WHO PUBLIC INSPECTION REPORT Finished Product Manufacturer

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(WHOPIR)

Finished Product Manufacturer

Part 1: General information

Name of Manufacturer	Famy Care Ltd.
Unit number	Unit II
Production Block	NA
Physical address	1608/1609, G.I.D.C, Sarigam, 396155 Valsad, Gujarat, INDIA.
Contact address	Mr. Sunil Singh, Vice President, Quality Assurance sksingh@famycare.com
Date of inspection	18 - 22 November 2013
Type of inspection	Routine inspection
Dosage forms(s) included in the inspection	Coated and Uncoated Tablets with focus on Reproductive Health products (Oral Contraceptives and support placebos).
WHO product categories covered by the inspection	1. RH013: Levonorgestrel 150mcg and Ethinylestradiol 30mcg Tablet (Oralcon) 2. RH035: Ethinylestradiol/Levonorgestrel + Placebo 30/150 µg Tablet 3. RH038: Ethinylestradiol/Levonorgestrel + Ferrous Fumarate 30/150 mcg + 75mg Tablet
Summary of the activities performed by the manufacturer	Manufacturing, packaging, quality control and batch release of Tablets.

Part 2: Summary

General information about the company and site

The facility inspected was **Unit II** of **Famy Care Limited, located at 1608/1609, G.I.D.C, Sarigam, 396155 Valsad, Gujarat, INDIA,** hereafter called **Famy Care, Sarigam**. The company was incorporated in 1990 with a focus on Hormonal and Reproductive Healthcare Products. Famy Care is engaged in the manufacturing of a wide range of Reproductive Healthcare Products:

- Oral Contraceptives
- Emergency Contraceptives
- Intrauterine Devices and
- Tubal Ligation Rings

The manufacturing facility is located at Sarigam (State of Gujarat), about 19 km from Vapi railway station, and approximately 170 km from Mumbai International Airport. The facility was acquired from an existing manufacturing set up from Pfimex and upgraded to meet Famy Care requirements in year 2005.The facility has dedicated and segregated manufacturing areas for oral contraceptive &inert tablets, including warehouses for raw material, packaging material, and finished goods.

According to the presentation given by the company at the beginning of the inspection, the plant employed a total of 105 people.

History of WHO and/or regulatory agency inspections

This was the fourth time the site of **Famy Care Ltd** was being inspected by WHO Prequalification team. Previous WHO-PQ inspections were conducted in April 2009, May 2010 and February 2011.

According to the company presentation, the site had also been inspected by the following regulatory authorities:

Sr. No.	***Country***	***Year of Inspection***
1	*MCC – South Africa*	*2009*
2	*EU GMP through INFARMED - Portugal*	*2010*
3	*Health Canada*	*2011*
4	*WHO (National)*	*2011*
5	*WHO (Geneva)*	*2011*
6	*Uganda*	*2012*

7	*Tanzania*	*2012*
8	*TGA*	*2012*
9	*US – FDA*	*2012*
10	*Egypt*	*2013*

Focus of the inspection

The inspection focused on the production and control of hormonal contraceptive tablets, focusing on RH013 & RH035 (both prequalified) and **RH038: Levonorgestrel 150mcg and Ethinylestradiol 30mcg plus Ferrous Fumarate 75mg Tablet**(currently under prequalification). 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
- Sanitization and hygiene
- Qualification and validation
- Complaints
- Recalls
- Self-inspection
- Personnel
- Training
- Personal hygiene
- Premises
- Equipment
- Materials
- Documentation
- Production
- Quality control

2.1 QUALITY ASSURANCE

In general Quality Assurance (QA) system was established and adequately maintained.

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. The concept of qualifications and validations was implemented. Operators were trained, and records were made during manufacture.

2.3 SANITATION AND HYGIENE

In general, premises and equipment were maintained at an acceptable level of cleanliness. Environmental monitoring was undertaken. Premises and equipment were cleaned and disinfected following written procedures.

2.4 QUALIFICATION AND VALIDATION

Qualification and validation was done according to a Validation Master Plan VMP. A V-model approach was followed.

A Romaco blister machine had been transferred from the other manufacturing site and re-qualified at this site with assistance from the vendor. Protocol F/PR/08 and associated records were reviewed with particular attention to the on-line camera and faulty blister rejection systems. No deviations were noted and the records appeared acceptable with the conclusion documented and signed by appropriate people on 16.11.2012.

Pressure suit cleaning validation had been performed in April 2007 according to protocol. This study was based on swabbing a 5 x 5cm area after cleaning the suit, but was not considered properly controlled as the level of contamination before cleaning had not been determined to ensure effective cleaning under worst case conditions or an appropriate recovery studies to demonstrate method reproducibility.

Analytical method validation protocol for determination of traces of Levonorgestrel and Ethinylestradiol present in air and SOP on the determination of traces of LNG & EE in air (air sample) was briefly reviewed.

2.5 COMPLAINTS

Complaints were handled according to SOP. Complaints from any source and through any medium were accepted and classified as critical, major or minor. They were then required to be further grouped into e.g. process related, packaging related, storage related etc. All complaints were channelled through the Head, QA. Complaints due to possible counterfeiting were considered as were possible effects on other products. CAPA is taken when applicable (CAPA for complaints included in above SOP).

According to the complaint log for 2013, 23 had been received to date. The complete records for 2 of these were selected for review. Both appeared to have been properly investigated and CAPA records available. Timeframes for closure were acceptable.

2.6 PRODUCT RECALLS

SOP described the procedure for handling product recalls. The Head of QA was ultimately responsible for recall decisions. The procedure also required a recall committee to be formed and described the composition of the committee.

According to the SOP, recalls could be voluntary or statutory. They were required to be classified as Class I, II or III, with a description of each. Regulatory authorities, including WHO PQP, were required to be notified.

Records indicated that there had been 1 recall for this site during 2013. One of the products was voluntarily recalled in 2013 as a result of an impact assessment following the recall of a similar product manufactured at another site. CAPA had been taken as a result of the original recall.

2.7 CONTRACT PRODUCTION AND ANALYSIS

Not inspected

2.8 SELF INSPECTION AND QUALITY AUDIT

Self-inspections were conducted according to SOP. The SOP required each area to be inspected at least every 6 months. The schedule for 2013 was reviewed and it appeared that self-inspections were being performed as per the SOP.

There was a mechanism for recording observations, taking CAPA if necessary and follow-up to ensure the action taken was effective. Actual records of self-inspections were not reviewed.

Supplier's audits

A procedure on vendor qualification SOP was reviewed. The vendors were qualified by evaluating the vendor questionnaire, request of samples & specification. Once this is acceptable, the vendor is qualified. On-site assessment of vendors was performed, whenever applicable. There were various vendors qualified for Levonorgestrel.

While making comment on the need to perform on-site audit based on risk based approach and as per audit schedule, the manufacturer shared difficulty of not getting audit dates and no cooperation from the Chinese API manufacturers.

2.9 PERSONNEL

The manufacturer had an adequate number of personnel with the necessary qualifications and practical experience. Job descriptions for selected key personnel were reviewed and although generally acceptable, some minor inconsistencies were noted.Minimum number of personnel required was present in clean areas. Periodic health checks were carried out for all personnel working in clean areas.

2.10 TRAINING

Training was conducted according to SOP. The procedure was comprehensive covering induction, on the job, scheduled and external training. Trainers were required to be qualified and there was an approved list of certified trainers.

Induction training was planned as a 2 day activity for new staff. Effectiveness was evaluated by questionnaire with a 80% pass mark. The records reviewed were satisfactory. On the job training was the responsibility of the relevant department head and conducted by pairing with a suitable experienced person in the department. Records were acceptable.

The annual training plan for 2013 was reviewed. Certified trainers were allocated in the plan and records showed that this training had been conducted as per the plan.

Complete training records for 2 recently qualified production and QA officers were reviewed and were generally acceptable.

2.11 PERSONAL HYGIENE

All personnel, prior to and during employment had to undergo health examinations. Direct contacts were avoided between the operator's hands and starting materials, primary packaging materials, intermediate and finished product.

Operators handling exposed hormone were required to wear self-contained pressure suits. These were numbered and cleaned and inspected for integrity according to a documented procedure. Logs for all the pressure suits in the facility were reviewed.

2.12 PREMISES

Production facilities had generally been adapted and maintained to an acceptable standard to suit the manufacture of non-sterile oral contraceptives. Hormone production was conducted in dedicated areas designed for containment i.e. negative pressure to corridors, with pressure differentials monitored by magnehelic gauges. Return air was filtered by HEPA filters at the point of return and again by HEPA filters installed in each AHU. Non-active tablets were produced in a separate and segregated part of the facility to avoid cross-contamination. This area was not inspected due to time constraint.

Each blister packaging machine was located in a separate room, feeding a general secondary packaging area provided with physical barriers to separate each packaging line.

Separate storage facilities were provided for active and in-active starting materials, packaging materials and finished products. Separation of quarantine and approved material was provided

The QC laboratory was considered rather small. However, it was noted that this had been recognized and there were plans to extend this area. The inspectors were concerned about the lack of specific facilities for handling hazardous substances such as hormones in the laboratory. For example, hormone APIs were weighed in a general weighing area with no proper facilities for containment and the instructions for handling spillages were not considered appropriate for this type of material.

2.13 EQUIPMENT

Production equipment was generally found to be suitable for its intended purpose. This had been demonstrated through equipment undergoing suitable qualification before use.

Purified water was produced by RO and EDI with in-line TOC and conductivity monitoring. The system was sanitized weekly by circulating hot water at 80 – 90^{o}C for 1 hour. SOPs for the operation of the system were available and records of monitoring and maintenance were available. The system appeared to be well maintained and under good control.

There was a manually managed preventive maintenance program and the 2013 schedule for process equipment was reviewed. This record showed that maintenance had been performed as scheduled. Detailed records for the auto coater and blister machine were reviewed and were satisfactory.

An approved master list of equipment requiring calibration was available. This showed the tag number, location, make, range and limit, calibration frequency, last done and due dates. Some calibration was contracted out, e.g. to Accurate Labs an accredited laboratory for this type of work. A sample of calibration records were reviewed and found acceptable.

2.14 MATERIALS

Incoming materials and finished products were quarantined after receipt until they were released for use or distribution. Consignments were checked for integrity of package and for correspondence between the order, the delivery note, and the supplier's labels. Damage to containers were recorded and reported to the quality Assurance department. If one delivery of material (starting and packaging) was made up of different batches, each batch was considered as separate for sampling, testing and release.

2.15 DOCUMENTATION

In general documents were designed, prepared, reviewed and distributed with care. Documents were approved, signed and dated by appropriate responsible persons. Documents were regularly reviewed every three years and kept up to date. Records were made or completed when any action was taken.
Two examples of completed batch records were selected for review. These had been properly completed, with in-process results and yields at key stages documented. Minor discrepancies in the number of decimal places stated in the BMR and the decimal places actually weighed were noted.

2.16 GOOD PRACTICES IN PRODUCTION

Production was carried out according to the detailed instructions in the batch manufacturing record and associated SOPs. A documented line clearance was performed before work commenced in each area.

Material weighing was carried out in separate dispensaries for active and inactive materials. The operation and cleaning of these areas was described in SOPs and suitable records maintained.

Considering that the cause of the recent recall due to incorrect placement of a placebo tablet had been attributed to a blister packaging challenge test being placed back on the line, particular attention was paid to primary blister packaging and corrective actions that had been implemented. At the stage of primary packaging the controls now in place would appear to make it unlikely that this would happen again in the future.

Adequate provisions for in-process quality control testing during bulk tablet manufacture and during packaging were available. All in-process batch records reviewed had been appropriately completed.

2.17 GOOD PRACTICES IN QUALITY CONTROL

The QC function was independent of other departments. At the time of inspection, there were 31 staff members working in QC. These were assigned into different sections such as raw material, packaging material, in-process, finished product & stability, good laboratory practices team and microbiology team. The analyst qualification matrix was available and reviewed briefly during the inspection of QC. The analysts were qualified on various modules (RM, PM, IPC, FP etc).

Samples were logged into a sample inward register for the purpose of tracking. A unique laboratory number was given to each sample. Raw data was recorded in the numbered analytical worksheets. Chemistry laboratories included:

- Wet chemistry laboratory

- HPLC room
- Balance room
- Instrumentation room
- FTIR

There were 6 HPLC available in the laboratory. The SOP on operation and calibration of HPLC was available whereby HPLCs were calibrated in-house every 6 month. The calibration included flow rate, repeatability, linearity, injection volume, GPV and carry over etc. Out of 6 HPLCs, 4 HPLC were equipped with UV & florescence detector. A procedure on the management of chromatography data station (integrity of electronic data) was reviewed during the inspection of QC. In addition, another procedure on manual integration was available. There were some ambiguities found in these procedures.

Microbiology laboratory: The laboratory performs microbial limit test (MLT) of raw materials and finished products, water monitoring and environmental monitoring of production areas. There were 4 microbiologists working in the lab. The MLT was performed using pour plate and membrane filtration methods. Media were tested for growth promotion test (GPT) in accordance with SOP on GPT. The ATCC live organism/cultures were procured from Microbiologics USA, and certificate of analysis was available for these cultures. The company policy is to perform not more than 3 passages on the reference cultures (mother cultures). A procedure on sub-culturing & maintenance of stock culture and operation and calibration of LAF Unit were reviewed during the inspection and found satisfactory.

Inspection of HVAC: A brief tour of technical area including filter cleaning area was conducted on day 4. The physical inspection of ducts revealed leakage in AHU. The air handling unit consists of 10µm pre-filter, a coil, blower and 5µm fine filter. The pressure across pre-filter and fine filter was monitored with limit of 4-12mm and 6-20mm respectively. There were two sets of HEPA provided both at terminal and return with 10µm placed to ensure adequate containment of hormone residues. Filter cleaning of pre-filter and fine filter were carried out in-house using filter cleaning machine. There were some issues noted on containment of hormone residue while opening/fixing pre-filter and fine filter at the plenum.

The waste water from the filter cleaning area goes to ETP where it gets treated with 2% Sodium Hypochlorite. There were three wet scrubbers provided to ensure hormones are contained and sent to ETP.

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, **Famy Care Limited, Sarigam, Gujarat, 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.