World Health Organization

20, AVENUE APPIA – CH-1211 GENEVA 27 – SWITZERLAND – TEL CENTRAL +41 22 791 2111 – FAX CENTRAL +41 22 791 3111 – WWW.WHO.INT

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

Part 1	**General information**
Manufacturers details	
Company information	
Name of manufacturer	**Egyptian International Pharmaceutical Industries Company (EIPICO)**
Corporate address of manufacturer	10th of Ramadan City, Industrial Area B1, Egypt P.O. Box 149 - 10th
Inspected site	
Address of inspected manufacturing site if different from that given above	10th of Ramadan City, Industrial Area B1, Egypt P.O. Box 149 - 10th
Unit / block / workshop number	Cephalosporin Block (Perry II, IMAI)
Manufacturing license number	24010071701057
Inspection details	
Dates of inspection	06 - 09 May 2019
Type of inspection	Follow up inspection
Introduction	
Brief summary of the manufacturing activities	Manufacturing and quality control of sterile and non-sterile finished pharmaceutical products including Penicillin and cephalosporin products. The latter products were manufactured in dedicated and separated production blocks.
General information about the company and site	EIPICO was established in 1980 and started production in 1985. EIPICO produces over 300 products covering various pharmaceutical dosage forms, including tablets, capsules, injections, eye drops, ointments etc. There are several segregated blocks on the site dedicated to various sensitizing and non-sensitizing products. These include dedicated filling blocks for penicillin finished products, cephalosporin powder for injections and lyophilized products, as well as other blocks for non-sensitizing products. In total, there were approximately 2555 employees working at the site.

History	This site had been inspected by WHO several times in the past. The last inspection was in May 2018. The site has recently been inspected by the Romanian Authorities in 2017 for the same product but with different specifications as per the registered specifications by the NRA.
Brief report of inspection activities undertaken	
Scope and limitations	
Areas inspected	• Quality management system • Cephalosporin Production Block • Validations-media fill • Sterile assurance • QC laboratories • CAPA verification • Changes made since last inspection
Restrictions	The inspection was restricted to the production of sterile powder Cephalosporin manufacturing lines, *IMA I and Perry II*.
Out of scope	All other products and workshops were outside of the inspection scope and were not visited.
WHO product numbers covered by the inspection	HA479 - Epicephin 500mg (Ceftriaxone sodium 500mg powder for solution for injection) HA480 - Epicephin 1g (Ceftriaxone sodium 1gm powder for solution for injection)

Abbreviations

AHU	air handling unit
ALCOA	attributable, legible, contemporaneous, original and accurate
API	active pharmaceutical ingredient
APQR	annual product quality review
BDL	below detection limit
BMR	batch manufacturing record
BPR	batch packaging record
CAPA	corrective actions and preventive actions
CC	change control
CFU	colony-forming unit
CoA	certificate of analysis
CpK	process capability index
DQ	design qualification
EM	environmental monitoring
FAT	factory acceptance test
FBD	fluid bed dryer
FMEA	failure modes and effects analysis
FPP	finished pharmaceutical product
FTA	fault tree analysis

FTIR	Fourier transform infrared spectrometer
GC	gas chromatograph
GMP	good manufacturing practice
HACCP	hazard analysis and critical control points
HPLC	high-performance liquid chromatograph
HVAC	heating, ventilation and air conditioning
IR	infrared spectrophotometer
IQ	installation qualification
KF	Karl Fisher
LAF	laminar air flow
LIMS	laboratory information management system
LoD	limit of detection
LOD	loss on drying
MB	microbiology
MBL	microbiology laboratory
MF	master formulae
MR	management review
NMR	nuclear magnetic resonance spectroscopy
NRA	national regulatory agency
OQ	operational qualification
PHA	process hazard analysis
PM	preventive maintenance
PpK	process performance index
PQ	performance qualification
PQR	product quality review
PQS	pharmaceutical quality system
QA	quality assurance
QC	quality control
QCL	quality control laboratory
QRM	quality risk management
RA	risk assessment
RCA	root cause analysis
SOP	standard operating procedure
TAMC	total aerobic microbial count
TFC	total fungi count
TLC	thin layer chromatography
URS	user requirements specifications
UV	ultraviolet-visible spectrophotometer

Part 2	Brief summary of the findings and comments

Brief summary of the findings and comments

1. PHARMACEUTICAL QUALITY SYSTEM (PQS)

A documented system for quality assurance was established, with procedures covering key quality elements in place. Operations were specified in written form and critical GMP requirements were essentially being met. The procedures reviewed and discussed during the inspection were generally of an acceptable standard, however in some cases improvements are sought.

The Quality Department was divided into QA and QC and are separate from the production department. The quality policy of the company states that the quality management system (QMS) applies to all areas of operation.

Product quality review (PQR):
An SOP for PQR was available and reviewed. Commercial batches of WHO Prequalified product within the scope of the inspection have not yet been manufactured by the site. The company has however manufactured product for other markets and the PQRs for Ceftriaxone Sodium Hemihydrate (Epicephin 0.5 gm IM/IV and Epicephin 1 gm IM/IV) for the period February 2018 to January 2019 were reviewed. Several change control, complaints and returns were reviewed. No recall and OOS was recorded. A change control (CC) for assigning a new code to the API from different source was ongoing at the time of inspection.

Non-compliances observed during the inspection that was listed in the full report regarding PQR were addressed by the manufacturer to a satisfactory level.

Quality risk management:
SOPs for quality risk management were in place and some assessments have been performed. Risk management for powder containment in IMA I was reviewed. In general, whilst the QRM has improved since the previous inspection, the company's implementation of QRM remains at a basic level.

Change control (CC)
A formal system for change control was described in written procedures. A change control log was available for inspection. Changes were classified into major or minor change. Several CCs including CC for microbiological laboratory were reviewed. Non-compliances observed during the inspection that was listed in the full report regarding risk management in CC were addressed by the manufacturer to a satisfactory level.

Deviation management
Deviations were recorded and investigated as per procedure. Deviation logs were maintained. Deviations included planned and unplanned deviations which were reviewed and discussed.

2. GOOD MANUFACTURING PRACTICES (GMPs) FOR PHARMACEUTICAL PRODUCTS

Production of cephalosporin products was performed in a dedicated production block with production equipment dedicated to the filling of several sterile cephalosporin powders into vials. However, the filling lines used for Ceftriaxone are not dedicated to this specific active but are used for the filling of other cephalosporin sterile powders. The CAPAs regarding the deficiencies made during the last inspection was checked and found acceptable.

Manufacturing processes were generally adequately defined in approved documents. Manufacturing steps were recorded in batch manufacturing and packaging records. Product was released by the authorized persons.

3. SANITATION AND HYGIENE

The facilities and procedures for sanitation and hygiene established on the site was found to be adequate with the relevant SOP's meeting GMP requirements. The disinfectants were sterilized before used in Grade A & B areas. Sanitation of clean areas is performed frequently in accordance with the SOP.

4. QUALIFICATION AND VALIDATION

Validations and qualifications were performed according to the site policy and documented procedures. Necessary resources in production were generally provided, including qualified and trained personnel, adequate premises, suitable equipment and services, appropriate materials, containers, approved procedures and instructions, laboratories and equipment for in-process and other controls.

Validation master plan was available for inspection. For equipment and process validation the company had identified what qualification and validation work was required. Revalidation was required to be performed periodically. The key elements of a qualification and validation programme were defined. During the inspection procedures and validations were reviewed for

- Media simulations using Perry II line performed in December 2018
- Smoke test of filling LAF validation for Perry II line, CAPAs to the deficiency of Perry line's air pattern made in last inspection were checked and found acceptable.
- Validation of aseptic filling procedure with media fill for powder filing.

Media fill was performed every six months. The MF protocol and report for Perry II line performed in December 2018 were reviewed and discussed.

Equipment were qualified according to the in-house procedure. Critical equipment was requalified every six months. The recent annual requalification of the autoclave used for parts sterilisation and the tunnel hot air steriliser was reviewed and found to be satisfactory.

Computerized systems were used in QC labs, for material management and BMS etc. Controls over data integrity with the computerized system validation were satisfactory with improvements identified since the previous inspection. Computer control of filter testing in the filter test system was checked. Some weakness was observed during the inspection that was listed in the full report were addressed by the manufacturer to a satisfactory level.

Tunnel qualification

Depyrogenation tunnel IMA line protocol and reports were spot checked. Thermo-mapping and endotoxin bacterial challenge were performed every 6 months. The integrity test of the filters of the tunnel was performed yearly. The approach was essentially unchanged from previous inspection.

HVAC Qualification

The qualification of "Sterile powder area of Perry II HVAC system" protocol for January 2019 was spot checked. Air flow velocity, air change rate tests, integrity testing etc. were considered and met normal expected standards.

Integrity test of the filters of grade A areas were performed at specified time intervals.

Water systems

The water systems were essentially unchanged since the inspection performed 12 months earlier. Water test trends were satisfactory.

5. COMPLAINTS

Complaints were managed according to a written procedure. Two complaints were received for the product in the inspection scope. They were addressed by the PQR review. This section was not inspected in detail.

6. PRODUCT RECALLS

A recall SOP was available and mock recall performed as per protocol. The company stated there had been two product recalls – none being for Ceftriaxone sodium 500mg powder for solution for injection. This section was not inspected in detail.

7. CONTRACT PRODUCTION, ANALYSIS AND OTHER ACTIVITIES

No external contracts available relating to the inspection scope.

8. SELF INSPECTION, QUALITY AUDIT AND SUPPLIERS' AUDITS AND APPROVAL

SOP for supplier qualification was in place. In accordance with the CAPA commitment, the company had recently audited a supplier of sterile API of Ceftriaxone sodium.

9. PERSONNEL

The personnel met during the inspection have awareness of the principles of GMP with appropriate initial and continuing training, including hygiene training, relevant to their responsibilities in the production process.

Steps taken to prevent unauthorized people from entering production and QC areas appeared to be effective. An organization chart was available. There were some changes at senior management which was reflected in the SMF. A new QA manager was appointed. Responsibilities for production and QC/QA were well separated.

10. TRAINING

General GMP training was not reviewed in detail other than the review of the steps and records of monitoring and authorization staff working in the aseptic areas. It was found that these records were complete and up to date.

11. PERSONAL HYGIENE

Hand washing, bathroom, and changing facilities were available in the first change room for each manufacturing area. The level of hygiene observed, and the measures taken to maintain the outer margins of the facility were found to be satisfactory.

12. PREMISES

Documented layouts of the facilities were available. Generally, premises were located, designed, constructed and maintained to suit the operations to be carried out. The layout and design of premises minimize the risk of errors and permit effective cleaning and maintenance in order to avoid cross-contamination. Premises were designed and constructed to facilitate good sanitation.

Production premises were designed to allow production in a unidirectional flow supported by the requisite cleanliness levels. The CAPA to the deficiency regarding the IPC testing was addressed and were found to be satisfactory.

13. EQUIPMENT

The production equipment installed was of good standard and appeared to be well maintained. The facility was well designed, and the equipment appeared to be running well. All production equipment reviewed was identified as to its content or purpose with cleanliness status identified by appropriate labeling.

There were two production lines equipped with Ima and Perry filling machine dedicated to Cephalosporin products in the dedicated production block. The filling line was designed using RABS. The equipment was in operation at the time of inspection.

Computerized systems were used in the warehouse for material management and logistic administration, as well as in the QC laboratory for management of testing results of the material and product testing and data management.

14. MATERIALS

Incoming materials were purchased from approved suppliers, sampled and tested according to specifications and testing procedure. Finished products were kept in quarantine until final release.

Product release
Product release was performed according to an SOP, using a check list. Finished products were held in quarantine until their final release and stored under appropriate and monitored conditions.

15. DOCUMENTATION

In general, documentation was designed, prepared, reviewed and distributed according to a documented procedure. Documents were regularly reviewed and kept up to date.

Approved, signed and dated testing procedures and specifications were available for starting and packaging materials and for finished products.

A Batch numbering system described in a written procedure was in place to ensure each batch number is unique. BMRs were retained for each batch processed. Ceftriaxone Sodium batch BMRs were reviewed and discussed.

16. GOOD PRACTICES IN PRODUCTION

Clean areas for the manufacture of sterile products were classified according to the expected required characteristics of the environment. Clean rooms and clean-air devices were routinely monitored during operation. For Grade A and B zones, particle monitoring was undertaken for the full duration of critical processing. To control the microbiological cleanliness of Grades A–D in operation the clean areas were monitored. Appropriate action limits were set for the results of particulate and microbiological monitoring. The general design of the facilities was adequate and both filling lines Perry II and IMA I line were equipped with RABS.

The machine set up of Perry II line and production area were inspected. CAPAs regarding vial inspection was in place and found to be satisfactory.

17. GOOD PRACTICES IN QUALITY CONTROL

The QC function was independent of other departments. QC laboratories including microbiological laboratory were separated from production areas. The Microbiology Laboratory and microbiology QC test was segregated from the Chemistry Laboratory.

Microbiological laboratories for sterility test and environment monitoring were inspected. The current facility where environmental monitoring as well as pour plate production adjoining the QC lab area was visited. The company is in the process of an upgrade project to relocate some operations to a new laboratory and to refurbish and remodel the area.

Microbiological laboratories for sterility test, environment monitoring and a new microbiological laboratory in Eipico 2, located in a separate building (for OSD production) across the road from the plot inspected were visited. The intention is to replace the current microlab with the new lab.

Stability study

The "walk in" stability chambers were briefly visited. Non-compliances observed during the inspection that was listed in the full report regarding stability study were addressed by the manufacturer to a satisfactory level.

OOS management

Procedure for OOS investigation was available. Statistic for OOS caused by chemical testing and microbiological testing last three years were checked. There were no rejections of sterile powders. No OOS for the product in the inspection scope was recorded.

PART 3

Conclusion

Based on the areas inspected, the people met and the documents reviewed, and considering the findings of the inspection, including the deficiencies listed in the Inspection Report, as well as corrective actions taken and planned: ***Egyptian International Pharmaceutical Company located at 10th of Ramadan City, Industrial Area B1, Egypt*** was considered to be operating at an acceptable level of compliance with WHO good manufacturing practices for pharmaceutical products.

All the non-compliances observed during the inspection that were listed in the full report as well as those reflected in the WHOPIR, were addressed by the manufacturer, to a satisfactory level, prior to the publication of the WHOPIR

This WHOPIR will remain valid for 3 years, provided that the outcome of any inspection conducted during this period is positive.

PART 4

List of GMP guidelines referenced in the inspection

1. WHO good manufacturing practices for pharmaceutical products: main principles. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-eighth Report Geneva, World Health Organization, 2014 (WHO Technical Report Series, No. 986), Annex 2.
   http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_986/en/

2. WHO good manufacturing practices for active pharmaceutical ingredients. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth Report. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957), Annex 2.
   http://www.who.int/medicines/publications/44threport/en/

3. WHO Good Manufacturing Practices: water for pharmaceutical use. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fourth-sixth Report. Geneva, World Health Organization, 2012 (WHO Technical Report Series, No. 970), Annex 2
   http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_970/en/

4. WHO guidelines for sampling of pharmaceutical products and related materials. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-ninth Report. Geneva, World Health Organization, 2005 (WHO Technical Report Series, No. 929), Annex 4
http://whqlibdoc.who.int/trs/WHO_TRS_929_eng.pdf?ua=1

5. WHO guidelines on good manufacturing practices for heating, ventilation and air-conditioning systems for non-sterile pharmaceutical dosage forms. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 5
http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

6. Supplementary guidelines on good manufacturing practices: validation. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fortieth Report. Geneva, World Health Organization, 2006 (WHO Technical Report Series, No. 937), Annex 4
http://whqlibdoc.who.int/trs/WHO_TRS_937_eng.pdf?ua=1

7. WHO Good Practices for Pharmaceutical Quality Control Laboratories. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth Report. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957, Annex 1
http://www.who.int/medicines/publications/44threport/en/

8. WHO Good Practices for Pharmaceutical Products Containing Hazardous Substances. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth Report. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957), Annex 2
http://www.who.int/medicines/publications/44threport/en/

9. WHO good manufacturing practices for sterile pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 6
http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

10. WHO guidelines on transfer of technology in pharmaceutical manufacturing WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 7
http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

11. Model guidance for the storage and transport of time-and temperature-sensitive pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 9
http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

12. General guidelines for the establishment maintenance and distribution of chemical reference substances. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-first Report Geneva, World Health Organization 2007 (WHO Technical Report Series, No.943) Annex 3
http://whqlibdoc.who.int/trs/WHO_TRS_943_eng.pdf?ua=1

13. WHO good practices for pharmaceutical microbiology laboratories. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 2
http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

14. WHO guidelines on quality risk management. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-seventh Report Geneva, World Health Organization, 2013 (WHO Technical Report Series, No. 981), Annex 2
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_981/en/

15. WHO guidelines on variation to a prequalified product. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-seventh Report Geneva, World Health Organization, 2013 (WHO Technical Report Series, No. 981), Annex 3
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_981/en/

16. WHO guidelines for drafting a site master file. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 14
http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

17. WHO Guidelines on good manufacturing practices: validation, Appendix 7: non-sterile process validation. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-ninth Report Geneva, World Health Organization, 2015 (WHO Technical Report Series, No. 992), Annex 3
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf

18. WHO General guidance on hold-time studies WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-ninth Report Geneva, World Health Organization, 2015 (WHO Technical Report Series, No. 992), Annex 4
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf

19. WHO Technical supplements to Model Guidance for storage and transport of time – and temperature – sensitive pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-ninth Report Geneva, World Health Organization, 2015 (WHO Technical Report Series, No. 992), Annex 5
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf

20. WHO Recommendations for quality requirements when plant – derived artemisin is used as a starting material in the prosecution of antimalarial active pharmaceutical ingredients. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-ninth Report Geneva, World Health Organization, 2015 (WHO Technical Report Series, No. 992), Annex 6
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf

21. WHO good manufacturing practices for biological products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fiftieth Report Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 3 http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex03.pdf

22. Guidance on good data and record management practices. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fiftieth Report Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 5 http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex05.pdf

23. WHO general guidance on variations to multisource pharmaceutical products. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fiftieth Report* Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 10 http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex10.pdf

24. WHO good manufacturing practices for biological products. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fiftieth Report* Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 3 http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex03.pdf