WHO PUBLIC INSPECTION REPORT Finished Product Manufacturer

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(WHOPIR)

Finished Product Manufacturer

Part 1: General information

Name of Manufacturer	**Acme Formulation Pvt Ltd**
Unit number	NA
Production Block	NA
Physical address	Ropar Road, Nalagarh-174101 District Solan, Himachal Pradesh, India
Contact address	Mr Viral Shah viralshah@acmeformulation.com Managing Director
Date of inspection	11 to 14 August 2015
Type of inspection	Initial inspection
Dosage forms(s) included in the inspection	Tablets
WHO product categories covered by the inspection	Misoprostol tablet 200µg (RH056)
Summary of the activities performed by the manufacturer	Production and control of finished pharmaceutical products

Part 2: Summary

General information about the company and site

Acme Formulation Pvt Ltd (hereafter Acme) was established in 2004 in Nalagarh, District Solan, Himachal Pradesh, India. Acme is a leading contract manufacturing organization (CMO) for various Indian & multi-national companies for domestic and international market. The Acme Group has 3 manufacturing facilities (Acme Formulation Pvt Ltd, Nalagarh Solan, Himachal Pradesh, Immacule Lifesciences Pvt Ltd, Nalagarh, Solan, Himachal Pradesh and Acme Generics LLP, Baddi, Solan, Himachal Pradesh) in India.

Acme Solan site commenced operation in April 2005 with General Block (oral solid dose for tablets & capsules). The Hormone Block was added to the site in 2007 to manufacture Levothyroxine tablets. In 2009, Sex Hormones suite was added to the site to manufacture female sex hormone tablets. The manufacturing facility was upgraded in 2014 to meet international guidelines to produce sex hormone tablets. In August 2015, Thyroxine Sodium tablets production was moved to a new dedicated facility at another site (Acme Generics LLP, Baddi, Solan, Himachal Pradesh).

History of WHO and/or regulatory agency inspections

This was the first WHO Prequalification inspection. The site was also inspected by several regulatory authorities.

Focus of the inspection

The inspection focused on the production and control of Misoprostol tablet 200µg product. 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

A system for quality assurance in general was established. Production and control operations were clearly specified in written procedures, arrangements were made for the manufacture, supply and use of the correct starting and packaging materials. Necessary controls on materials, calibrations and validations were carried out. There was a system for Quality Risk Management (QRM). Product quality reviews were conducted for domestic market and export products.

The SOP on risk assessment procedure was reviewed and found to be satisfactory.

The SOP on annual product review was reviewed and found to be satisfactory.

The SOP on change control procedure was reviewed and noted that procedure described handling of changes pertaining to processes, documents, systems, equipment in all departments.

Deviations were handled as per SOP, and were classified as critical, major and minor. Trending of deviations was performed once per year.

The SOP on corrective action and preventive action was reviewed which defined corrective action and preventive action terms used in the procedure.

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

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

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

2.3 SANITATION AND HYGIENE

In general, premises and equipment were maintained at an acceptable level of cleanliness. The company had a standard operating procedure as the basis for its approach to personal hygiene and sanitation in its production facility.

Clean areas were cleaned frequently in accordance with an approved written programme and SOPs. Microbial monitoring was regularly undertaken.

2.4 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 Validation Master Plan (VMP). The VMP for sex hormone plant generally covered validation activities resulted from risk assessment of equipment/systems/processes, facilities, equipment, process, cleaning, analytical, computer system, supplier qualification and analyst qualification.

Process validation protocol for Misoprostol tablet 200mcg was reviewed and noted that three batches were taken into account. The data from these batches were submitted. The three consecutive batches were selected with a batch size of 102,500 tablets and shelf-life of 24 months.

Cleaning validation was performed by taking into consideration that the sex hormone plant was a shared facility for the production of four different sex hormone products.

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

2.5 COMPLAINTS

The company had established procedure for logging, investigation, communication and corrective and preventive actions implementation for any market complaint received directly from the market or from principle customer/party/foreign country. The complaints were evaluated based on severity and investigation was carried out jointly or individually by QA based on nature of complaint.

This section was not inspected in detail.

2.6 PRODUCT RECALLS

The company had a procedure on product recall which described procedure for recall of the products based on the outcome of a complaint, self-inspection or internal findings if product is found to be of sub-standard quality/non-conforming to quality standards.

This section was not inspected in detail.

2.7 CONTRACT PRODUCTION AND ANALYSIS

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

2.8 SELF INSPECTION AND QUALITY AUDIT

As per procedure non-compliance identified during internal audits can be classified as critical, major and observation. The SOP contained checklist, format for recording of audit team and format for inspection quarterly schedule. 2015 schedule was verified.

2.9 PERSONNEL

The manufacturer had an adequate number of personnel with the necessary qualifications and practical experience. Responsible staffs, specific duties were recorded in written job descriptions. Personnel were aware of the principles of GMP and received initial and continuing training, including hygiene instructions, relevant to their needs. Steps were taken to prevent unauthorized people from entering production, storage and QC areas.

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

2.10 TRAINING

The training SOP described the procedure for training of personnel. New employees received induction training, GMP training followed by a job description. Training need identification (TNI) chart was also prepared. According to the procedure on job training was also provided. Individual records were kept in personal files in the respective dept.

2.11 PERSONAL HYGIENE

Personnel employed received initial and regular training. Periodic health checks were carried out. Changing and washing followed a written procedure. Direct contact was avoided between the operator's hands and starting materials, primary packaging materials and intermediate or bulk product. Smoking, eating, drinking, chewing, and keeping plants, food, drinks, smoking material and personal medicines was not permitted in production, laboratory and storage areas.

2.12 PREMISES

Exposed surfaces were smooth, impervious and unbroken. Changing rooms were designed as airlocks and used to provide physical separation of the different stages of changing. Changing rooms were flushed with filtered air. There were seven air handling units (AHUs) provided in sex hormone section including ventilation & exhaust units to maintain ISO 8 at rest in the manufacturing area such as granulation, dispensary, compression, coating room, paste preparation room, blister cubicle, alu-alu blister cubicle room etc. The AHUs had variable frequency drives provided to control air changes per hour and differential pressure within the area. Photos explaining changing procedures were available in all changing rooms; changing rooms were equipped with mirrors. Airlock doors did not open simultaneously.

Storage areas were of sufficient capacity. Receiving and dispatch bays protected materials and products from the weather. Segregation was provided for the storage of rejected, recalled, or returned materials or products. All materials in the warehouse were stored in fixed racks. Separate sampling areas were provided for APIs and inactive materials. Packaging materials were sampled in the warehouse.

QC laboratories 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.

Microbial laboratory was separated from production and QC laboratories. Separate air-handling units were provided for microbiological laboratories.

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

2.13 EQUIPMENT

Fixed pipework was clearly labelled to indicate the contents and the direction of flow. Balances and other measuring equipment of an appropriate range and precision were available for production and control operations and were calibrated on a scheduled basis. Balances were verified daily, full scale calibration was carried out Monthly for the balances located in the warehouse, production areas and QC. Production equipment was cleaned on a scheduled basis. Laboratory equipment and instruments suited to the testing procedures undertaken.

Major production and laboratory equipment were subject to planned preventive maintenance.

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

2.14 MATERIALS

Incoming materials and finished products were quarantined after receipt until they were released for use or distribution. Materials and products were stored under the appropriate conditions. Food grade oil was used for punches and dies lubrications.

Starting materials were purchased from approved suppliers. Approved suppliers lists for starting materials (active and inactive) and packaging materials were available. For each consignment, the containers were checked for integrity of package and seal. Damage to containers and any other problem that might adversely affect the quality of a material recorded and reported to the QA department. Check-lists were used for materials receipt.

Packaging materials were purchased from approved suppliers. Printed packaging materials were stored in secure conditions. Each delivery of batch of printed or primary packaging material was given a specific reference number.

Rejected materials and products were stored separately.

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

2.15 DOCUMENTATION

In general documents were designed, prepared, reviewed and distributed with care. Documents were approved, signed and dated by the appropriate responsible persons. Documents were regularly reviewed and kept up to date. Records were made or completed when any action was taken.

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

2.16 GOOD PRACTICES IN PRODUCTION

Handling of materials and products were carried out in accordance with written procedures. Deviations from instructions or procedures were done in accordance with an approved procedure. Checks on yields and reconciliation of quantities were carried out. During processing, all materials, bulk containers, major items of equipment and rooms were labelled. Equipment spare parts as FBD filter bags, sieves, stereos and screens were stored secure in locked cabinets. Punches and dies were product dedicated and rotation was ensured.

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

2.17 GOOD PRACTICES IN QUALITY CONTROL

The quality control (QC) function was independent of other departments. Adequate resources were available to ensure that all the QC arrangements are effectively and reliably carried out. QC personnel had access to production areas for sampling and investigation as appropriate.

A validated Oasis LIMS system was recently introduced and used for the generation of analytical reference numbers for the samples received in the laboratory.

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, Acme Formulation Pvt Ltd, Nalagarh, 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.