



**WHO PUBLIC INSPECTION REPORT
(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 person and email address.	Mr. K Anand , Chief Operating Officer, Famy care Ltd , Brady House, 3 rd Floor, 12 / 14, Veer Nariman Road, Fort, Mumbai - 400 001, INDIA. Tel.: +91-22-30289655, +91-22-30289628 Fax.: +91-22-30289656, E-mail: kanand@famycare.com
Date of inspection	7 - 9 September 2011
Type of inspection	Follow-up 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	Finished Pharmaceutical Products (FPPs) used in Reproductive Health (RH): <ul style="list-style-type: none">• RH013: Levonorgestrel 150mcg and Ethinylestradiol 30mcg Tablet (Oralcon) - Oral contraceptive.
Summary of the activities performed by the manufacturer	Manufacturing, packaging, quality control and batch release of Tablets: Oral contraceptives.



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, Unit II**. According to the Site Master File, Doc No.: SMF/FC/19, effective August 28th, 2011, and the presentation by the company at the start of the inspection, Famy Care Limited was incorporated in 1990 and had its registered office at Famy Care Limited, Brady House, 3rd Floor, 12/14, Veer Nariman Road, Fort, Mumbai 400 001, INDIA. According to the SMF and the company presentation, the company had another facility for injections and tablets at Pharma-Special Economy Zone at Ahmedabad, Gujarat and another for R&D Formulations at Mahape, Mumbai. It had also recently tied up with Mylan Pharmaceuticals Inc. for the supply of contraceptives in USA. Further discussions revealed that the company also owned a facility for production of IUDs in Goa.

The factory site of **Famy Care Limited** at Sarigam, Vapi, Gujarat, is about 180km North of Mumbai on Mumbai- Ahmedabad highway on a plot of 6210m². There were two main buildings, one being the main production block and the other one dedicated to packaging.

1. Packaging block:

According to the company, the separate packaging block served only Unit I. This was confirmed during the previous inspection and therefore this block was not re-inspected.

2. The main Production block

The production building had two floors:

- **Ground floor** accommodated the production activities of **Unit I of Famy Care Ltd**. It was connected to the next packing block by a built up covered tunnel which led to the primary packing section. Unit I had a separate entrance, change rooms, warehouses, production areas, packaging areas and QC laboratory (except microbiology laboratory). There was no connection between this Unit with Unit II. As the company assured the inspectors that there was no activity any more regarding the inspected products in this Unit and it was visited during the first inspection, this was not re-inspected.
- **First floor** accommodated Unit II of Famy Care Ltd which was under the scope of this inspection. This floor comprised of separate sampling, dispensing, warehouses, production and coating areas for Oral Contraceptive Pills (OCP) and general tablets (Placebos and Ferrous Fumarate). It had a common packaging area and QC laboratory. These premises were renovated in August 2006.

The two units shared the Microbiology laboratory, Engineering personnel, Human Resources and Administration services, water purification system, compressed air system and QMS for SOPs. The site had common heads of Quality Assurance, Production and Warehouse but with separate supervisors and personnel for each unit.

Famy Care Limited, located at 1608/1609, G.I.D.C, Sarigam, 396155 Valsad, Gujarat, INDIA was licensed by the Food and Drugs Control Administration of Gujarat State and issued with **licenses No. Form 25: G/1476** and **Form 28: G/1072** (*granted on 20.11.1998, currently renewed up to 31.12.2011*) to manufacture General tablets and Sex Hormonal. The licence did not differentiate between Units I and II. The two units manufactured a similar range of products which were differentiated by the batch numbering system described in SOP No. QAD/U022, Rev.10, effective 01.01.2011.

According to the SMF and the presentation given by the company at the beginning of the inspection, the plant employed a total of 120 people: 41 in Production, 23 in Quality Control, 30 in Quality Assurance, 9 in Storage and distribution, 9 in Engineering and 8 in Personnel & Administration.



History of WHO and/or regulatory agency inspections

This was the third time the site of **Famy Care Ltd** was being inspected by WHO Prequalification team. Previous WHO-PQ inspections were conducted in April 2009 and May 2010. Two other planned follow up inspections were cancelled by the company at the last minute for various internal reasons.

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

- MOH Zimbabwe - 2007
- MOH Yemen - 2007
- MOH Nepal - 2007
- INVIMA, Columbia - 2007
- INFARMED, Portugal - 2007, 2008 and 2010
- MOH Botswana - 2008
- MOH Cuba - 2009
- MCC, South Africa - 2009
- FDCA, Gujarat State - 2009 and 2011
- MOH, Iraq – 2009 and
- MOH, Uganda - 2009
- WHO-PQ, Geneva – 2009 and 2010
- MOH Kazakhstan – 2009
- MOH Namibia – 2010
- MOH Ivory Coast – 2010
- MOH Congo – 2011
- Health Canada - 2011(*Desk review*)

Focus of the inspection

The inspection focused on the production and control of hormonal contraceptive tablets with special focus on **RH013: Levonorgestrel 150mcg and Ethinylestradiol 30mcg Tablet (Oralcon)**. The inspection is a follow-up of the previous WHO medicines prequalification programme (WHO-PQ) inspections and reviewed implementation of the corrective actions to the deficiencies raised during the last inspection.

Inspected Areas

Day I: 07 September 2011

On arrival and after introductions, the inspectors updated the company on the procedures for WHO Prequalification Programme, the procedures and standards used for inspection, and the timelines for processing the report and company responses to the inspection observations. The procedures for WHO Public Inspect Report (WHOPIR) and Notice of Concern (NOC) were also discussed.

The inspection plan was confirmed followed by a presentation about the company and the site to be inspected. The presentation highlighted the company profile, the description of Unit II, a summary of manufacturing capacities, the site inspection history, status of implementation of CAPAs to the observations of the last inspection and changes since the last WHO inspection. A copy of the presentation was obtained and has been filed in the company file at WHO.



The major changes highlighted include the following:

- System related changes:
 - Added user points to the existing water system.
 - Fixed HEPA filters in washing area of general tablets.
- Facility related changes:
 - Renovated facility for new conference room.
 - Created new wet granulation facility.
 - Hormone store, sampling and dispensing facility shifted and refurbished.
- Equipment related changes:
 - New 75 Station compression machine installed.
 - New 48 inch tablet coating machine installed.
 - Walking stability chamber for 30°C/75%RH installed.
 - New FTIR installed.
 - New Hi Cart Cartoner machine installed.
 - New glassware washing machine installed in QC.
- Organogram related changes:
 - New head of warehouse
 - New Head of QC
 - New Head of QA (Jan. 2011).
 - New Vice President Corporate Quality (2011).
 - New Senior Vice President Operations (02.09.2011)

The review of the following areas and documents followed:

- Site Master File
- Personnel Policies: *Organization charts, Job descriptions, Training, Health and Hygiene.*
 - Training Plan 2010/2011
 - List of Employee on 7th September 2011;
 - Reviewed 20 individual files (training, job description, health and hygiene), 8 of them hired in 2011;
- List of product codes and/ Batch numbering system: SOP No. QAD/U022, Rev.10, effective 01.01.2011.

The batch numbering system for products manufacture and packed in Unit II was 'ABCD' where:

- A = two-digit alphabet product code, e.g.
 - LE = *Levonorgestrel and Ethinylestradiol Tablets;*
 - OA = *Oralcon;*
 - OP = *Oralcon with Inert Tablets;*
 - ST = *Levest 150/30 Coated Tablets or Famicept 150/30 Coated tablets;*
 - OR = *Oralcon P (with yellow coloured inert tablets).*
- B = two-digit numerical code for combination and strength of the product, e.g.
 - 01 = *Levonorgestrel 0.15mg and Ethinylestradiol 0.03mg Tablets;*
 - 04 = *Levonorgestrel 0.15mg and Ethinylestradiol 0.03mg with Placebo/Inert Tablets;*
 - 38 = *Levonorgestrel 0.15mg and Ethinylestradiol 0.03mg Tablets;*
 - 42 = *Levonorgestrel 150mcg and Ethinylestradiol 30mcg Tablets*
 - 48 = *Levonorgestrel 0.15mg and Ethinylestradiol 0.03mg Tablets BP (0% Ethinylestradiol overages)Uncoated;*
 - 49 = *Levonorgestrel 0.15mg and Ethinylestradiol 0.03mg Tablets BP (1% Ethinylestradiol overages)Uncoated;*
 - 50 = *Levonorgestrel 0.15mg and Ethinylestradiol 0.03mg Tablets BP (3% Ethinylestradiol overages)Uncoated;*
 - 65 = *Levonorgestrel 150mcg and Ethinylestradiol 30mcgTablets with Inert Tablets (yellow coloured)*



- C = last digit of the year, e.g. 9 for 2009, 0 for 2010 and 1 for 2011.
- D = three digit numerical serial number starting from 001.
- The format is ABSCD where S = P for pilot batches, R for Registration samples and T = for Tender samples.

The batch numbering system for products (Except product code CF and FC) manufactured in Unit I was 'XYZ' where:

- X = one/two digit alphabet product code, e.g. LE, OA and OP with similar product as in Unit II. ST here represents Sutura.
- Y = last digit of the year, as in Unit II.
- Z = three-digit numerical serial number for one digit alphabets starting from 001.

The format is XSYZ where S = P for pilot batches, R for Registration samples and T = for Tender samples.

The following would, for example, be the corresponding batch numbers the first batches of the similar products manufactured in the respective units in 2009:

	Product	Unit II B/No 'ABCD'	Unit I B/No 'XYZ'
1.	<i>Oralcon</i>	OA429001	OA9001
2.	<i>Oralcon with Inert tablets</i>	OP049001	OP9001
3.	<i>Oralcon P with Yellow Inert Tablets</i>	OR659001	OR9001
4.	Levonorgestrel/Ethinylestradiol 0.15/0.030mg Tablets	LE019001	LE9001
5.	Levonorgestrel/Ethinylestradiol 150mcg/30mcg Tablets	LE429001	-

Oralcon presented to WHO had a bulk product code of LE which was similar to the one packed and marketed in Europe as Levest or Famicept under a commercial pack code ST. It was however noted that the product marketed in other markets as Oralcon had a different formulation (bulk code: 300000575/LE01) and presentation (OP04: 21 active, 7 inert) from that presented to WHO (bulk code: 300000571/LE42; presentation: OA42: 21 active). This may lead to confusion and mix-up and the company was asked to address it urgently.

- Product quality review SOPs + Reports

The PQR presented for reviewed was that of Levest 150/30 Coated Tablets covering the period December 2009 to November 2010.

- It covered 14 batches of size 1,400,000 tablets and BMR 300000015 Revisions 01 and 02 (changes in yield limits and addition of 75 station compression machine).
- The review covered process validation, OOS, raw materials used in the core tablets, primary packaging materials, from approved vendors, complaints, deviations, stability studies, retention samples, marketing authorization variations, technical agreements.
- Data was tabulated to show variability but was not adequately evaluated using appropriate statistical tools.

- OOS SOPs + Registers (2010/11)

- Complaints handling system SOPs + Register (2010/11)

- Handling product recall: SOP + Register (2010/11).

- Handling returned goods: SOP + Register (2010/11)

- This was guided by SOP No. QAD/U082 Rev.00 effective 14.02.2011. It provided for segregation of the returned good under lock and key, review of the storage conditions outside the company and disposal as determined by QA after evaluation.

- Deviations SOPs + Registers (2010/11)

- Change control SOPs + Registers (2010/11)

- Incident SOPs + Registers (11)

- Self-inspection SOP, Plans and reports (2010/11)

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- Product Master Files, codes, specifications for APIs and FPPs, plus List of approved vendors.
 - Specifications for in-process control indicated that a shelf life of 36 months for the FPP was already in force.
- Finished product release SOP.
- Contract production and analysis (contracts)
- Pest Control procedures, contracts and records
- Temperature mapping.

Day II: 08 September 2011

Inspectors provided feedback on the observations of the previous day. The programme of the day was discussed and agreed upon.

The following documents and areas were reviewed and inspected during day II:

- Site layout, floor plans with material and personnel flow, area classification and Pressure differentials, AHU distribution
- Inspection of receiving and storage areas plus related procedures and records:
 - There was a checklist for document review and physical inspection of the consignment before offloading into the warehouse.
 - There was adequate storage space and materials were stored in an orderly manner with appropriate status labelling. Separate stores, sampling and dispensing areas existed for hormones and non-hormonal raw materials.
 - The monitoring of retest dates of raw materials was reviewed and was operated using a manual system.
- Inspection of Production activities: Dispensing, production, packaging and in process controls.
 - The flow of personnel and materials was adequate with material and personnel airlocks with monitored pressure differentials.
 - Balances were calibrated and records of daily verification using standard weights were available.
 - Non-hormonal/inert tablet production section.
 - The granulation room had several pieces of equipment which were not always used for the same batch at the same time. Issues of protection and cleaning of unused equipment were noted.
 - Portable water was the only source of water in the paste preparation room. Purified water was obtained from the wash areas across the granulation room.
 - A batch of Lactose granules was on hold time study initiated on 30/05/2009.
 - IPQC room with test apparatus for disintegration, Friability, hardness, Vanier Callipers and moisture balance.
 - Coating machine was a convention with manual spray of coating solution. Air supplied to the pan was obtained from the room, filtered and pumped into the pan.
 - The inspection belt of the tablet sorting machine was Teflon coated canvas, not shedding particles as was the case during the first inspection.
 - Pass-box between the inert section and hormonal section was a bubble airlock with interlocking mechanism, with air supplied from the inert section and pressure differential monitored with a magnehelic gauge with set alert and action.
 - The hormonal tablet section:
 - Operators in areas where the product was exposed wore pressurised suits supplied with filtered breathing air.
 - There was a separate dispensing area, with a balance with appropriate weighing range (25g – 6000g, d=0.5g).
 - Blending room had 5 double cone blenders (5L, 30L, 50L, 200L and 600L) and 1 octagonal blender (30L). There was a machine for preparation of a pellet from



blend samples for containment and easy transportation. The integrity of pellet samples (in butter paper, poly bags and placed in a container) was validated and compared with other modes of packing and transporting hormonal samples.

- Compression machine (double rotary 75 station) had on line weight check (automatic PLC controlled), deduster and metal detector.
- There was a tablet Auto Coater with spray gun.
- There was one blister packing machine with a No-Fill Detector (NFD). This was challenged for various defects (missing tablets, different coloured tablet, broken tablet, interchanged position of different coloured tablets) during inspection and was found to be effective. It was noted that rejections were high. Rejected blisters were immediately defoiled and tablets collected for destruction without segregating reasons for rejection (classification of defects) to facilitate investigation in case of a deviation and designation of appropriate CAPA.
- Finished goods warehouse + distribution records
 - Set conditions were $22^{\circ}\pm 5^{\circ}\text{C}$ and NMT 60%RH and monitoring records indicated that these were under control.
- Validation Master Plan: Qualification, validation and calibration policies, schedules and status.
 - Sampling Technique for blend samples: Sampled from 10 locations and the following were evaluated:
 - Blend in butter paper.
 - Blend in a vial.
 - Compacted tablet in butter paper and polybag.
- Requalification/Monitoring the HVAC System
 - Operated in accordance with SOP which included the sequence for stopping and switching on AHUs for adjacent areas.
 - Filtration system was Fresh air filter (10μ), pre-filter ($10\mu = \text{G4}$), micro-filter ($5\mu = \text{F9}$) and terminal fine filter (HEPA, $0.3\mu = \text{H13}$).
 - All filters were monitored with magnehelic gauges of appropriate scale and limits. The G4 and F9 were cleaned weekly and fortnightly respectively with compressed air and portable water in a dedicated room.
 - Reviewed the report of last area qualification of the wet granulation area in the OCP area served by AHU 3.12. PQ followed ISO14644 guidelines under at rest conditions, though these conditions were not adequately and precisely defined. Instruments of adequate capacity and calibration were used.
- Equipment qualification/Requalification (DQ, IQ, OQ and PQ for selected equipment)
- Preventive maintenance schedules and records
- Calibration schedules and records
- Vendor Qualification
 - List of Approval Vendor reviewed biannual.
 - Were reviewed by sampling 5 entities files.
 - Since 2010 an Audit Vendor Plan was in place.

Day III; 09 September 2011

Inspectors provided feedback on the observations of the previous day. The company provided preliminary reaction on the wording of some deficiencies and it was agreed that this would be reviewed. The programme of the day was discussed and agreed upon.

Inspection of the following areas and activities followed:

- Inspection of the HVAC technical area.



- Physical status of AHUs (3.12, 3.4, 3.2, 3.7, EXU-V-2)); magnehelic gauges and limits; marking and labeling; balancing and damper positions; filter cleaning; preventive maintenance. There were no spare filters in stock.
- Wet scrubber for the Auto Coater.
- Hot air filtration and supply to the FBP and exhaust.
- Dust collector with a cartridge filter with a pneumatic shaker.
- Review of the Purified Water generation and distribution system
 - Requalification/Monitoring the PW system (Sampling and trend analysis)
 - Inspection of Water Generation and Purification System installations
 - Trend analyses of purified water system
 - Quarterly water system review April 2011 to June 2011
 - Cleaning overhead tank and records
- Review of the design and monitoring of the Compressed Air system
 - Inspection of the installations for Compressed Air with a refrigerated dryer and cartridge filter with a fitter at the point of use.
- Validation Master Plan
 - Qualification, validation and calibration policies, schedules and status.
 - Doc No. VMP/14, effective 20.05.2011
- Equipment qualification and preventive maintenance:
- Equipment qualification/Requalification (DQ, IQ, OQ and PQ for major equipment)
 - Rapid Mixer Granulator
 - Fluidized Bed Processor
- Preventive maintenance schedules and records 2010/2011
- Calibration schedules and records
 - Instrument Calibration Planner Unit II, 2011
 - QC Analytical Instrument calibration Calendar, 2011
- Validation
- Process validation and revalidation for the product in focus: protocols and reports.
 - Blister line validation: protocol and report.

The inspection of the following areas and aspects of quality control followed:

- Wet chemistry laboratory
- Instrumental laboratory
- Hot room with a fume cupboard.
- Glassware washing machine. It used raw water, RO water and 12% alkaline liquid cleaning agent at 25^o - 75^oC in a 1 hour 15 minutes washing cycle. All volumetric glassware was confirmed to be class A (e.g. certificates for Burette, pipette and volumetric flask were reviewed).
- Analyst training and competencies
- Sample receipt, storage and allocation
- Qualification, calibration, preventive maintenance
- Laboratory materials management (Samples, Reagents, Stock Solutions, Reference and Working Standards).
- Working standards:
 - Each time, 48 vials were prepared to last NMT 1 year and each vial was used within 15 days of opening.
 - Working standards were prepared from approved API batches. The batch was fully reanalysed, IR (Bruker attenuated total reflection - ATR), LOD, related substances, assay by two analysts each in duplicate (4 results, RSD NMT1.0%) and standardised against Ph.Eur and USP reference standards. Raw data was reviewed with no issues noted.
- Starting materials and finished products specifications, testing and release.
- Testing of Packaging Materials and Components



- Microbiological laboratory
 - Analyst training and competencies
 - 5 Microbiologist full-time (2 newly hired, July/August 2011)
 - 100% reviewed training records and qualification
 - Qualification, calibration, preventive maintenance 2010/2011
 - Facilities lay-out and flows, dress code and hygiene
 - Laboratory materials management
 - Media preparation and product testing
 - Organization, procedures, records and results
 - PW monitoring
 - Organization, procedures, records and results
- Review of BMRs/BPRs/Testing records - selected batches
- Stability testing programme (*Protocols, programme, records and data*)
 - Stability conditions 40⁰C/75%RH and 30⁰C/65%RH:
 - 3 batches of size 200,000 tablets completed up to 36m (22.11.2010) will continue up to 72m.
 - 3 batches of size 1,400,000 tablets completed up to 18m (28.07.2011) will continue up to 24m (27.01.2012).
 - Charging, withdrawal and testing records and results were reviewed with no major issues noted.
- Retention samples
 - With appropriate physical and technical conditions but with limited free space;

At the end of the day, the inspection team gave feedback on the observations of the day and preliminary conclusion on the entire inspection. The company presented preliminary reactions on the observation and conclusions which focused on some of the compliance actions they had either implemented or initiated. There was consensus on all the observations made and conclusions reached and the company gave commitment to address the deficiencies in a timely manner. The lead inspector thanked the company for the cooperation and closed the inspection activities.

2.1 QUALITY ASSURANCE

There were arrangements for evaluations and monitoring of the quality of the systems, procedures and products through self-inspection procedures and annual product reviews. There were procedures for equipment and systems qualification and validation of procedures and processes. There were written and approved procedures to investigate, assess the impact of and control changes, deviations and Out-of-Specification results. More emphasis needed to be placed on continuous maintenance and improvement of system. Noted issues were consequently resolved.

Product Quality Review

This was managed under an SOP. Compiling the product quality review report was the responsibility of QA. This covered the production anniversary and had to be completed within 60 days from the end of the anniversary. All the elements of the PQR were provided for in the SOP and it provided for graphical presentation of the data for analysis of trends.

Tabulated data showed variability in some parameters but these were not adequately evaluated using appropriate statistical tools. Statistical evaluation with appropriate tools has been incorporated in the revised SOP.



Change Control

There was system for handling changes including SOP, registers and forms for initiation, evaluation and approval of changes. Although the management of changes was generally satisfactory, some aspects of the change control documentation were not comprehensive.

Deviations

There were procedures, log for deviations and records of selected deviations were reviewed in detail. The procedures and documentation of deviations were generally acceptable but areas of weakness and fragmentation of documentation were noted. Training has been imparted of the staff concerned.

Out of Specification Results

The SOP on handling OOS was comprehensive and selected cases evaluated were appropriately handled. The SOP was not clear on which results to report after justified repeat analysis. There was a register for OOS and selected cases were reviewed and no matters of concern were noted.

2.2 GOOD MANUFACTURING PRACTICES (GMPs) FOR PHARMACEUTICAL PRODUCTS

Famy Care, Unit II had premises and equipment in a reasonable condition and systems had been designed and put in place to support the manufacture and control the quality of products under focus in compliance with good manufacturing practices. Attention, however, need to be paid to routine equipment and building maintenance especially the secondary areas and compiling of documentation and records. Evidence of appropriate renovations and maintenance of the areas has been provided.

2.3 SANITATION AND HYGIENE

Cleaning procedures for equipment and premises in place were adequate to enhance hygiene on the site. Personnel were trained on how to maintain good hygiene. There were comprehensive factory entrance and changing procedures.

Manufacturing areas, corridors and change room were cleaned. Attention needed to be paid to secondary area like receiving areas, external corridor and immediate factory environment. The design of some of the waste bins used in the production areas were not of the appropriate design as they had crevices that were acting as dust traps and difficult to clean. Appropriate corrective action has been taken and acceptable evidence provided.

2.4 QUALIFICATION AND VALIDATION

There was a Validation Master Plan (Doc No. VMP/14, effective 20.05.2011). It outlined the policy and approaches to be followed in qualification of equipment and validation of systems and processes. Appropriate protocols were followed and reports were compiled, although assembly of documents could be improved to facilitate logical review.

2.5 COMPLAINTS

The SOP on handling complaints provided for classification as critical, major and minor and response within 30 days. There was a system to record, investigate market complaints. This included a register and an investigation checklist which was comprehensive.



2.6 PRODUCT RECALLS

Recalls were guided by an SOP. The recall team included Head QA, Head QC, Head Production and Plant Head. Recalls were classified as I to IV and the responsibility to approve recall was vested in the Managing Director. The levels and timelines for the recall, means of communication and determinants for closing a recall were not defined. There was no provision for evaluating the effectiveness of the recall procedures, through a protocol for a mock recall has consequently been put in place. There had been no recall since the last WHO inspection.

2.7 CONTRACT PRODUCTION AND ANALYSIS

There was an SOP covering the procedure for developing agreements with contractors and a number of agreements with contractors were in place. These procedures needed to be strengthened in the minimum requirements for the contract and the means of communication between the parties in order to facilitate consistency.

2.8 SELF INSPECTION AND QUALITY AUDIT

There were procedures to conduct self-inspection at least twice a year for the purposes of monitoring the quality system and continuous improvement of the procedures. Provisions to ensure that the auditors were trained needed to be strengthened.

2.9 PERSONNEL

There were personnel with adequate skills and GMP consciousness of to perform the duties commensurate to the levels of activity in Unit II. The numbers were generally adequate but more engineering staff were required to strengthen preventive maintenance of equipment and premises.

Personnel were guided by an organisation chart and job descriptions. However, these needed to be regularly reviewed to reflect the managers who had oversight over both Units I and II and to ensure that they are complete and up-to-date.

2.10 TRAINING

Training procedures were found generally satisfactory. They provided for induction training, basic GMP training, on the job and SOP training and routine review of training needs and retraining. There was need to strengthen the design of the induction modules so they are version controlled and have reference to the quality system followed and also to include specific aspects on safety procedures related to hormones.

2.11 PERSONAL HYGIENE

Personnel were trained in personal hygiene procedure and facilities were provided in form of change rooms, protective garments and disinfectants.

2.12 PREMISES

Storage, production and testing activities for Unit II were located on the first floor. All storage, production and testing areas were accessed through primary changing rooms on the first floor where factory clothing was donned. A “No jewellery” policy was in force. The change procedure was displayed on the wall. The toilet and washing facilities were located such that staff and visitors could use them before changing into factory clothing. Factory clothes were washed by an outsourced laundry service.

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Production areas

There were two modules in Unit II, one for Oral Contraceptive Pills and the second one for General Placebo tablets. The design allowed unidirectional flow of activities (materials and personnel), from granulation, compression, coating, sorting, primary packaging and secondary packaging. Rooms were provided for quarantine of intermediate materials and IPQC. Different processing areas were segregated with material and personnel airlocks with monitored pressure differentials and allowing for the adequate flow of personnel and materials. There were independent dust extractors at or near the point of generation. At the exit point from the OCP area, there was an air shower to ensure hormone containment. The furniture in the production office was not appropriate for the area.

HVAC System

Most of the areas had independent AHUs to facilitate segregation and avoid cross contamination. The AHUs were located in and obtained their fresh air supply from the technical area which was supplied with filtered air. The inert and hormonal sections were connected with a bubble airlock pass-box with interlocking mechanism. The air to the pass box was supplied from the inert section and its pressure differential was monitored with a magnehelic gauge with set alert and action limits.

Water purification system

Source water was potable water from the GIDC which was collected in an underground tank of 18,000L and then pumped to an overhead RCC tank of 10,000L. It was then chlorinated using sodium hypochlorite and then filtered through a multi-grade sand filter (MGSF) to remove impurities, odour, suspended particles and colour. It was then de-chlorinated by dosing with sodium metabisulfate and then passed through a softener to remove heavy metals and minerals. The soft water was dosed with antiscalant to avoid scale formation on the RO surface, filtered through 10 μ and 5 μ filters then through double RO pass. The RO I reject was drained to the ETP while the RO II reject was re-circulated through RO I. The RO II permeate was transferred through a Rotameter to a 200 litres tank where its pH was adjusted to about 7.0 (5.0 - 7.0) by on line dosing with 1%NaOH (Dosing with 1% NaOH is prior to 10 μ filter) solution. The water was fed into the CEDI (regenerated continuously with electricity to remove charged ions) with an output with conductivity between 0.1 and 1.0 μ S/cm which was then sanitised with UV-I sanitizer to produce purified water which was stored in a sanitary heat jacketed SS316L 500L tank.

The water from this tank was sanitised using UV-II sanitizer and circulated through an SS316L closed loop that runs through Unit II and then Unit I. The return water was monitored on line for TOC, flow rate and conductivity and either damped or returned to the storage tank.

Minor issues were noted with records on monitoring system.

2.13 EQUIPMENT

There were adequate numbers of equipment for the production and testing products manufactured at the site. For tablet manufacturing, which was the focus of this inspection, these included vibratory sifters, Fluid Bed Processor, Multimill, Double cone blender, V-blender, Octagonal Blender, double rotary compression machines, metal detectors, dedusters, Auto-coater, Coating pan, tablets inspection belts, a blister packing equipment with an online NFD devices (camera) and batch coding printers. The product contact parts for all equipment were made up of SS316.

The QC laboratory had enough glassware for wet chemistry and other instruments like HPLCs, GCs, FTIR and UV/VIS spectrophotometer and Auto-Titrators.



The equipment reviewed were well designed, qualified and were regularly calibrated. Balances were calibrated and records of daily verification using standard weights were available. There were procedures and records for equipment use, cleaning and maintenance.

2.14 MATERIALS

There was a system for development, qualification, dequalification and requalification of vendors of Raw Materials and Packaging Materials. The system included site audits but needed to be improved to ensure consistency. A list of approved vendors existed and was always followed in procurement and receiving of materials reviewed. Records showed that raw materials were sourced from approved sources.

There was a checklist for document review and physical inspection of the consignment before offloading into the warehouse. All starting and packaging materials were tested and approved before they could be accepted for use.

There was adequate storage space and materials were stored in an orderly manner with appropriate status labelling. Separate stores, sampling and dispensing areas existed for hormones and non-hormonal raw materials. All containers (100%) were sampled for identity testing per container mainly by IR. The rest of the tests were performed of a composite sample, 1 for all excipients samples while up to 10 samples for actives.

The monitoring of retest dates of raw materials was reviewed and was operated using a manual system.

The hold time of intermediate material or products had been established. A batch of Lactose granules was on hold time study initiated on 30/05/2009. The last test date was 13/06/2011 and the next was 19/06/2012.

2.15 DOCUMENTATION

For product under review, there was a master formula, specification of starting and packaging materials, production and packaging instructions, batch processing and packaging records, finished product specifications, standard testing procedures and corresponding results. The documents carried a unique number and their documentation, change and retrieval were well controlled by the quality assurance department.

Issues related with comprehensiveness, review and assembly of some documents, records and reports were noted and needs improvement.

2.16 GOOD PRACTICES IN PRODUCTION

Production activities

Production activities in Unit II were in two modules:

In the general tablets area, dry powders were sifted, mixed, granulated with the appropriate solution in the fluid bed processor (FBP). The granulation room had several pieces of equipment which were not always used for the same batch at the same time. Issues of protection and cleaning of unused equipment were noted. Granules were dried in the processor, sized in the Multimill. Lubricated granules were then compressed and coated as required. This section had one 61-station compression machine. For lactose granules, the dried granules were blended with sifted lubricants in an FBP and then stored for use as excipients in blending with hormones in the Oral Contraceptive Pills (OCP) area.



In the OCP area, hormones were geometrically mixed with lactose granules in a double cone blender and the premix was blended with lactose granules and sifted lubricants in a double cone blender. The lubricated granules were then compressed and coated, as required. This section had one double rotary 75-station compression machine with on line weight check (automatic PLC controlled), de-duster and metal detector. Operators in areas where the product was exposed wore pressurised suits supplied with filtered breathing air. Blend samples were compacted into pellets for containment and easy transportation.

There were adequate procedures to ensure that materials of suitable quality were used in production. In-process checks were performed at appropriate stages.

Packaging

Tablets were packed in either Alu/PVC or Alu/PVdC blisters. The only blister packing machine in Unit II with a No-Fill Detector (NFD) camera was in the OCP section. This was challenged for various defects (missing tablets, different coloured tablet, broken tablet, interchanged position of different coloured tablets) during inspection and was found to be effective. It was noted that rejections were high. Rejected blisters were immediately defoiled and tablets collected for destruction without segregating based on reasons for rejection (classification of defects) to facilitate investigation in case of a deviation and designation of appropriate CAPA.

2.17 GOOD PRACTICES IN QUALITY CONTROL

There were quality control and quality assurance departments whose functions were independent of other units including production. Quality assurance department was involved in approving new vendors for starting and packaging materials and equipment.

The quality control laboratory had adequate facilities in form of space, equipment, reagents and chemicals to test all starting material, packaging materials, intermediates and finished products before release for use or distribution.

The documentation and records that support the different activities and routines seem appropriate to ensure the necessary traceability in their different perspectives.

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 Ltd, Unit II, located at 1608/1609, G.I.D.C, Sarigam, 396155 Valsad, 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

The WHOPIR is valid for a maximum of 3 years, unless the site is found to be non-compliant in another inspection before the 3 years had lapsed.