World Health Organization

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WHO PUBLIC INSPECTION REPORT

(WHOPIR)

Finished Product Manufacturer

Part 1: General information

Name of Manufacturer	Mission Vivacare Limited
Unit number	N/A
Production Block	Pharmaceutical Block
Physical address	Indore SEZ, Phase II Pharma Zone, Sector 3 Pithampur, Disttrict Dhar M.P. 454 775 India
Contact address	As above
Date of inspection	28 to 31 March 2011
Type of inspection	Routine GMP (FPP - new site for PQP)
Dosage forms(s) included in the inspection	Tablets (including film coated)
WHO product categories covered by the inspection	HIV/AIDS products
Summary of the activities performed by the manufacturer	Production and quality control

Part 2: Summary

General information about the company and site

Mission Vivacare Ltd (hereafter referred to as MVL) is located in the Special Economic Zone (SEZ) in Dhar district, Pithampur, near Indore. It has two manufacturing blocks on site one being the Pharmaceutical block, and one the Dietary Supplements block. This inspection was focusing on the Pharmaceutical block. The company manufactured tablets and capsules on site. There were about 300 people employed on site. According to the Site Master File - the company headquarters was located in Mumbai, and another manufacturing site was located at Sarigam.

History of WHO and/or regulatory agency inspections

This was the first inspection by WHO HQ. The site was licensed by the Indian Authorities and was also inspected once by UK MHRA.

Focus of the inspection

The inspection focused on the production and control of oral solid dosage forms, in particular film coated 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

During the opening meeting, the scope of the inspection was clarified and it was mentioned that several of the WHO GMP texts had been revised. The activities and scope of PQ was explained including the procedures for the publication of WHOPIRs and NOCs. The inspectors explained that the inspection would focus on the production and control of the product applied for prequalification (but may also include other products - as only three validation batches were produced of this product to date) and presented the inspection plan to the company.

All the company representatives present in the opening meeting signed the attendance sheet (filed with this report). The company made a brief presentation about the site.

There was a Pharmaceutical product block, a Dietary supplement block, a quality control / quality assurance block, admin block and a utility block.

The inspection focused on the pharma block.

According to the company presentation, the following features were in place:

- Unidirectional flow.
- Epoxy floors
- ISO 8 air classification for some areas

- Electronic access controls
- Three dispensing booths
- PLC controlled critical machines
- Bar code and pharma code readers
- On line ink jet printing
- Tablets and capsules production
- Blister packs only (No bulk packing was done at the time, provision was made for an area, but it was not yet equipped)
- Separate storage areas for different types of materials
- Temperature controlled areas where relevant

QA features included:

- Validation
- Training
- Release of products
- Deviation control
- Change control
- Review of batch records
- Complaint and recalls
- Self inspections
- Technology transfer
- Risk management

QC features included::

- Dedicated teams were available for wet chemistry and instrumentation
- Microbiology laboratory
- The laboratory was common for pharma and dietary supplements
- Walk in chambers for stability were in place
- Instruments included:
    - AA
    - HPLC s
    - FTIR
- Sampling and testing
- FPP analysis
- Water testing
- Environmental monitoring
- Stability testing

Engineering services and utilities features included:

- UPS
- Air compressors
- Boiler
- Chiller
- AHUs
- Planned Preventive Maintenance

- Calibration
- Installation
- HVAC validation

Water system features included:
- Potable from government supply
- Underground storage tank
- Hot circulation loop
- On line TOC and conductivity monitoring

Personnel administration features included:
- Recruitment and training of personnel
- Safety
- Medical examination organization
- Laundry

After the opening meeting, the inspectors started the inspection by reviewing the organization chart and job descriptions. They reviewed various job descriptions, section organization charts and training records for selected persons (in relation to key responsibilities and delegations).

The following documents were inspected:
- The SOP for batch number allocation
- SOP for Product Quality Review
- SOP for reworks
- SOP for complaints handling
- SOP for Recalls
- SOP and register for Deviations including the trend report for 2010
- Change control SOP

On the second day, they then proceeded to review the process validation and reviewed the batch records and related documentation

The following steps were included in the verification during the inspection for process validation:
- Dry Mixing
- Drying
- Blending
- Coating

The source data were reviewed (chromatograms) and back calculations from the peak areas were checked for selected samples.

The quality control laboratory was then inspected, including a sample receiving area, stability chamber room, GC room, UV - polarimeter and FTIR area; HPLC room; balance - moisture

analysing and friability testing area, wet chemistry and microbiology laboratory. Checks were done by the inspectors reviewing some SOPs, records and interviewed some analysts. The following was reviewed:

- Glassware maintenance and storage as well as cleaning;
- Volumetric solution preparation, records, labelling and standardization;
- pH meter calibration;
- dissolution testing apparatus calibration and operation;
- FTIR calibration.

In the afternoon they continued by reviewing the source data including tests and results such as:

- Identification (printed spectra and electronic stored spectra);
- Optical rotation;
- IR (verification of polymorphic form II - in house method);
- Chromatographic purity;
- Assay;
- Code transfer;
- Microbiology
- Stability testing procedure and protocols
- Stability testing results

On the third day, the inspectors then proceeded to review the source data for the test for related substances. Then they inspected the documentation relating to the HVAC system design and qualification, area classification, layout of the site and specifications.

The procedures; schedules and reports for preventive maintenance were checked for selected equipment as well as SOPs and checklists, and compliance. All checks were done in accordance with the schedule / plans and were in general accepted.

The system and procedure for calibration was checked, including the list of instruments and equipment - critical and non critical - limits and calibration plan.

The IQ, OQ, PQ records for selected AHU was reviewed. Selected aspects and components were checked in the records including but not limited to installed filter leakage testing, air volume, air exchange rate, particle count and balancing.

The schematic drawing for the purified water system was discussed and questions were raised regarding the design, maintenance, validation and monitoring of the system. The inspection focused on the design of the system, verification of components installed including spray balls, MOC, PW tank, loop, valves, UV treatment, slope, sensors, dead legs, daily monitoring, and sanitization - specifications, procedures, and records.

The inspectors then reviewed the documents remaining from the plan of the previous day(s) including the OOS procedure and records.

After lunch the inspectors inspected the warehouses - receiving of materials, storage and sampling areas. The warehouse was spacious and much of the area was not utilized yet.

Selected SOPs and records were inspected including GRNs, check lists for materials received, temperature monitoring, sampling and cleaning (starting materials) and sampling of packaging materials.

On the fourth day, they proceeded by inspecting:

- the VMP,
- cleaning validation,
- selected IQ, OQ, PQ data;
- the production area.

Production areas visited on site included the transfer of materials from the stores to production for dispensing, staging areas, dispensing area, tools (including punches and dies), FBD bags, in process storage, granulation areas, and compression areas, coating areas, tablet inspection and primary packaging areas.

In the afternoon they briefly inspected the service area (HVAC) for selected AHUs and checked the PW system and its monitoring log on site. They then went back to the laboratory to check the HPLC systems and results. They challenged the settings of the Waters HPLC (date and time settings), found some raw data in drawers and verified some of these results.

At the end of the day, a summary of the findings was presented in the closing meeting.

2.1 QUALITY ASSURANCE

The company had systems in place to attempt to ensure the quality of products manufactured. There was a designed system of quality assurance incorporating GMP and quality control. It was generally documented. The quality assurance system was staffed but it was noted that there was a turnover of staff in recent months. Several members of staff were new to the site including the QC /QA unit.

- In general, production and control operations were specified in SOPs;
- Managerial responsibilities were not always clearly specified in job descriptions;
- Arrangements were made for the manufacture, supply and use of the correct starting and packaging materials - but were not always sufficient;
- Controls on starting materials, intermediate products, and bulk products and other in-process controls, calibrations, were carried out;
- deviations were reported, investigated and recorded - but the system required improvement;
- the system for approving changes was in place;
- Product Quality Reviews were done.

2.2 GOOD MANUFACTURING PRACTICES (GMPs) FOR PHARMACEUTICAL PRODUCTS

A limited number of products was being productd on site (as it was a new facility awaiting approvals). Products were produced and controlled.

Systems were generally in place to reduce the risk of cross-contamination and mix-ups. These included:

- manufacturing processes were defined
- qualification and validation were performed;
- resources were provided, including:
  (i) personnel;
  (ii) adequate premises and space;
  (iii) suitable equipment and services;
  (iv) materials, containers and labels;
  (v) approved procedures and instructions;
  (vi) suitable storage and transport;
  (vii) personnel, laboratories and equipment for in-process controls;
- instructions and procedures were written;
- records were made during manufacture;
- records covering manufacture and distribution, which enable the complete history of a batch to be traced, were retained;
- storage and distribution of the products;
- a system was available to recall any batch of product from sale or supply - but needed improvement;
- a system was available to handle complaints about marketed products

2.3 SANITATION AND HYGIENE

An acceptable level of sanitation and hygiene was practised on site. The scope of sanitation and hygiene covered personnel, premises, equipment and apparatus, production materials and containers, products for cleaning and disinfection, and anything that could become a source of contamination to the product. The QA / QC unit required attention. In some areas, walls were dirty.

2.4 QUALIFICATION AND VALIDATION

MVL identified what qualification and validation work was required to prove that the critical aspects of their operations were controlled.

Qualification and validation were performed for:

- the premises,
- supporting utilities,
- equipment,
- processes.

Validation studies were conducted in accordance with predefined and approved protocols and written reports summarized the results and the conclusions reached.

2.5 COMPLAINTS

There was an SOP for handling complaints.

2.6 PRODUCT RECALLS

There was a system to recall from the market.

2.7 CONTRACT PRODUCTION AND ANALYSIS

Contracts were said to be in place - this was not inspected.

2.8 SELF-INSPECTION AND QUALITY AUDIT

A self-inspection programme was not inspected.

PERSONNEL

There were sufficient numbers of personnel to carry out all the tasks for which the manufacturer was responsible at the time. Individual responsibilities were defined (some lacked details) and recorded as written descriptions. Delegated duties were not always clearly defined. Organization charts and job descriptions were in place, however, some discrepancies were noted (see observations below).

2.9 TRAINING

Training was provided - training records were generally kept. Assessment after training had to be more relevant to the topics presented.

2.10 PERSONAL HYGIENE

An acceptable level of personal hygiene was observed. Direct contact was avoided between the operator’s hands and starting materials, primary packaging materials and intermediate or bulk product. Personnel were wearing clean body coverings appropriate to the duties they performed, including appropriate hair covering. Used clothes were stored in separate closed containers until properly laundered.

Personal hygiene procedures included the use of protective clothing for all persons entering production areas including contractors’ employees, visitors, senior managers, and inspectors.

2.11 PREMISES

The premises was located, designed, constructed, adapted, and maintained to suit the operations carried out. The layout and design of the premises aimed to minimize the risk of

errors and permit effective cleaning and maintenance in order to avoid cross-contamination, build-up of dust or dirt, and, in general, any adverse effect on the quality of products.

In areas where dust was generated (e.g. during sampling, weighing, mixing and processing operations, packaging of powder), appropriate measures were taken to avoid cross-contamination and facilitate cleaning. However, dust (product residue) was noted in the dispensing area after cleaning of the area.

2.12 EQUIPMENT

Equipment was located, designed, constructed, adapted, qualified and maintained to suit the operations to be carried out. The layout and design of equipment also aimed to minimize the risk of errors and permitted effective cleaning and maintenance in order to avoid cross-contamination, build-up of dust or dirt, and, in general, any adverse effect on the quality of products.

2.13 MATERIALS

Materials were mainly sourced from approved suppliers. All incoming materials and finished products were quarantined immediately after receipt until they were released for use or distribution. All materials and products were stored under the appropriate conditions established by the manufacturer and in an orderly fashion to permit batch segregation. Control of packaging materials required attention.

2.14 DOCUMENTATION

Documents were designed, prepared, reviewed and distributed. Some reports were on loose pages. Documents were approved, signed and dated by the appropriate responsible persons. Documents were laid out in an orderly fashion and were easy to check, but in some cases details were lacking. Reproduced documents were clear and legible.

2.15 GOOD PRACTICES IN PRODUCTION

Production operations followed defined procedures. Checks on yields and reconciliation of quantities were carried out. Materials, bulk containers, major items of equipment, and where appropriate, the rooms and packaging lines being used were labelled with an indication of the product or material being processed. Access to production premises were restricted to authorized personnel.

2.16 GOOD PRACTICES IN QUALITY CONTROL

The quality control unit was responsible for sampling, specifications and testing, and with the organization, documentation and release procedures which ensure that the necessary and relevant tests were carried out and that materials were not released for use, nor products released for sale or supply, until their quality had been judged to be satisfactory.

There was:

- adequate facilities,
- personnel;
- approved procedures for sampling, inspecting, and testing starting materials, packaging materials, and intermediate, bulk, and finished products, and for monitoring environmental conditions for GMP purposes;
- samples of starting materials, packaging materials, intermediate products, bulk products and finished products were taken by methods and personnel approved of by the quality control department;
- records were made demonstrating activities performed;

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 and corrective and preventive actions taken by the company, *Mission Vivacare Limited, Indore SEZ, Phase II Pharma Zone, Sector 3, Pithampur, Disttrict Dhar, M.P. 454 775 India* was considered to be operating at an acceptable level of compliance with WHO GMP.

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.