products and materials might be exposed to environment were classified as EU GMP class D, other areas were classified as social clean areas (see below for further details of the HVAC system).

### **Quality control areas**

The quality control laboratories were located on a single floor and consisted of several instrumental laboratories along with a microbiology laboratory. It was generally clean and well maintained.

### **HVAC system**

System description “Environmental service heating, ventilation and air conditioning (HVAC) system / Al-Razi-Site and SOP for preventive maintenance were available.

Installation of the air handling units (AHU’s) was done under the roof of the building. The area was visited by the inspectors and found clean and in good condition.

Areas where products and materials might be exposed to the environment were classified as EU GMP class D, other areas were classified as “social clean areas”.

Air handling units that serve class D areas were equipped with EU13 HEPA filters. Pre-filters (class EU 8) were installed. Pressure difference at the pre-filters and HEPA filters was monitored with the BMS. Additional check of the differential pressure was documented monthly.

The production area was supplied with four AHU’s.

AHU 1A and AHU 1B supplied 100 percent fresh air to primary production areas (except for primary packaging). Differential pressure in between production rooms was regulated by the BMS controlled system, with a clean corridor concept to prevent cross contamination between different areas.

Additional AHUs with re-circulation and final HEPA filters were installed for primary packaging (AHU 02) and the microbiological laboratory (AHU 06). Secondary packaging was supplied by air from an AHU with final EU8 filtration (AHU 03).

Maintenance and calibration status was labelled at the technical installations.

Example: AHU 1B, integrity check for the HEPA filter was done at 16 January 2015 and the next date should be 16 January 2016.

Details of filter integrity testing and re-qualification were evaluated.

Documentation for turning AHUs on and off was available from the BMS.

Additionally, documentation for checking pressure differentials was available on an hourly basis.

### **Dust extraction system**

Dust extraction was installed for all relevant areas. Dust collection was done with a central SINTAMATIC unit (SINTAMATIC cased dust filters). The HEPA filter system was fitted after the dust collector as a backup filter. Pressure differences at dust and HEPA filters were controlled by the building BMS.

SOP about preventive maintenance and operation of the system was available.

## **3.13 EQUIPMENT**

Balances and other measuring equipment with appropriate range and precision were available for production and control operations and were calibrated on a scheduled basis. Calibration due-date labels were attached to the equipment.

## **3.14 MATERIALS**

### **General**

In production, dispensed starting material and intermediate products were identified during the different production stages using proper labels that include the identity and status of each material or product.

Materials were obtained from approved suppliers. Separate lists for manufacturers and suppliers of active and inactive starting materials were available. The SOP entitled “Qualification, approval and rating of material suppliers” was reviewed. API suppliers were rated as first choice if they had supplied at least six times with satisfactory quality. USDMF / EDMF or CEP must be provided. Suppliers with more than four deliveries were rated as second choice manufacturers. “Other choice” suppliers had to supply JPM with a minimum of one accepted delivery or samples.

A dual electronic and bin card system was used for material management.

### **Starting materials**

All incoming starting materials were stored in the "Hold" area until QC sampling, testing and release procedures were completed. Then, materials were moved to the "Released" area, from which they can be delivered to production (dispensing was done after passing material airlock in the production area).

Starting and packaging material cards were filled for every batch. Annual inventory checks were done. Additionally, a computerized system was installed to allow better control of amount and storage location. A separate procedure was in place for R&D materials.

The procedure for receiving of goods, quarantine, sampling and storage was well explained by JPM personnel. Relevant SOPs were available.

Examples: the SOP for receiving and handling of raw materials up to release (Arabic version only, authorized on 08.03.2015).

First check for the correct delivery was done on the base of the order confirmation. Furthermore, label and certificate of analysis were compared.

Details of sampling and evaluation of starting materials after receipt in the warehouse were reviewed. The SOP entitled "General sampling plan for starting and packaging materials" (authorized on 19.11.2014) was reviewed. 100 % identity checks for active materials were determined..

The SOP entitled "Sampling of starting and packaging materials" (authorized in 14.05.2015) was reviewed. Sampling room, techniques, equipment to be used, amount to be withdrawn, details of label checks were described.

### **Rejected, recovered, reprocessed and reworked materials**

There were four batches of raw materials seen in the rejected material stores and four batches of active raw material on hold in storage area.

### **Purified Water generation plant**

The installation of water generation unit was done at separate areas with good hygienic and maintenance state. All areas were seen by the inspection team.

A detailed purified water system description was available (No. VD/40/003/03, authorized on 0.02.2013).

Raw drinking water (chlorinated) was supplied to the system from private ground well. The water treatment consisted of 3 stages:

#### Pre-Treatment stage:

Included Pre-Filtration, dual softeners to eliminate water hardness, soft water storage tank, afterwards that water was passed through UV unit; de-chlorinated through injection of Sodium meta-bisulfite.

#### Water Purification stage:

Included Reverse Osmosis unit and de-ionisation step,

Additional return circulation loops to RO water tank and soft water tank were installed.

#### Post-Treatment Stage:

After purification, purified water was pumped to the production storage tank (6 m<sup>3</sup>) at the upper level of the production area. Water was held at a temperature of 65 – 80 °C. Information about the material quality was part of the system description (e.g. SS316L for the Purified Water tank, 6 m<sup>3</sup> and for the distribution loop, welding was done under argon gas, welding joint was orbital stainless steel, reference to welding report was given).

#### Distribution of Purified Water:

Purified water was circulated continuously between the purified water storage tank and three parallel stainless steel loops that feed the labs and production areas. The circulation path of purified water back to re-enter the purified water tank was through a main return line. Temperatures at the end of the return loop (65 – 80 °C) and after heat exchanger were controlled by the BMS.

The sanitisation process of system components with hydrogen peroxide, 0.2%, was evaluated.

Under normal circumstances sanitisation was done every six months.

The last sanitisation was done on 20/Nov/2014 after the change of the vent filters (purified water storage tank). QC checks for absence of the sanitisation agent were documented.

#### Water monitoring:

SOP Sampling and testing of water from water treatment system and purified water from points of use / Al-Razi Site (No.QC/01/06/14, authorized on 08.02.2015) was available.

The frequency of sampling and testing was defined. Specification for Purified water (No. QC/03/080/08, authorized on 10.10.2014) was verified.

The alert limit for microbial contamination was defined at  $\leq 30$  cfu/mL.

#### Reports:

The purified water points of use microbial trend evaluation report for 2014 (authorized on 14.04.2015) was available.

According to the conclusions section and the data seen, all microbial results were within acceptance limit and below alert limit and free from specific organisms.

Also trend evaluation was done on a regular basis. The actual trend of microbial count based on 2014 microbial count results was 5 cfu/ml.

Additional report for chemical testing for the whole water generation site was available for 2014 (authorized on 20.04.2015). No problems were identified.

Revalidation of microbial status of the point of use was done annually.

The last report from 2015 (authorized on 29.04.2015) was available.

#### **Compressed air**

Detailed compressed air system description was available (authorized on 03.04.2011). 2 two stages-dry screw air compressors (INGERSOLL-RAND SH 150AC/Sierra), 2 air receivers, two refrigerated air dryers, prefilter (1  $\mu$ m) and final filter (0.01  $\mu$ m) were installed. All pipe materials were galvanized steel. Point of use filtration was not implemented.

### **3.15 DOCUMENTATION**

#### **General**

In general documents were designed, prepared, reviewed and distributed with care. Documents were also approved, signed and dated by the appropriate responsible persons. Documents were laid out in an orderly fashion and were easy to check. Reproduced documents were clear and legible. Documents were regularly reviewed and kept up to date.

The SOP entitled “Preparation, approval, authorization and updating of controlled documents”, authorized on 08.09.2013, was reviewed. Preparation of new and updated documents, approval and authorization process was described. After finalization, documents were ready for document control (separate SOP about document control available, document distribution / withdrawal records in place. The blue-coloured version of the document was defined as the “master”).

New documents have to be implemented to the training system web application. In the case of updated documents, relevant employees are informed electronically about the change of the document and of the additional training needs.

The SOP entitled “Revision policy and types of updating of JPM controlled documents”, authorized on 01.08.2011 was reviewed. Revision of SOPs should be one year after first version and the every three years. Working guidelines should be revised every three years. There was no revision period defined for other documents (e.g. system documents, job descriptions).

#### **Batch processing records and batch packaging records**

Batch processing records and batch packaging records for Moxifloxacin Tablets were reviewed. Master formulae and processing instruction, including critical parameters, were included in BPRs. In general, BPRs contained the necessary information for each step of processing and packaging.

The SOP entitled «System for Assigning Batch Numbers», authorized on 16.5.2013 was reviewed. Batch numbers consisted of 6 or 7 digits, XXYYZZ.

XX: indicates the year of manufacturing

YY: indicates month of manufacturing

ZZ: Serial number for the batches manufactured during each months, starting from 01 (monthly). Serial number may exceed 99, and thus, three-digit numbers and 7-digit batch numbers may exist.

### **3.16 GOOD PRACTICES IN PRODUCTION**

#### **General**

In general, raw materials for manufacturing of tablet were dispensed, processed, packaged and distributed under appropriate conditions. Actual yields were compared with expected yields at designated steps in the production process. Processing status of operation room was labelled with product names and batch numbers. In-process controls were performed by QC analysts. The production area was access-controlled.

At the time of the inspection, weighing, compressing, blister packaging and secondary packaging for Monozide 25mg Tablet were carried out.

The production area was used for the manufacturing of tablets, capsules, liquids of finished pharmaceutical medicines as well as natural products.

### **Prevention of cross-contamination and bacterial contamination during production**

The following measures to prevent cross-contamination and bacterial contamination were noticed in the inspection.

- Campaign production was adapted to use the SOP for Clearance for Production Area was established. The same procedure was used even if product change-over.
- The SOP for equipment cleaning was established.
- Airlocks were designed for production area, sampling area. Appropriate air supply and dust extraction systems existed.

### **Processing operations**

Until this inspection, no commercial batches of moxifloxacin tablets were manufactured and packaged except three validation batches (Batch No. 0110901, 0110902, 0110903) and one batch used for BE study (Batch No. 0120103).

Information was given, that previous batches were produced with the same equipment but lower batch size.

Equipment for dispensing (Dispensary Dust Control booth), sieving, blending (Gallay Tumble Blender with different blending containers), compaction and milling (Vector Roller Compactor TFC-520 with integrated mill on the front of unit) steps were installed on the first production floor.

Granules were transferred to intermediate level which was used for powder discharge to compression machines, making use of gravity.

Rooms with compression machines (two machines Fette 2100 with dedusters and metal detectors, rooms A9 and A 6), coating room (A17, accelacota 75) and separate coating solution preparation room were situated in the ground floor.

The Vector Roller Compactor was not working since October 2014. This was resolved in the CAPAs after the inspection.

### **Storage of compression tools**

Appropriate compression tools, dedicated for Moxifloxacin Tablets, were available and stored appropriately. Characters “MX4” were imprinted.

### **Packaging operations**

Two blister lines (BOSCH) were installed.

An automatic camera system was available but not working. According to the information by JPM, this would be replaced by a new system during the next months.

After blistering, airlocks were used to transfer the primary packaged tablets to the secondary packaging.

Secondary packaging was done as a manual process. Appropriate number of workers was available to allow appropriate speed and carefulness of the process. Explanation was given, that visual check of every blister was part of the procedure.

In general, packaging operations were performed properly, but in-process controls were partly conducted not properly or without documentation.

The SOP entitled «General Sampling Plan for Blisters during Blistering Operation», authorized on 05.04.2015, was reviewed.

It was required to take ten blisters from the last bag or from the line for the leakage test (in order to cover the whole roller mold). For Moxifloxacin tablets, where the individual blisters had only five tablets, there was no consideration of the necessity to increase the sample size to include that all of the blisters were adequately sealed.

In-process control secondary packaging (authorized on 05.04.2015) included the check of all relevant parameters, e.g. printed information, number of blisters in each box. However, the check of the correct content of the boxes with 100 blisters was not documented (form No. QC/02/024/01). These issues were resolved in the CAPAs.

### **Environmental and compressed air monitoring**

Annual reports for 2014 and SOPs were available. Sampling for microbial monitoring of the production area was done every four months and all results were  $< 200 \text{ cfu/m}^3$ . Results for compressed air (weekly monitoring at the main branch, monitoring at the point of use every six months, every three months for coating area) were below  $3 \text{ cfu/m}^3$ .

Measurement was done by filtration through  $0.2 \mu\text{m}$  filter at 2 bar. Possibility of usage of  $0.45 \mu\text{m}$  filters should be evaluated.

## **3.17 GOOD PRACTICES IN QUALITY CONTROL**

QC contained an adequate variety of quality control instruments

### **Control of starting materials and intermediate, bulk and finished products**

Control of the raw materials and finished product, as well as stability samples, was being done in four different sub-laboratories. An additional R&D laboratory was also available.

### **Batch record review**

The SOP entitled «Batch Record Review for Solid Dosage Forms» (authorized on 01.10.2014), the SOP entitled «Batch Record Approval for product release» (No.QA/01/014/00, authorized on 8.12.2014) and related checklists were reviewed. The batch record for Ranitidine 150mg Tablet (Batch No. 1502320) was spot-checked. Batch record review SOPs were followed. But the checklist that was used for batch review of deviations was not included in the SOP for Batch Record Review.

### **Stability studies**

One of stability chambers was out-of-use ( $30^\circ\text{C}/75\%\text{RH}$ ) in quality control, but a stability room in the finished product warehouse was available. Stability test results for batch No. 0110902 were reviewed. The presence of the 4 stability batches was confirmed in the stability room.



### **Reference standards**

This area was acceptable in general.

### **Microbial laboratory**

The SOP on “Testing of prepared culture media”, authorized on 06.02.2014, was reviewed. According to the procedure, representative samples of each batch of media should be checked for sterility and growth promotion. Additionally inhibitory (Mossel broth) and indicative properties (e.g. VRBD agar) were checked for special media. Test reports and Log book (Binder incubator II) were available. Start and end of incubation was documented.

The SOP for sampling and testing of purified water (authorized on 08.02.2015) was reviewed together with water reports and documentation of raw data. A filtration method was used. It was considered acceptable.

## **PART 4: 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, **Jordanian Pharmaceutical Manufacturing Co P.L.C, located at Al-Razi Site: P.O.Box 151, Um Al-Amad 16197 Jordan** 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.