WHO PUBLIC INSPECTION REPORT Finished Product Manufacturer

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(WHOPIR)

Finished Product Manufacturer

Part 1: General information

Name of Manufacturer	**Alkem Laboratories Limited**
Unit number	NA
Production Block	G- Block
Physical address	167/2, Mahatma Gandhi Udyog Nagar, Dabhel, Amaliya, Daman – 396 210 (U.T.)
Contact address	Mr Dilip Jain, Site Head (Vice President: Operations) *dilip.jain@alkem.com* Mr Mukesh Dalal, Site QA Head (QA Manager) *mukesh.dalal@alkem.com*
Date of inspection	17 to 20 August 2015
Type of inspection	Routine GMP inspection
Dosage forms(s) included in the inspection	Tablets
WHO product categories covered by the inspection	Zinc Sulfate 20mg tablet (DI004)
Summary of the activities performed by the manufacturer	Production and control of finished pharmaceutical products (FPP)

Part 2: Summary

General information about the company and site

Alkem Laboratories Limited, Daman (hereafter Alkem Daman) was inspected by WHO Prequalification Team (WHO-PQ) on the above mentioned dates. Alkem was established in 1973 and it is one of India's leading companies engaged in the development, manufacture and marketing of pharmaceuticals. Alkem has 16 manufacturing facilities (formulations 13 and API 3).

Alkem Daman site was commissioned in year 2001 and caters to international and domestic markets. Daman- Amaliya has two sites comprising of three Production Blocks:

Site – 1

- G-Block: General Drug Product: Tablets, Capsules & Oral Liquid.
- C-Block: Dedicated to Cephalosporin product: Tablets, Capsules, Dry powder for suspension.
- The "G" & "C" blocks are approved by WHO, Geneva/ US-FDA/UK-MHRA and are approved by many others regulatory agencies.

Site – 2

B-Block: Dedicated to Beta lactam product: Tablets, capsules, Dry powder for Suspension, Dry powder for Injection and is approved by TGA, Australia, MOH, Ukraine and other many regulatory agencies.

History of WHO and/or regulatory agency inspections

The site was last inspected in November 2012, and was found to be compliant.

Focus of the inspection

The inspection focused on the production and control of Zinc Sulfate 20mg tablets. The inspection covered most of the sections of the WHO GMP text, including premises, equipment, documentation, materials, validation, sanitation and hygiene, production, quality control and utilities.

Inspected Areas

- Quality Assurance
- Qualification and validation
- Complaints
- Recalls
- Supplier qualification
- Premises
- Equipment
- Materials
- Documentation
- Production
- Quality control

2.1 QUALITY ASSURANCE

In general PQS was implemented. 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 in batch release and regular reviews of the quality of pharmaceutical products were conducted. Periodic management reviews were performed.

Quality risk management procedure was available which provided two approaches adopted by the site as proactive and reactive.

Product quality review was available which provided clear purpose for reviewing PQR, responsibilities and procedure.

Change Management System procedure essentially covers changes pertaining to new production introduction, new material introduction and changes triggered due to complaint, recall, complaints, QRM, training, OOS, deviation and management review.

Handling of Deviations procedure described identification, investigation, approval and trending of deviations. The deviations were classified into minor, major and critical deviations and were supported with examples. The procedure included root cause analysis, impact assessment and a process flow chart.

Corrective action and preventive action system was in place.

The observations raised from this section were addressed satisfactorily, and will be verified during future inspections.

2.2 GOOD MANUFACTURING PRACTICES (GMPs) FOR PHARMACEUTICAL PRODUCTS

In general good manufacturing practices were implemented. The necessary resources generally were provided. Manufacturing processes were clearly defined and systematically reviewed. Qualification and validation were performed. Instructions and procedures were written in clear and unambiguous language. Records were made during manufacture and significant deviations were recorded and investigated. Records covering manufacture and distribution were retained and system was available to recall any batch of product from sale or supply.

The observations raised from this section were addressed satisfactorily, and will be verified during future inspections.

2.3 SANITATION AND HYGIENE

Premises and equipment were maintained at acceptable level of cleanliness. The scope of sanitation and hygiene covered personnel, premises, equipment and apparatus, production materials and containers, products for cleaning and disinfection.

2.4 QUALIFICATION AND VALIDATION

The key elements of a qualification and validation program were defined and documented in the Validation Master Plan. The SOP for Process validation provided procedure for performing process validation including responsibilities, preparation & execution of protocol and report. The procedure also stated that revalidation will be carried if changes pertaining to API, manufacturing formula, change in raw materials etc were made. The cleaning procedure for the general plant uses water whereas no solvent and or detergent was applied. Dirty and clean equipment hold time studies were also carried out. Prior to cleaning, microbiological load was verified and after cleaning of residue of the product, microbiological load was tested.

The observations raised from this section were addressed satisfactorily, and will be verified during future inspections.

2.5 COMPLAINTS

Complaints and other information concerning potentially defective products were reviewed according to written SOP and the corrective actions were taken. The market complaints were handled through handling of market complaint procedure. The procedure links with recall procedure in case critical complaint was reported.

2.6 PRODUCT RECALLS

There was a system in place to recall products from the market. The SOP for product recall for export market was reviewed and noted that procedure provided flowchart for recall activity. It was noted that recall can be triggered through OOS, complaints, adverse drug reaction, stability failure and field alerts etc. The recall was classified into Class I, II and III (24 hour, 48 hour and 5 days respectively). It had been noted that the Head Quality was responsible for coordinating recall with the help of cross functional team.

The observations raised from this section were addressed satisfactorily, and will be verified during future inspections.

2.7 CONTRACT PRODUCTION AND ANALYSIS

It was noted that the site did not contract out any of the production activities for Zinc Sulfate tablet. For laboratory testing, the site uses contract laboratories for some of the tests.

2.8 SELF INSPECTION AND QUALITY AUDIT

Internal audits were performed according to SOP prepared the internal audit schedule and organized the internal audit. The audit group included Local Inspection Team and Central Inspection Team. There were two schedules available for the execution of internal audits: in house and corporate. Both, corporate as well as in-house teams conducted audits two times per year at each location.

2.9 PERSONNEL

In general, there were sufficient qualified personnel to carry out the tasks for which the manufacturer was responsible. Individual responsibilities were clearly defined and recorded as written descriptions. Personnel were aware of the principles of GMP received initial and continuing training, including hygiene instructions.

The observations raised from this section were addressed satisfactorily, and will be verified during future inspections.

2.10 TRAINING

Personnel training were carried out according to the procedure. Forms for recording of training related information, including the trainer authorization form, were part of the SOP. Requirement was in place for the head of the department to review the annual training schedule. At the time of inspection, the total number of permanent employees was 524. A training matrix was available covering all job titles. An induction training program was in place for new employees, consisting of basic GMP and SOP training followed by on-the-job training with a time limit for completion of 30 days.

2.11 PERSONAL HYGIENE

Employee health evaluation was performed yearly; medical records were retained by the Human Resources department. The availability of medical records for employee was verified during inspection and found to be satisfactory.

2.12 PREMISES

In general premises were located, designed, constructed, adapted and maintained to suit the operations to be carried out. Premises used for the manufacture of finished products were suitably designed and constructed to facilitate good sanitation. Premises were designed and equipped so as to afford maximum protection against the entry of insects, birds or other animals.

2.13 EQUIPMENT

Equipment was located, designed, constructed, adapted and maintained to suit the operations to be carried out. Balances and other measuring equipment with appropriate range and precision were available for production and control operations and were calibrated on a scheduled basis. Calibration due-date labels were attached to the

equipment. Current drawings of critical equipment and support systems were maintained. Calibrated standard weights used for in-house verification of balances were available. The calibration certificate for the set of standard weights was presented to the inspectors.

2.14 MATERIALS

In general materials used for operations such as cleaning, lubrication of equipment did not come into direct contact with the product and was of a food grade. Incoming materials and finished products were quarantined after receipt or processing, until they were released for use or distribution. Materials and products were stored under the appropriate conditions and in orderly fashion to permit batch segregation and stock rotation by a first-expire, first-out rule.

2.15 DOCUMENTATION

In general documents were designed, prepared, reviewed and distributed with care. In general, documents were approved, signed and dated by the appropriate responsible persons. Documents were regularly reviewed and kept up to date. Alterations made to documents were signed and dated. The documentation system was mainly based on corporate guidelines and procedures. At Plant level, SOP on SOP described how to prepare BPR, specifications and standard test procedures. At Corporate level guidance documents were in place for the preparation of Master documents, STP and Specifications.

The observations raised from this section were addressed satisfactorily, and will be verified during future inspections.

2.16 GOOD PRACTICES IN PRODUCTION

In general, production operations followed defined procedures. Deviations from procedures were recorded and investigated. Checks on yields and reconciliation of quantities were carried out. Operations on different products were not carried out simultaneously or consecutively in the same room or area. Materials, bulk containers, major items of equipment, rooms and packaging lines being used, were labelled to identify the product or material being processed and the batch number. Access to production premises was restricted to authorized personnel. In-process controls were performed by IPQA within the production area. Precautions were taken to prevent the generation and dissemination of dust by providing airlocks, pressure differentials, air supply and extraction systems. In general contamination and cross-contamination of starting material or of a product by another materials or product were avoided. Production areas were subject to periodic environmental monitoring.

2.17 GOOD PRACTICES IN QUALITY CONTROL

The QC function was independent from other departments. The QC personnel had access to production areas for sampling and investigations if required. The QC laboratories (RM testing, finished goods testing, stability lab and microbiology laboratory) were located on the first floor of the main administration block.

The observations raised from this section were addressed satisfactorily, and will 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, as well as the corrective actions taken and planned, **Alkem Laboratories Limited**, **Amaliya, Daman, India** 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.