

**WHO PUBLIC INSPECTION REPORT
(WHOPIR)
Finished Product Manufacturer**

Part 1: General information

Name of Manufacturer	European Egyptian Pharmaceutical Industries Co. (EETI)
Unit number	N/A
Production Block	N/A (single unit)
Physical address	Cairo Desert Road KM. 25 – PO Box 111 Amriya, Alexandria
Contact person and email address.	Dr. Mohamed Ebeid, Export Regulatory Affairs, Deputy Manager: mebeid@europeanpharm.com.eg Dr. Ayten Saleh, General Manager, Quality Assurance: aytensaleh@europeanpharm.com.eg
Date of inspection	19 – 22 November 2012
Type of inspection	Routine
Dosage forms(s) included in the inspection	Ibuprofen 400 mg soft gelatin capsules
WHO product categories covered by the inspection	HA
Summary of the activities performed by the manufacturer	Production, quality control, packaging, stability testing

Part 2: Summary

General information about the company and site

EEPI was established in 1998 and was licenced in 2002. It operates under the umbrella of the PHARCO Group which includes 6 manufacturers and holds about 30% of the Egyptian market. Scherer USA has sold their share to FARCO for the soft-gelatin ibuprofen capsules under inspection.

EEPI included 1 manufacturing block with solid and liquid oral dosage form manufacturing capabilities (sachets, tablets and capsules).

Total site area was of 33,336 m² which included 4,503 m² for production, 2,753 m² for warehousing and 1480 m² for administration. The site was engaged in the manufacturing of solid dosage forms which included effervescent granules, tablets, soft and hard capsules as well as liquid dosage forms. The site did not engage in the manufacture of high-potency or potentially hazardous substances such as hormones, penicillins, other beta-lactams or cephalosporins.

History of WHO and/or regulatory agency inspections

This was the first WHO inspection of this site.

It was certified ISO 9001:2008 by Bureau Veritas as a manufacturer of medical products for human use as of 27 August 2012 and by the Ministry of Health National Agency for Medicines and Medical Devices of Romania (GMP compliance certificate No. 037/2010/RO, dated 12/08/2010). It was also ISO/IEC 17025:2005 certified by the Arab Republic of Egypt Egyptian Accreditation Council (EGAC) from June 1, 2011 (Issue 3) and valid to 31 May 2015. This certification was valid for the testing of "some raw materials and pharmaceutical products". The company was accredited for ISO 14001 on May, 2012 and for OHSAS 1800 (renewed on November, 2011).

Focus of the inspection

The inspection focused on the production and control of ibuprofen 400 mg soft gelatin capsules (commercial name: Profusol 400 mg SGC). 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

Day 1

The meeting began with introductions from both sides. The company presentation outlined the development of the business since its inception and its current production programme. All presentation material was based on the details found in the site master file.

The WHO outlined the objectives of the inspection with respect to the requirements for prequalification.

After the company presentation and introductions, inspectors reviewed the following:

- Organization charts, and job descriptions.
- Training records of key members of staff.
- Site validation plan.
- Pre-programmed maintenance and documentation management.
- Change controls and register for 2011.
- Complaints and register for 2012.
- Product quality review for 2011.
- Deviations.
- Warehouse (packaging and starting materials) and sampling area.
- Near Infrared spectrophotometer.

Day 2

The day commenced with the presentation of the observations and non-compliances noted in day 1.

The inspection continued with further inspection of the materials management system. The water purification plant was then inspected followed by that of the air handling units pertinent to the environmental control of the soft gelatine capsule (SGC) manufacturing area.

The afternoon was occupied with inspection of component testing and quality control (chemistry).

The day ended with a summary of the activities inspected.

Day 3

The day commenced with the presentation of the observations and non-compliances noted in day 2.

Inspection of the quality control laboratory continued followed by that of the microbiological laboratory and the monitoring of water quality and the environment. The afternoon was occupied by inspection of the dispensary and manufacture and filling of soft gelatin capsules (SGC).

The day ended with a summary of the activities inspected.

Day 4

The day commenced with the presentation of the observations and non-compliances noted in day 3.

Inspectors then proceeded to Production. The inspection of the manufacture of SGC continued with assessment of the capsule drying process, in-process quality control and final visual inspection and sorting. Inspection of the primary and secondary packaging process ended the morning session.

The afternoon was occupied by continued inspection of the Quality System. This included a review of the following documents:

- Testing records for nitrogen.
- Process validation report.
- Procedure for recalls and out of specifications as well as the applicable registers.
- Records for pest control and temperature mapping of the warehouse.
- Quality risk management.
- Cleaning validation.

The day finished with the final close-out discussions which were preceded by a summary of the activities inspected and non-compliances noted.

2.1 QUALITY ASSURANCE

The Quality System was reviewed at various intervals during the four days.

Organisation and management

The current organisation from senior management level to bench /workshop levels showed that production, quality assurance, research and development, stability studies and technical services were independent of each other and reported to the CEO.

Job descriptions and qualifications of key personnel were in accordance with GMP guidelines.

Product quality reviews

The product quality reviews (PQR) standard operating procedure (SOP), effective date 24 November 2012, was reviewed along with the PQR for 2011 for the product under the scope of this inspection. The PQR listed the necessary elements such as process deviations, number of batches manufactured, recalls, returned goods, OOS, stability results, change controls, customer complaints, equipment use and storage conditions. Some important details were nevertheless missing but this was resolved in the company corrective and preventive actions (CAPAs).

Change controls

The SOP dated September 26, 2012, effective 26 October, 2012 was reviewed. Changes to SOPs and other documents other than packaging were not covered by the scope of this SOP but by the document control SOPs.

The example of a change control, approved by the QA manager and implemented, was reviewed in detail.

Deviation

The SOP entitled “Deviations Handling”, effective date 19 October, 2012, was reviewed. It covered all deviation cases related to production and QC.

Out-of-specifications

With regards to out-of-specifications: The SOP on investigation of out of specification (OOS)/ out of expectation (OOE) test results, effective 23 June 2010, was reviewed. It was found to be acceptable overall with a specified number of retests in the case of an OOS where no assignable cause can be found. The company was requested to add provisions as to which results will be reported in the procedure. CAPA reports were issued. The example of Ketoprofen OOS was chosen and showed the CAPA to be adequately done.

2.2 GOOD MANUFACTURING PRACTICES (GMPs) FOR PHARMACEUTICAL PRODUCTS

Good manufacturing practices generally were implemented. The necessary resources were provided. Manufacturing processes were defined and reviewed. Qualification and validation were performed. Operators were trained to carry out procedures correctly, and records were made during manufacture.

2.3 SANITATION AND HYGIENE

In general, good sanitation and hygiene practices were implemented at the site. Adequate gowning and garments were used. Production and other controlled areas were clean.

2.4 QUALIFICATION AND VALIDATION

Validation master plan

The validation master plan was managed using UVM-75-0005. Equipment was revalidated according to importance. Three broad classifications were listed namely, production-related equipment (machinery and cleaning), service and support equipment, analytical equipment and assay procedures. Any major changes made to equipment required a revalidation exercise.

Equipment qualification

Qualification of encapsulating machine No.1 was reviewed.

The installation qualification protocol specifications were met and signed off as complete.

The operational qualification protocol was reviewed and considered to be satisfactory overall.

Cleaning Validation

The overall cleaning policy was reviewed. It covered and evaluated the solubility of all raw materials used in production in various solvents.

Materials were grouped into categories ranging from “soluble” to “difficult to dissolve”.

Cleaning was evaluated against its ability to remove the most obstinate material within its class (worst-case scenario).

The cleaning validation of the capsule filling machinery and the CIP of the preparation tanks was assessed. Each piece of equipment has a schematic instructing where to sample, either with a swab or rinse sample. Analytical methods have been validated for accuracy, specificity limit of detection and other parameters. No matters of concern were noted.

Process validation

The process validation report was consulted and covered 3 consecutive batches. The validation report was signed off on March 18, 2011. The conclusion stated that 'no deviation had been found' although the product quality review listed the finding of out of specification results for seal for some batches. However, as this was a seal thickness issue found only for a small proportion of capsules tested, this was not considered to be sufficient to render the validation invalid.

The validation protocol dated 15 December 2010 was supported by a quality risk assessment which each different step and sorting the necessary elements for the most-part with a description of the actions to be taken, the effect, cause, function, possible failure mode, step of the process, etc.

Validation of analytical methods

The validation of the procedure for ibuprofen and 4-isobutyl acetophenone was reviewed for the old method which was used in 2007 for stability testing. It included, for both analytes, specificity using placebo, linearity, accuracy, repeatability, ruggedness, intermediate precision. Issues were raised with regards to the limit of detection and limit of quantitation which are to be resolved subsequently in conjunction with the assessment team.

The validation of the new method, dated 27 July 2012, used placebo included all of the necessary parameters (specificity, ruggedness, intermediate precision, linearity, accuracy, etc.). Average and overall percentage relative standard deviation was calculated but there was no statistical comparison of data.

2.5 COMPLAINTS

The SOP entitled "Customer Complaints", No. URP-85-2000, effective date 26 October 2012 was reviewed. It covered all complaints relating to potentially defective products in internal and external markets. Issues raised by inspectors were resolved in the company CAPAs.

2.6 PRODUCT RECALLS

The procedure and system for recalls were acceptable further to CAPAs.

2.7 CONTRACT PRODUCTION AND ANALYSIS

Production and analysis were performed in house hence this area was not inspected.

2.8 SELF INSPECTION AND QUALITY AUDIT

No issues of significance were noted.

2.9 PERSONNEL

Personnel in general, had appropriate qualification and experience.

2.10 TRAINING

The SOP on training was reviewed (dated 1 April 2012). Aspects covered included but were not limited to objectives, scope, responsibilities, training needs, strengths and weaknesses, tick box Q&A tests, outside training and retraining. It had provisions for different types of trainings. It was inferred that training on new or revised SOPs was covered but this point lacked clarity.

Training records were reviewed different members of staff. Training was comprehensive and certified either by in-house trainers or outside course organisers. Competence was further evidenced during discussions with personnel at all levels during the inspection.

2.11 PERSONAL HYGIENE

Personal hygiene was found to be satisfactory overall through the appropriate hand sanitization stations, change rooms and toilet facilities for staff and visitors. No issues of concern were noted.

2.12 PREMISES

Air-handling and environmental monitoring

Air pressure differentials and magnehelics

Strategically sited pressure differential gauges continuously monitored the differentials. The air cascade was sufficiently strong enough to be clearly discernable when moving from outer to inner areas.

Issues raised with regards to the absence of Magnehelic[®] gauges in some areas were satisfactorily resolved in the company CAPAs.

Air handling units (AHUs) and Filters

The production areas were operating under class C (10,000) conditions.

The entire manufacturing area was supplied with filtered air from several AHU's, each department having its own dedicated unit.

The system was controlled by a BMS with a single monitoring screen located in the engineering office, a considerable distance from the production area

Pressure drops across filters and airflow rates were measured by gauges mounted on the AHU's as well as the BMS.

Room qualification was carried out annually. The HEPA filters were checked for secure mounting and leakage using an aerosol particulate generator (not DOP) and photometer detector. Recent records showed satisfactory results, typically 99.995 arrestance.

The AHU supplying the air to the Gelatin Solution Preparation Room was inspected as well as the AHUs to the Medicinal Formulation Preparation Area and the Capsule Filling Area. Air temperature and relative humidity for all rooms were recorded as 20°C and 20% respectively.

No matters of concern were noted.

Particulate Measurements

Particulate measurements were performed annually and their levels were within the class C maximum.

No matters of concern were noted.

Microbiological Monitoring

Both active air sampling (one cubic metre) and settle plate measurements were made in accordance with their procedures.

Trend charts for the past year were reviewed for consistency.

Summary

The SGC area is fitted with AHU units supplying appropriately filtered air at a pressure differential of 30 Pa with room air changes of the order of 20/hr.

Particulate monitoring trends satisfy class C (10,000) clean room requirements as do microbiological active air and settle plate levels.

People Flow

Staff entered the building through side doors into a toilet and washing/shower area.

They then proceed to a locker room where street clothes were removed and factory shoes put on. They then moved into the gowning area where factory whites were donned together with bonnets and snoods. Visitors entered via a separate route where gowns, bootees and bonnets were donned by a step-over barrier. Jewellery was removed for safe storage. Hands were disinfected using an in house preparation of 70% ethanol solution.

Entry to the service corridor was through an airlock with interlocking doors. During the four days of the inspection there were no failures of the interlocking system.

Entry to work areas was via a second change room and air lock where over-gowns facemasks were donned.

Warehouse

The entrance to the warehouse was via a door with a password protected lock.

The building had three main areas, the unloading dock and preliminary inspection area, the quarantine area where goods were temporarily stored before removal to the proper warehouse. Goods were stored on wooden pallets but were transferred to metal prior to moving to dispensing and production areas.

The material store consisted of 6 to 7 high storage racks sited across 4 bays. Although random storage was possible, components and raw materials were stored in separated locations. Printed packing materials were kept in a dedicated locked area.

Location coordinates followed the conventional pattern (eg. Bay No, Rack No, Location No.)

Rejected goods were kept in a locked area. They were subjected to a monthly review by a committee drawn from QA/QC/Warehousing/Finance. QA was empowered to make the final decision to reject.

There was a cold room which was not inspected but temperature validation data was presented which showed that the temperature was maintained at a constant 15°C throughout.

All three areas were in an excellent state of cleanliness and maintenance, the area being reportedly regularly cleaned at levels above manageable head height.

Pest control was managed in house in accordance with its procedure. Bait stations and insecticutors were in place throughout as given on the site plan. Regular inspections reported no activity.

The temperature profile has been validated and records showed that 23°C was maintained throughout the area at all locations.

Data was collected during the Egyptian summer (July) and it can be inferred that the cooler months will produce lower temperatures.

No matters of concern were noted regarding the warehouse construction, layout and routine maintenance.

Material Flow

Raw materials requisitioned for production were transferred to metal pallets and thence to the service corridor. Removal to work stations was via air locks operating at a positive pressure differential.

Quality Control Areas

The laboratory has several rooms, to accommodate wet chemistry and instrumentation. The construction and finish was adequate, as was the furniture.

It was noted that the switch operating the extractor fan of the fume cupboard was hanging by its wiring.

2.13 EQUIPMENT

Pre-programmed Maintenance

Maintenance was carried out according to the annual maintenance schedule. All equipment was listed together with the due date.

The key pieces of equipment listed below were serviced according to schedule and the job sheets tallied with the service protocols. Retrospective reports showed that servicing was carried out in a timely manner. Reports were reviewed for the following equipment:

- Encapsulating machine No.1
- Gelatine mixing tank
- AHU's PRD 21,22 and 23 servicing the SGC production area.

No matters of concern were noted.

2.14 MATERIALS

Incoming materials

Blue sheets were used to notify QC of the arrival of goods to be sampled. Issues raised with regards to the approved supplier list were resolved in the company CAPAs.

Materials management followed its SOP. Goods were ordered from authorised suppliers by the purchasing department. Deliveries were checked against the PO and delivery (GI) note and unloaded under a canopy onto the receiving bay. There were interlocking shutter doors between the warehouse and the curtilage area. Their proper working was challenged and found satisfactory.

If all documentation (eg, CA/TSE certification) was in order, the goods were moved to the quarantine area. Copies of GI notes were sent to the QC laboratory who issued a sequential control number and a computer generated yellow "Quarantine" status label.

The label was bar-coded with the component number and control number. QC also maintained a ledger of received goods which detailed product description, manufacturer's lot no., quantity and number of containers.

The data was entered into the electronic database and a retest date (one year) was generated automatically.

Following satisfactory testing, release to free stock was achieved by attaching a green bar coded label, signed by authorised QC personnel.

The location coordinates were maintained on the database and could be read from on board screen displays on the fork lift trucks. Satisfactory retrieval of goods was amply demonstrated when selecting materials for evidence of QC testing.

Examples of released materials were taken to follow-up QC testing and approval. No matters of concern were noted in the management of raw materials.

Sampling

The material sampling room was accessed from the warehouse with separate air lock entries for materials and sampling personnel. Samplers donned gowns, bootees, hats and beard snoods. Hands were sanitised with an in-house 70% ethanol solution. The solution was labelled with a control number and expiry date.

The room operated at a positive pressure and was equipped with a dedicated air handling unit with terminally mounted ceiling HEPA filters. Air was swept downward and exited through ducts fitted at floor level.

The sampling area within the room was indicated by a red demarcation line on the floor and segregated by a plastic curtain. Magnehelic[®] gauges showing pressure differentials were not annotated with minimum and maximum pressure limits.

Room cleaning was managed by following the relevant SOP.

Balances used to dispense material were within calibration date and were regularly checked for performance throughout their specified ranges.

Apart from the lack of annotation of the magnehelic gauges and missing HEPA mounting screw no matters of concern regarding management of the area were noted.

Sampling was performed in accordance with its procedure. The company used a near infra-red spectrometer (NIR) for sample identification as per the SOP describing its operation and use. There were enough measurements on all raw materials to provide sufficiently accurate reference parameters to give a high degree of probability of a fit when identifying an unknown. Issues raised during the inspection were resolved in the company CAPAs.

Rejected materials

Rejected goods were kept in a locked area. They were subjected to a monthly review by a committee drawn from QA/QC/Warehousing/Finance. QA was empowered to make the final decision to reject as per the relevant SOP.

Rejected medicinal products and raw materials are destroyed under strict control with official destruction certificate.

Visual witness of any destruction is also mandatory.

No matters of concern were noted.

Authorised Supplier Audits

Records for all API's were available either through actual site audits or a comprehensive questionnaire. The company requirement is for 10 successive batches

to be approved before authorisation. The company had yet to implement a system for excipients.

Nitrogen gas, which was used as a blanketting gas in production, was provided by an external supplier and was tested for particulate count, assay, impurities (Oil and H₂O). It was tested every 2 months for chemical parameters and tested every month for microbiology.

2.15 DOCUMENTATION

The predominant script was Arabic, work was in hand to produce English versions.

However there were sufficient documents in English to mitigate time consuming translations.

An SOP controlled the writing, circulation and review of all SOP's. All copies recorded signatures of the writer, the checker and the authoriser.

Specimen signatures were held by Human Resources (HR). Each department was responsible for reviewing its SOP's. If no changes were made within the review period, the front sheet was updated. Any change caused a complete re-issue. No changes after 3 years caused a complete re-issue as well.

Reviewing SOP's specifications and maintenance documentation during the inspection gave further evidence of a system fit for purpose.

2.16 GOOD PRACTICES IN PRODUCTION

Dispensary

The dispensary was equipped with two dispensing booths of conventional design and operation. Pressure differentials of the HEPAs and airflows were clearly displayed and the BMR included a check for correct operation before dispensing commenced.

Balances used were correctly calibrated. Daily calibration records were satisfactory.

Daily cleaning records were available. The area was re-cleaned if left idle for more than 7 days. Clean dispensing utensils were bagged and labelled with an expiry date of 7 days.

As part of the dispensing procedure, the bar-coded approved label was used to identify the raw material. Raw materials dispensing record labels were placed within the sealed polythene bags into which the material was weighed. Materials were then transported to the manufacturing area along a class D corridor.

Processing areas

Ibuprofen solution preparation room, gelatin solution preparation, soft gelatin capsule manufacturing and packaging areas were inspected in detail.

In summary the whole process complied with the process control parameters given in the SMF. No matters of concern regarding the process were noted and all issues raised were addressed in the company CAPAs.

A pressure differential of 30Pa was maintained between the manufacturing areas, gowning rooms, adjacent ancillary areas and access corridors all of which in turn operated at 5Pa differential to the outside.

Utilities

Water used in production

The water plant room was located in the technical block and was found to be in an excellent state of repair and maintenance. The installation pipework was of adequate construction. And allowed by an adequate output with virtually no dead legs at the supply points.

Town water was automatically chlorinated by a dosing tank reliant on chlorine sensor readings. Phosphates were added at the defloculation stage followed by filtration through sand and carbon beds which were backwashed every 6 hours and finally through a 5µm particulate filter. Two stage RO preceded a final CDI treatment before final storage. The RO units were regularly chemically cleaned using solutions of HCl and NaOH. The CDI was used after the RO. Conductivity was measured before and after the RO as well as before and after the CDI. TOC was done in the laboratory but was connected to the loop on a continuous basis. UV irradiation treatment was carried out after carbon filtration and the CDI units. UV lamps were changed annually.

The schematic diagram in the SMF provided a sufficiently detailed description of the purification process.

Detailed records of daily servicing and monitoring were available on request. No matters of concern were noted.

The microbiology laboratory monitored water quality and water was sampled as per the appropriate procedure.

No matters of concern were noted.

2.17 GOOD PRACTICES IN QUALITY CONTROL

The Wet Chemistry laboratory, instrumentation, high performance liquid chromatography (HPLC) and stability chambers were inspected.

Issues were raised with regards to the protection of HPLC data as Admin and analyst passwords and user access rights were the same. Runs were not documented prior to and after injection. Data was backed up only once a year.

There was no protection of the data as windows was not locked and runs could be readily deleted without being captured by an audit trail. Date and time could be changed readily. There was no audit trail. These issues were resolved in the company CAPAs.

Microbiology

The laboratory had three main areas. Media preparation, media sterilisation and plating. The plating area was accessed via an airlock and over gowning was a requirement.

The laboratory refrigerator was validated for even temperature distribution.

The three main services provided were purified water testing, environmental monitoring and validation of the efficacy of the disinfectants used throughout the factory.

Preparation of media from the comprehensive stock of solid media followed the appropriate SOP. The preparation records and results of positive and negative controls were available. A full range of stock reference culture media was available. A maximum of 5 regenerations was permitted.

Data for purified water quality and environmental monitoring is to be found in the relevant sections of this report.

The validation of disinfectants was briefly reviewed. The minimum concentration required to reduce bio-burdens to zero together with the exposure times to achieve this were well documented.

Components

The testing of foil, cartons, PVC, PVDC was examined. Hard foil was used for the Profusol product. Sampling and testing followed the appropriate SOP. It was based on British Standard 6001, inspection by attributes.

General level 1 reduced inspection was applied and there was a provision for switching if the need arises. Critical, Major and Minor AQL's are defined in the relevant SOP.

All examples reviewed met the required AQL and no matters of concern were noted.

Screw micrometers and thickness gauges were calibrated and were within their recalibration dates.

General documentation

A raw materials received ledger was kept and recorded all batch details.

Details were entered into the database which was password protected. The sequential control number and the number of containers received were entered. Samples were allotted to analysts trained and authorised in the discipline required.

Materials were tested against compendial specifications. It was noted that Gelatin was certified as conforming with BSE/TSE requirements. Test records seen were satisfactory.

Compliant raw materials were released to free stock by authorised QC personnel.

No matters of concern were noted.

Standard Reference Sample Management

All reference samples were listed and maintained as dictated by the USP reference sample requirements. The samples held in the laboratory corresponded with the USP lot Number which was current at the time of the inspection. Records of issue for use were maintained by a designated analyst.

Preparation and usage of secondary reference standards followed the relevant SOP.

No matters of concern were noted.

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, as well as the corrective actions taken and planned, *European Egyptian Pharmaceutical Industries Co. (EEPI) Cairo Desert Road KM. 25 – PO Box 111, Amriya, Alexandria* 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.