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

| **Part 1** | **General information** |
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| **Manufacturers details** | |
| Name of manufacturer | Farmak JSC |
| Corporate address of manufacturer | 63 Kyrylivska St., Kyiv, 04080, Ukraine |
| **Inspected site** | |
| Name & address of inspected manufacturing site if different from that given above | Manufacturing site: 74 Kyrylivska St., Kyiv, 04080, Ukraine<br><br>Warehouse Site 4: 49ж (Block F), Kyivska Street, Kalynivka Village, Makarivskyi District, Kyiv Region, 08004, Ukraine. |
| Unit / block / workshop number | Workshop 5, (Sites 2, 4) and Warehouse (Sites 1, 4)<br>Quality Control (building no. 8 floors 1, 3,4) |
| **Inspection details** | |
| Dates of inspection | 20-23 January 2020 |
| Type of inspection | Initial |
| **Introduction** | |
| Brief description of the manufacturing activities | Workshop No.5 is located in building no. 2 and includes sites 1,2,3,4.<br>Twenty-seven products are manufactured in Site 2. These products are classified in three major categories: sex hormones (androgens, progestogens, antiandrogens – 5 products), glucocorticoids (4 products), different therapeutic areas (18 products).<br>Dexamethasone ampoule labelling and secondary packaging takes place in Site 4 (Workshop 5).<br>Warehouse -Site 1 is used for storage of raw materials. Warehouse-Site 4 is used for storage of finished products, retained samples and packaging materials (including physical testing on packaging material)<br>Quality Control laboratories are in building no.8 and are shared among all manufacturing workshops. More specifically analytical chemistry laboratories were located on the 4th floor and microbiological laboratories on the 3rd floor. Stability rooms were located on the 1st floor with the exceptions of the accelerated studies stability chamber which was in the R&D department. |
| General information about the company and site | Farmak was established at the premises of M.V. Lomonosov Chemical and Pharmaceutical plant which originally specialized in manufacturing API and X-ray contrast media. Since 1995 Farmak is specializing in manufacturing FPPs although small API batches are still manufactured on site. Finished |

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| | products are exported to more than 20 countries. The company is governed by a CEO and a Board of Directors.<br>There are 3 warehouses (Site 1 raw materials, Site 2 narcotics and psychotropics and Site 4 finished products, retained samples and packaging materials). Warehouse sites 1 and 2 are located on Kyrylivska 74 and Chornomorska 2 respectively, where the manufacturing facilities are located. Warehouse Site 4 is located off campus at Kalynivka Village, Komodor Logistics Centre.<br>Major changes since 2017 included:<br>Senior/top management structure change (CEO post created)<br>Reconstruction of sampling room commissioned in 2017<br>The new warehouse for finished product and packaging materials (operational in Jan 2019)<br>Modifications in PW and WFI systems. |
| History | Several Farmak workshops were inspected by Croatian and Polish NRAs in 2017 and 2019 respectively |
| **Brief report of inspection activities undertaken – Scope and limitations** | |
| Areas inspected | Quality management system<br>Production operations with focus on Workshop 5 (Sites 2, 4)<br>Packaging Operations<br>QC Laboratories including analytical, microbiological laboratories<br>Materials management system<br>Facilities management and engineering support systems including HVAC, water etc.<br>Warehouses site 1 and site 4<br>*Note: The company uses the terms "Workshop" and "Site" to indicate areas that are either physically or organizationally separated.*<br>The manufacturing of the aseptically produced small volume injection dexamethasone phosphate in ampoules takes place in Site 2 which is a part of the 2nd floor of Building no. 2. Inspection and packaging are performed in Site 4, located on the 1st floor of Building no. 2. The responsible organizational unit is Workshop 5. |
| Restrictions | N/A |
| Out of scope | All other Workshops and sites not applicable to WHO Prequalification application |
| WHO products covered by the inspection | HA734 Dexamethasone Phosphate Solution for injection 4mg/ml, 1ml ampoule |
| **Abbreviations** | **Meaning** |
| AHU | Air handling unit |
| ALCOA | Attributable, legible, contemporaneous, original and accurate |
| API | Active pharmaceutical ingredient |

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| APR | Annual product review |
| APS | Aseptic process simulation |
| BMR | Batch manufacturing record |
| BPR | Batch production record |
| CC | Change control |
| CFU | Colony-forming unit |
| CIP | Cleaning in place |
| CoA | Certificate of analysis |
| CpK | Process capability |
| DQ | Design qualification |
| EDI | Electronic deionization |
| EM | Environmental monitoring |
| FMEA | Failure modes and effects analysis |
| FPP | Finished pharmaceutical product |
| FTA | Fault tree analysis |
| GMP | Good manufacturing practices |
| GPT | Growth promotion test |
| HEPA | High efficiency particulate air |
| HPLC | High performance liquid chromatography (or high performance liquid chromatography equipment) |
| HVAC | Heating, ventilation and air conditioning |
| IQ | Installation qualification |
| LAF | Laminar air flow |
| LIMS | Laboratory information management system |
| MB | Microbiology |
| MBL | Microbiology laboratory |
| MF | Master formulae |
| MFT | Media fill Test |
| MR | Management review |
| NC | Non conformity |
| NRA | National regulatory agency |
| OQ | Operational qualification |
| PHA | Process hazard analysis |
| PLC | Programmable logic controller |
| PM | Preventive maintenance |
| PQ | Performance qualification |
| PQR | Product quality review |
| PQS | Pharmaceutical quality system |
| PW | Purified water |
| QA | Quality assurance |
| QC | Quality control |
| QCL | Quality control laboratory |
| QMS | Quality management system |
| QRM | Quality risk management |

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| RA | Risk assessment |
| RCA | Root cause analysis |
| RO | Reverse osmosis |
| SIP | Sterilization in place |
| SMF | Site master file |
| SOP | Standard operating procedure |
| URS | User requirements specifications |
| UV | Ultraviolet-visible spectrophotometer |
| WFI | Water for injection |

| **Part 2** | **Summary of the findings and comments** |
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## 1. Pharmaceutical quality system

GMP principles for the site. This system included the fundamental compliance principles and standards of the company, in the areas of quality, safety and environmental protection. Operations were specified in written form. Managerial responsibilities were appropriately detailed in written job-descriptions. Product and processes were monitored, and test results considered during batch release; regular monitoring and reviews of the quality of pharmaceutical products were being conducted according to documented schedules and procedures. Management review meetings were periodically held.

### Product Quality Review

PQRs of all authorized products were conducted annually with the objective of verifying the consistency of the manufacturing process, the adequacy of approved specifications for starting materials and finished products, to analyze any trends and to identify any potential product and process improvements. The company had recently introduced an Electronic Documentation Management System (MyProcess) and PQRs were prepared using this system. Input from 18 different departments was used in preparing the different PQR sections. The PQR was reviewed by QA and QP and upon initial approval was transferred to the Quality Director for final approval. A PQR plan was drafted and used to monitor completion of the work which should be done within 3 months.

PQR Dexamethasone phosphate solution for injection 4mg/ml, 1ml ampoule, 5-10 ampoules per pack was assessed. This PQR covered the period 01-04-2018 until 31-03-2019.

The PQR covering 01-04-2017 until 31-03-2018 was also assessed. The general conclusion was that the process was under control and no negative trends were found.

### Quality Risk Management

The company's procedures on "Quality risk management" were reviewed as well as their application in different areas of the QMS. It was observed that in certain occasions informal risk assessments were carried out without use of any relevant tool.

The risk assessment for Workshop 5, Site 2 was discussed in detail. At the basis was a methodology document. This described all types of considerations that should be taken when performing a risk assessment. "Combined shared manufacturing assessment report for Workshop 5" was seen. This was a revision of an earlier assessment in 2010. 13 APIs were rated as high potent. The conclusion of calculations was that the risk of cross contamination was still under control. The risk could further be reduced if the cleaning of surfaces was improved. To this end technical measures were implemented. An important one was the introduction of a single use containment system. This allowed for dispensing of high potent active substances in a disposable isolator. From the "Plan of updating the documents of risk assessment" it was seen that the effectiveness of the new measures would be checked by 30-3-2020.

**Data integrity management**
Policies and procedures were introduced and updated to better assure data and record management systems. Installation of electronic systems and software in the laboratory had taken account of the ALCOA principles.

**Change and deviation management**
The company had SOPs in place for change and deviation management. The change controls for the modification of PW and WFI loops were reviewed in detail. Deviations were not always trended and reviewed periodically. CAPAs in relation to deviations were documented but their effectiveness was not verified, especially for minor deviations. At the end of December 2019, a change in the CAPA management was introduced to assess the effectiveness of minor CAPAs, too. All identified observations were appropriately addressed by the company.

The 2019 register of deviations in Workshop 5 was reviewed.

## 2. Good manufacturing practices for pharmaceutical products

Good manufacturing practices generally were implemented. Necessary human and physical resources were provided, including qualified and trained personnel, adequate premises, suitable equipment and services, appropriate materials, approved procedures and instructions, for in-process and other controls. Qualification and validation activities were generally being performed and documented. Technical agreements with service providers describing responsibilities of relevant parties, were in place. Manufacturing steps were recorded in batch manufacturing and packaging records. Manufacturing processes were defined and reviewed. Product was released by the authorized persons (QP).

## 3. Sanitation and hygiene

Premises and equipment were maintained at a satisfactory level of cleanliness. The company had procedures in place as the basis for its approach to personal hygiene and sanitation in its production facility, with appropriate hand washing required. Clean areas were cleaned frequently in accordance with an approved written program.

Personnel were seen to be performing their duties in a generally organized and diligent manner. There was a procedure available regarding "personnel and visitor access to the facilities". Procedures were in place for the preparation and control of sanitizing materials used in production areas.

Non-viable particle and microbial monitoring of facilities were performed. The risk basis for the sampling plans was discussed with the company and documentation in support of the locations chosen for monitoring as well as qualification was presented

**4. Qualification and validation**

The company approach to validation was detailed in procedures and in the Validation Master Plan. A validation program was available. In general, the company had identified what qualification and validation work was required. Revalidation/requalification was performed periodically. The key elements of a qualification and validation program were defined. Documentary evidence was available that the equipment and processes had been designed, installed and operated in accordance with their design specifications. Equipment and devices used for qualification were calibrated and certificates were available.

A requalification was done of the ampoule washing machine by an external vendor, and of the sterilizing tunnel by Farmak staff. For the washing machine a list of tests was observed. In this list there was no reference to testing of the filters for WFI and compressed air. For the sterilizing tunnel the relevant report was reviewed in detail. The conclusion was that the tunnel complied with acceptance criteria. The company appropriately addressed all observations.

Environmental qualification in the ampoule filling area was carried out every 6 months. The latest qualification was contracted out and the technical agreement between the two parties was presented. Tests performed included:

- Filter integrity using a particle counter
- Air velocity
- Laminarity- Air flow visualization
- Non-viable particles
- Microbiological
- Differential Pressure -Temperature

Environmental Qualification of the sampling room in the warehouse where highly potent compounds were sampled, was reviewed. Qualification was performed once per year and it included functionality test of the installed equipment as well as review of procedures and instructions for operating the sampling booth. Filter integrity testing was performed using a photometer and upstream concentration was measured before initiating measurements of the downstream concentration. Air velocity, air exchange, recovery and non-viable particles as well as differential pressure, temperature and microbiological qualification (swab testing, contact plates and air sample) were performed. Certificates for the calibration of equipment used during qualification were presented. The qualification was contracted out and a technical agreement between the two parties was available.

Environmental Qualification of the Personnel Airlock (Grade L/D). Despite the Airlock being depicted in lay out as Grade L and Grade D without having any wall partition, the room was qualified as Grade D. All the necessary tests were performed annually. All observations were appropriately addressed by the company.

There were 29 operators who were annually qualified to perform ampoule visual inspection. The qualification test was based on identifying defects on ampoules with various defects. Acceptance criteria for detection of each category of defects were established. The test was performed using all sizes and colours of ampoules used in production and it took into consideration viscous and coloured solutions/emulsions.

In case of failing the test operators were given 3 chances of passing the test while extra training was provided.

Media fills were performed twice per year. The last media fill was carried out in October 2019. In general, as minimum one 100Lt batch was filled in 1ml ampoule and one 100Lt batch was filled in 5ml ampoule. In the October media fills two batches of 5ml and one batch of 1ml were filled. Tryptone soy broth was used as a medium and the concentration was determined. The following parameters were considered during media fills: number of operators, filling speed, unusual interventions, spills, time for filling a batch. Acceptance criteria were established.

Mapping of the stability room (T=25°C/RH=60%) was reviewed. The room was mapped empty during OQ for one day and full during PQ for one day. 27 dataloggers were used with an accuracy of 0.5°C. Calibration certificates were available. Worst case locations were considered, and locations of minimum and maximum temperature and relative humidity were determined.

Following removal of some user points in the PW loop and the installation of monitoring equipment in the return part of the WFI loop the water systems were requalified. For the PW system Phase 1 was applied for one month and it included sampling and testing of each user point every day except weekends. Phase 2 was applied for 11 months and all user points were sampled and tested on a rotational basis within a week. During summer 2019 some extra user points were removed and the qualification exercise was repeated. Qualification of the WFI system was initiated in January 2019 and followed a similar approach. At the time of inspection Phase 2 qualification was completed. Alarm and action limits were established based on the qualification findings and results were trended.

Qualification of HPLC No. 46 was reviewed. Standard equipment used for qualification was calibrated and certificates were available. The following test were performed:

- Column oven temperature
- Wavelength accuracy
- Absorbance
- Drift and noise
- Reproducibility/injection volume
- Detector linearity
- Gradient
- Autosampler accuracy/linearity

## 5. Complaints

There was a procedure in place for complaints handling. Responsibilities were described, and an appointed person was responsible for coordinating complaint handling. The Qualified Person was also involved in the investigations and review of complaints. Quarterly and annual reviews were performed. The annual review also included a comparison study with the previous year and was used as an input to management review meetings. The lists of 2018 and 2019 complaints were briefly reviewed. A logbook was used to register complaints.

## 6. Product recalls

A procedure for handling product recalls was available. Responsibilities were defined. There was provision of carrying out a mock recall every year, during the fourth quarter if no recall had been conducted during the rest of the year. Two recalls were performed in 2019. The recalls were initiated by the Ukrainian authorities as a result of a global recall due to efficacy issues. Reconciliation took place and the recall effectiveness was assessed.

## 7. Contract production, analysis and other activities

Production and quality control of Dexamethasone injection was not contracted out. Two toxicological experts were contracted to carry out work on HBEL. Their contracts and CV were presented during the inspection. Farmak had also established contracts for environmental qualification of their facilities. These contracts with were reviewed during the inspection. Responsibilities for each party were appropriately defined.

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

Self-inspection was not reviewed in detail due to time constraints.

There was a procedure in place for qualification and requalification of suppliers. The company had started auditing suppliers of materials intended for sterile products. There were two Dexamethasone Sodium Phosphate manufacturers. In recent years Dexamethasone was procured from only one manufacturer through a distributor, located in Germany. The API manufacturer was audited in September 2019 and the distributor was audited in April 2018. It was noted that requalification of suppliers was performed every 3-5 years unless an earlier review was triggered by management review.

## 9. Personnel

There were approximately 260 staff working in two shifts of 12 hours per day. In general, personnel had the necessary qualifications and practical experience. Responsibilities of staff, and their duties were documented in written job descriptions. Job descriptions for Qualified Persons, Heads of Workshops, Heads of FPP Warehouse, Head of Microbiology department as well as filling area operator and supervisor were reviewed. These were generally very detailed. CVs were found to comply with the requirements in job descriptions. It was noted that there was no versioning system to job descriptions. These documents were dated and signed by relevant personnel.

**10. Training**

There was a procedure in place describing training activities. Self-training by studying new or revised procedures was also documented but the evaluation of this type of training was not detailed. Training records for the Head of Microbiological department were reviewed as well as for one of the operators performing visual inspection. All observations regarding training were appropriately addressed by the company

**11. Personal hygiene**

Smoking, eating, drinking, chewing, and keeping smoking material and personal medicines were prohibited in production, laboratory and storage areas. Gowning procedures were available for personnel and visitors and pictorials were available in personnel dressing rooms. Safety information for visitors was given orally. Visitors had to sign for information received. The relevant SOP was later shown. Different disinfectants were used for hands and surfaces. Disinfectants were rotated, and expiry dates were determined based on certificates provided by the suppliers. The most stringent expiry dates were applied. However, the company had not verified the expiry date on most disinfectants, and it is recommended that they perform this verification exercise.

**12. Premises**

Entry to Workshop 5, sites 1 and 2 for personnel was shared. In this area street clothes were stored. Then personnel entered a common corridor (unclassified) for site 1 and 2 and further entered separate dressing rooms for site 1 and site 2. Dexamethasone was considered a highly active substance, sampled at the warehouse. Sent from warehouse to production through passbox. Weighing and dispensing and solution preparation took place in the solution preparation room 245, then filtered to sterile vessel. One bioburden sample was taken before filtration. After filtration no bioburden sample was collected. One or two operators were involved in the filling process. One filling machine with capacity to fill 1ml- 5ml ampoules was installed. The batch size for Dexamethasone was 250Lt. Sterile filtration in Class A with surrounding area Class B and filling area in Class A with background Class B.

The Class D area for ampoule washing and collection of filled and closed ampoules was accessed by airlock 231.

The storage facilities on the first floor were visited. In room 136 uninspected and inspected blank ampoules were found in identical boxes, without sufficient segregation. Product on pallets were kept together by incomplete wrappings of plastic. Hand written labels were seen. The status of individual boxes was not indicated on the outside. The only visible difference between uninspected and inspected units was whether the bottom half of a pallet label was filled out. The company explained that a change was being implemented to use different types of boxes for uninspected and inspected product. The status of product in the system ORSOFT was “Quarantine” for both types.

The storage room was extremely full. A cart with metal boxes containing sterilized ampoules was blocking a temperature/RH sensor on the wall. All identified observations were appropriately addressed by the company.

Storage room 140 for 2-8ºC products was also full, with product and empty sterilization carts. A batch of Farmasulin product was kept in this room awaiting transportation to the Kalynivka warehouse site 4 on 22-1-2020.

Warehouse Site 1 was visited. Raw materials were received and stored in this warehouse. Upon arrival materials were checked in accordance with a receipt checklist and paperwork was entered in SAP from where the material labels were issued. SAP was used to segregate and identify the status of materials since the barcode labels generated by the system were used to manage stock. LabWare(LIMS) was bridged with SAP allowing release of materials by QC. Temperature was monitored. Rodent traps were placed on the outside perimeter of the building and insecticutors were installed near the receiving and loading bays. There were three sampling rooms in the same building. One sampling room was dedicated to high potent compounds. Quality control personnel were responsible for collecting samples and cleaning of the sampling areas. Logbooks for the sampling rooms were available.

A visit was made to warehouse site 4 at the Komodor Logistics Centre in Kalynivka. This warehouse was opened in December 2018. The Logistics Centre and the warehouse were both access-controlled. There were separate receiving bays for primary and secondary packaging materials and for finished goods, as well as dispatch bays for materials to be sent to the Farmak main site and for external customers. Bays were protecting against the weather. In the main warehouse conditions of 15-25ºC were maintained and monitored with a sufficient number of T and RH sensors. There were two cool chambers, 2-8ºC and 8-15ºC (not for WHO product). A project had been started to connect individual sensors to a BMS. A well-designed mapping study was seen for the 15-25ºC area which was performed in summer. As soon as it would be cold outside this study would be repeated for winter conditions. The 2-8ºC study was also seen. No comments were made.

Incoming goods were checked and recorded on paper protocols and put into SAP that was used as the warehouse inventory system. A product would be given the release status on the basis of a certification document transmitted from LIMS. Materials for production would be ordered from the Kyiv site and assembled at the warehouse. Labelling of pallets was done with a production order number. Transportation between warehouse 4 and Kyiv was done in conditioned trucks. Printouts from the temperature and humidity controls were seen. Products for customers would be picked and assembled on pallets. It was possible to deliver to customers less than a full tertiary package. In that case the remaining items would be placed in a new carton, which had handwritten labels. For this labeling activity there was no supervision by QA.

Returned quantities of labels were received with a waybill from internal logistics and given a new location in SAP to manage the risk of wrong placement.

In the warehouse areas were seen for rejected goods, including raw materials, and for storage of retention samples.

**13. Equipment**

Water and compressed air entering the ampoule washing machine were filtered by one of three filters. Tags for the identification of two of the filters were missing. In the qualification documentation no reference to these filters could be found. In MBRs filter pressure values to be set per product were seen. Valves would be manually set by an operator and settings recorded in the BMR. Manometers were installed to allow for monitoring of the pressures. The only alarm that was listed on the recipe screen was for recirculated WFI, which was outside the range for this valve. The company claimed that other alarms were set but that these could only be seen on screens accessible to mechanics. All observations were appropriately addressed by the company.

Filling took place in a Class A/B area. The filling machine was inside a RABS. Gloves attached to the RABS were tested every month according to a work order by maintenance technicians. A procedure adequately described the method to check the air tightness of the gloves. A calibrated device was used for this.

**14. Materials**

Incoming materials were checked for container integrity and quantity against documentation received and then they were registered in SAP. This system was used to manage material stock and status and was bridged with LIMS. Quantities of raw material received were not checked against the placed order. Temperature at the warehouse was monitored. Starting materials and packaging materials were purchased from approved suppliers. The principle of FI/FO was built in SAP for management of materials. All observations were appropriately addressed by the company.

**15. Documentation**

EDMS included all docs, QM, SMF, SOPs, Instructions, Master batch records, Validation Documentation, Qualification documentation, PQRs, Self-inspections, Qualification of Suppliers, Change Management, Deviations, CAPA, Change Management in Computerized Systems.

Laboratory related docs, test results, stability, OOS, OOT managed in LIMs. Batch Release in SAP, manual batch certification.

Batch records were paper based. Inside the aseptic core, sterilized pages of the BMR were used.
The Batch Manufacturing Record for Dexamethasone phosphate injections 4mg/ml, 1ml ampoule was observed. The record looked well laid out and well legible entries were made. Specifically, the process of preparing and filtering the dexamethasone solution was checked. The active substance was transferred quantitatively using some of the liquid from the tank. Nitrogen was blanketed over the solution. When the solution was ready a sample for chemical analysis was taken on 19-08-2019 at 10:32 and the result came back at 15:00. Filtration started at 19:23. Therefore, the time between addition of the active substance and the beginning of filtration was 8hrs 51mins, which was well within the validated bulk hold time of 24hrs. Shortly before filtration the bioburden sample was taken. On the results report from the lab there was no reference to the stage of production, the time the sample was taken or the tank from which the sample was taken. The company stated that only one bioburden sample is taken during production.

Filtration lasted from 19:23 until 20:08 and the solution remained in the tank until filling started at 21:50. Filling was finished on 20-08-2019 at 13:43. The filtered solution was therefore kept for 18hrs 20mins, well within the validated hold time for sterile bulk of 24hrs. A list of events referenced in this case only the 4 hourly change out of settle plates. Samples for final product analysis were taken from beginning, middle and end of production. In this batch no un-validated interventions had taken place, hence there was no reference to extra samples taken. All observations were appropriately addressed by the company.

To certify a batch, the QP considered the BMR plus results of testing which could be accessed on a shared drive. In this case the bioburden test result was 0 CFU/100ml. The company did not use sterile dexamethasone. In the process validation report that was made with the WHO product validation batches 10218 (which later became 40218), 20218 and 30218 the bioburden results were 0, 1 and 2 CFU/100ml respectively. The limit was set at ≤10CFU/100ml. The hold time studies for filtered bulk were all done for the full 24hrs.

The BMR for ampoules batch 50120 was seen. During production of this batch the ampoule sterilizing tunnel was stopped when the inspectors noted a deviation in the tunnel on 21-01-2020. The intervention in the process was recorded under Deviations on page 57 of the BMR. Also, the deviation was recorded in the EDMS under DEV003176. Corrective action was taken, and production resumed, but no extra samples were taken from the line because the company saw the intervention outside the aseptic area as not significant. ALL observations were adequately addressed by the company

**16. Good practices in production**

Supervision of the filling operation could not be done by direct observation. Instead a video system was set up to monitor and record activities in the filling area. Logbooks were seen for the video checks that supervisors performed.

A live feed was observed for some time. The images from three cameras were of good quality and covered the entire operation in the Class A/B area. The setup of a filling operation that took place on 17-01-2020 was observed.

In the Class D area filled and closed ampoules were collected from the filling line. Ampoules with closing defects were taken out by the operator. These were recorded in the BMR for reconciliation purposes. Plastic trays were filled with ampoules and identified with a label inside the box. The labels had sequential numbers allowing for the later sampling of ampoules from beginning, middle and end of the filling process. It was not clear if samples would be taken after the stopping of the line, which could be considered a significant intervention. The company claimed that only after un-validated manipulation extra samples would be taken. In that case a deviation would have been written and samples would be recorded on that form. All observations were appropriately addressed by the company.

The visual inspection room 137 was seen. An automatic inspection machine was used. This machine discharged 2 types of rejected ampoules, both of which were subsequently inspected by a human inspector. Defects were classified and recorded in the BMR, other ampoules were added to the batch. In the room the separation of inspected from uninspected ampoules is by procedure only. No physical barriers are used. This was particularly important when both types of ampoules were packed in the same type of carton boxes. There was just one inspection station. Operator visual inspection qualification was observed.

The room on the 1st floor was visited where labelling of primary packaging took place. Batch number and expiry date were printed in-line. The input of variable data into the printing machine was done by a repair mechanic and checked by a supervisor. From the numbers of labels on the batch record it could be seen that leftover amounts were sent back to the warehouse. The risk of mix-ups was controlled by issuing a new SAP number and a separate storage location for returned labels.

## 17. Good practices in quality control

The Quality Control Unit was made up by three major departments: a) Quality Control, b) Laboratory Equipment and c) Specifications and Method Transfer. The analytical chemistry laboratories were located on the 4th floor and the microbiological laboratories were found on the second floor. The laboratories were shared among the different workshops and sites. Microbiological samples were collected separately from analytical samples. Different labels were used depending on the sample (e.g. excipient, API, bulk product, finished product). Sampling labels for finished product were generated by LIMS. The Planning Engineer was responsible for prioritizing testing and a spreadsheet was used to monitor testing activities and deadlines.

The Chromatography laboratory was visited. 37 HPLCs and a Triple Quad LC/MS were installed. LC and GC equipment were linked through software to a server installed in the laboratory. A backup server was also available and was installed in a different Farmak location on the same campus. Specifications for raw materials and finished products were established. Specifications of Dexamethasone injection (РАΦТ) were presented as well as the specifications for the ampoules used for dexamethasone. Physical testing on ampoules was conducted in Warehouse Site 4 where packaging material were stored. The analytical method of Dexamethasone API and finished product were reviewed. Chromatographic columns were not generally dedicated to material/product. A dedicated area for storage was available and a logbook for usage was maintained. Stability rooms were located on the 1st floor of the same building except for the chamber for accelerated studies which was located in the R&D department. A BMS was installed in stability rooms and its qualification was reviewed.

The laboratory for microbiological control was briefly visited. The rooms and equipment looked well maintained. Sterility tests were performed in a Class A cabinet. Most of these tests were done with commercially bought media. These were released based on vendor certificates. In-house prepared media were sterilized and submitted to Growth Promotion Testing. There were no compiled data showing how many batches of in-house media were prepared and what their performance was in GPT. ATCC strains and House Isolates were kept and maintained. A machine was used for identification purposes. Dedicated autoclaves were seen for incoming materials, destruction and media preparation.
Environmental monitoring samples were incubated in dedicated incubators and read in a dedicated cleanroom. Testing of WFI and PW was also done at the lab.
Samples to be tested were delivered by production to a sample receiving room. Analysts had to keep track of the arrival of samples by regularly checking the logbook for sample receipt. Also, in LIMS a request was generated from the SAP system.

Logbooks for incubators were seen. No comments were made.

WFI for use at the lab was generated by Reversed Osmosis. The equipment looked well maintained. Daily samples were taken and tested.

Results were seen for active air sampling for the Class B rooms 234 to 240. All rooms complied with the requirements. Contact plates and swab samples from these rooms were also within spec. Graphs were presented of the 3 months monitoring data for the filling machine. No excursions were seen. All observations were appropriately addressed by the company.

| Part 3 | Conclusion – Inspection outcome |
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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, ***FARMAK JSC*** located at ***74 Kyrylivska St., Kyiv, 04080, Ukraine*** 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.

| Part 4 | List of WHO Guidelines referenced in the inspection report |
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1. WHO good manufacturing practices for pharmaceutical products: main principles. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-eighth Report Geneva, World Health Organization, 2014 (WHO Technical Report Series, No. 986), Annex 2. ***Short name: WHO TRS No. 986, Annex 2***
   http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_986/en/

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