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

Part 1	**General information**
Manufacturers details	
Company information	
Name of manufacturer	**European Egyptian Pharmaceutical Industries Company (EEPI)**
Corporate address of manufacturer	Alexandria-Cairo Desert Road Km 25, Amriya, Alexandria, P.O. Box 111, El Manshia Alex. Egypt
Inspected site	
Address of inspected manufacturing site if different from that given above	Same as above
Unit / block / workshop number	Oral solid dosage section
Manufacturing license number, (delete if not applicable)	26001140202074 (Code No. FM-LPM-02) Date of issue of first license: 14/4/2002
Inspection details	
Dates of inspection	8-11 May 2017
Type of inspection	Initial GMP inspection
Introduction	
Brief summary of the manufacturing activities	Medicinal products' dosage forms for human use are manufactured in the facilities including: o Liquid dosage forms (syrups, oral drops, lotions) o Solid dosage Form (tablets, hard gelatin capsules, effervescent granules and powders) o Soft gelatin capsules

General information about the company and site	European Egyptian Pharmaceutical Industries Company (EEPI) is a pharmaceutical company located in Alexandria city, Egypt and is a member of Pharco Corporation Group (PHARCO). EEPI was established in 1998. The plant is designed to manufacture oral solid and liquid dosage forms and soft gelatin capsules.
History	EEPI is ISO 9001:2008, ISO 17025, ISO 14001, OHSAS 18001, 13485:2012 certified. Pharmaceutical plant license and GMP certificate from the MOH of Arab Republic of Egypt was available. Additionally, GMP certificate from Romania National Agency of Medicines and Medical Devices with regard to compliance with the GMP requirements referred to in European directive 2003/94/EC was presented (last inspection on 14/May/2015). This was the second WHO GMP inspection of EEPI. The site was previously inspected in 2012. The product was not accepted for bio-equivalence (BE) study, hence EEPI site was not prequalified.
Brief report of inspection activities undertaken	
Scope and limitations	
Areas inspected	• Quality Assurance • Sanitization and hygiene • Qualification and validation • Complaints • Personnel • Training • Personal hygiene • Premises • Equipment • Materials • Documentation • Production • Quality control
Restrictions	None
Out of scope	Oral liquids, hard and soft gelatin capsules were excluded from the inspection.
WHO product numbers covered by the inspection	HP003

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 (where applicable)

Brief summary of the findings and comments

1. Pharmaceutical quality system

Production and control operations were specified in written form and GMP requirements were generally followed. Managerial responsibilities were specified in job descriptions. Product and processes were monitored and the results taken into account at batch release; regular reviews of the quality of pharmaceutical products were conducted.

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

2. Good manufacturing practices for pharmaceutical products

Manufacturing processes were defined and reviewed. Qualifications and validations were seen to be performed according to prepared protocols. Significant deviations from the initial protocol were recorded and investigated, root causes were determined and CAPAs were implemented where necessary. Systems were in place for handling complaints and recalling any batch of product from sale or supply.

The production capabilities were divided into three areas, namely, oral solid dosage forms (OSD), soft gelatin capsules and liquid dosage forms, all located in one building. The production was performed in a multi-product facility. Production equipment was not dedicated. Validations, qualifications were performed according to the site policy and documented procedures.

Adequate premises and equipment were available for production, in-process quality control and storage.

Manufacturing processes and quality control test requirements were generally well defined in approved documents.

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

3. Sanitation and hygiene

The facilities and procedures for sanitation and hygiene established on the site were found to be adequate to ensure that premises and equipment were properly cleaned.

The gowning and changing procedures for entry into the manufacturing facilities were adequate – and procedures were displayed where necessary.

Generally the facilities were noted to be clean and well organized during the inspection.

4. Qualification and validation

The company identified what qualification and validation work was required. The key elements of a qualification and validation programme were defined in general terms. The validation Master Plan (VMP) contained the general policy of the site on the qualification and validation. The VMP described qualification, revalidation, acceptance criteria, analytical method, cleaning validation and process validation.

The issues related to this section have been adequately addressed by the laboratory, and the same shall be verified during future inspections.

5. Complaints

The SOP described the procedure of market complaint handling. Complaints are to be indicated in a register together with a unique compliant number. The deadline for investigation depends on the classification of the complaints.

Complaints log book for 2016 was presented to the inspectors.

A number of complaints were discussed.

6. Product recalls

Procedure for recalls was in place. Procedure included classification of recalls according to Class I to III. Mock-up recalls were planned to do every two years and its effectiveness should be expected 100 %.

7. Contract production, analysis and other activities

Manufacturing operations were not contracted out.

Manufacturing services agreement between CAD Middle East and its parent company was in place.

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

Internal audit procedure and internal audit annual plans were available. According to the explanation, all audits were done as per scheduled. Some reports were checked randomly. Non-conformities were handled by the CAPA system. GMP audit checklist was available but very general and not specific for EEPI. List of auditors was maintained by QA. Auditor qualification programme was in place.

The supplier qualification SOP was in place. The procedure described that suppliers will be approved based on the questionnaires, physical audit and acceptable quality control tests. Re-audit for certified suppliers was done every three (3) years. Initial approval of a supplier was not done before the usage of the material Sofosbuvir from CAD Middle East. On the list of approved suppliers there were only four suppliers listed after successful audit.

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

9. Personnel

An organization chart was available. Quality control, quality assurance and production department were independent. The manufacturer had an adequate number of personnel with the necessary qualifications and practical experience in general, however some observations were made. The SOP on company organization chart was discussed. It was noted that QC is a separate department which reports directly to the managing director. Similarly, R&D director who is responsible for the stability studies and analytical method development and validation reports directly to the managing director.

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

10. Training

Training procedure was discussed. It was the responsibility of QA where training needs were first identified. Monthly and annual training plan was finalized to be organized internally or externally. There was system in place to assess trainer and training program.

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections

11. Personal hygiene

The level of hygiene observed and the measures taken to maintain the facility were considered to be of a good standard in the oral solid dosage (OSD) section. The approach to sanitation and hygiene was acceptable in general. Photos describing the gowning procedures were appended to the changing procedures and provided on the walls of changing rooms in the OSD section.

12. Premises

The premises for manufacturing, storage and quality control of products were generally of a satisfactory standard. The production facility of OSD was with soft gelatin and oral liquid section situated in one building.

The inspected production OSD section is a multipurpose area. The equipment and the facilities inspected were generally in good condition. Layouts of the facilities were available and up-to-date.

The plant was designed to manufacture oral solid and liquid dosage forms and soft gelatin capsules in classified clean room environmentally monitored and controlled through highly qualified HVAC system. Production areas were classified into two main hygienic zones (100 000 and 10 000 particles 0.5 µm per m3). All employees change over twice, one time when entering from black zone to 100 000 zone and another when entering from 100 000 to 10 000 zone.

Premises were designed to have a logical flow of materials and personnel. The production areas had adequate space for the placement of equipment and materials to prevent mix-ups and contamination.

Warehouses were situated in a separate building and materials and products were controlled by a computerized system.

QC laboratories including the microbiology laboratory were separated from production areas. Sufficient space was given to avoid mix ups and cross-contamination. Adequate storage space was provided for samples, reference standards, solvents, reagents and records.

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

13. Equipment

Process equipment was installed and maintained in a way to minimize the risk of contamination and cross contamination. Production equipment was identified as to its content or purpose and cleanliness status.

The majority of the equipment was of European origin. The maintenance and cleaning status appeared in a good condition.

Intermediate bulk container (IBC) blending was done with bin blender. CIP system was used for the cleaning of the containers.

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

14. Materials

A brief inspection of the (Oracle based electronically controlled) material warehouse was undertaken. Materials and finished products were stored. The storage conditions (temperature and humidity) of the inspected products were controlled at a level below 30 °C. Oracle was used for material management which printed list of material codes for all materials used by the site.

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

15. Documentation

A paper system was in place for documentation management. Documents were designed, prepared, reviewed and distributed according to SOPs. Documents were approved, signed and dated by the appropriate responsible persons.

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

16. Good practices in production

The inspected finished dosage form facilities were multi-product facilities. There were 2 tableting lines. One of the tableting machines was in operation for a different product during the inspection.

The temperature, relative humidity and air pressure differentials were monitored according to written procedures.

The site inspection of the production areas covered following areas used for production of oral solid dosage forms:

- Granulation
- Blending
- Compression
- Coating
- Packing lines

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

17. Good practices in quality control

The QC function was independent from other departments. Adequate resources were available to ensure that all QC arrangements were carried out in a timely and orderly fashion. QC personnel had access to production areas for sampling and investigations as appropriate.

The QC laboratories were responsible for physical, chemical and microbiological testing of starting materials, packaging materials, API and FPP finished products, environmental monitoring samples, and purified water samples.

Reference and working standards were available, stored in a refrigerator, usage was recorded. Working standards (WS) were qualified against pharmacopoeia reference standards.

The SOP "Investigation procedure for OOS and OOT" was applicable for all investigation of OOS/OOT results of raw materials and excipients, packaging materials, APIs, intermediates, validation samples, water for pharmaceutical uses, gases and environmental monitoring, finished products and stability studies. SOP and its flow chart were discussed.

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

PART 3
Conclusion

Based on the areas inspected, the people met and the documents reviewed, and considering the findings of the inspection, including the observations listed in the Inspection Report, *European Egyptian Pharmaceutical Industries Company (EEPI), located at Alexandria-Cairo Desert Road Km 25, Amriya, Alexandria, P.O. Box 111, El Manshia Alexandria, 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-eight 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-six 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. Fifties 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. Fifties 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. Fifties 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. Fifties 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