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Prequalification Team Inspection services
WHO PUBLIC INSPECTION REPORT
(WHOPIR)
Finished Product Manufacturer

Part 1	**General information**
Manufacturers details	
Company information	
Name of manufacturer	**Jai Pharma Limited** ***(Mylan Laboratories Limited)***
Corporate address of manufacturer	Jai Pharma Limited (Mylan laboratories Limited), 2nd Floor, Brady House ,Veer Nariman Road, Fort, Mumbai-400 001 Tel.: +91-22-30289655, Fax- +91-22-30289656 email: ho@jaipharma.in
Inspected site	
Address of inspected manufacturing site if different from that given above	Plot No.1606 to 1609, G.I.D.C, Sarigam, 396155 Valsad, Gujarat, India.
Unit / block / workshop number	Unit II
Manufacturing license number, (delete if not applicable)	G/25/1476 & G/28/1072
Inspection details	
Dates of inspection	12 to 15 April 2016
Type of inspection	Routine GMP inspection
Introduction	
Brief summary of the manufacturing activities	Coated and Uncoated Tablets with focus on Reproductive Health products (Oral Contraceptives and support placebos).
General information about the company and	The facility inspected was Unit II of Jai Pharmaceutical Limited, located at Plot No.1606 to 1609 , G.I.D.C, Sarigam, 396155 Valsad, Gujarat, INDIA, was previously known as Famy Care, Sarigram. The manufacturing facility is located at Sarigam (State

site	of Gujarat), about 19 km from Vapi railway station, and approximately 170 km from Mumbai International Airport. The facility had dedicated and segregated manufacturing areas for oral contraceptive & inert tablets, including warehouses for raw material, packaging material, and finished goods.
History	The manufacturing site had been inspected by WHO-PQT since April 2009, and this was the fifth WHO-PQT inspection.
Brief report of inspection activities undertaken	
Scope and limitations	
Areas inspected	Production and control of coated and uncoated tablets with focus on reproductive health products (Oral contraceptives and support placebos).
Restrictions	none
Out of scope	none
WHO product numbers 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

Abbreviations

AHU	air handling unit
ALCOA	attributable, legible, contemporaneous, original and accurate
API	active pharmaceutical ingredient
APQR	annual product quality review
BDL	below detection limit
BMR	batch manufacturing record
BPR	batch packaging record
CAPA	corrective actions and preventive actions
CC	change control
CFU	colony-forming unit
CoA	certificate of analysis
CpK	process capability index
DQ	design qualification
EM	environmental monitoring
FAT	factory acceptance test
FBD	fluid bed dryer
FMEA	failure modes and effects analysis
FPP	finished pharmaceutical product
FTA	fault tree analysis
FTIR	Fourier transform infrared spectrometer
GC	gas chromatograph
GMP	good manufacturing practice
HACCP	hazard analysis and critical control points
HPLC	high-performance liquid chromatograph
HVAC	heating, ventilation and air conditioning

IR	infrared spectrophotometer
IQ	installation qualification
KF	Karl Fisher
LAF	laminar air flow
LIMS	laboratory information management system
LoD	limit of detection
LOD	loss on drying
MB	microbiology
MBL	microbiology laboratory
MF	master formulae
MR	management review
NMR	nuclear magnetic resonance spectroscopy
NRA	national regulatory agency
OQ	operational qualification
PHA	process hazard analysis
PM	preventive maintenance
PpK	process performance index
PQ	performance qualification
PQR	product quality review
PQS	pharmaceutical quality system
QA	quality assurance
QC	quality control
QCL	quality control laboratory
QRM	quality risk management
RA	risk assessment
RCA	root cause analysis
SOP	standard operating procedure
TAMC	total aerobic microbial count
TFC	total fungi count
TLC	thin layer chromatography
URS	user requirements specifications
UV	ultraviolet-visible spectrophotometer

Part 2	Brief summary of the findings and comments (where applicable)

Brief summary of the findings and comments

1. Pharmaceutical quality system

The implementation of quality system was in general satisfactory; however a number of specific deficiencies were observed and listed under Part 5, observations. Production and control operations were specified in written form and GMP requirements were generally followed. Managerial responsibilities were specified in job-descriptions. The organization chart was available and reviewed.

The actions taken or proposed to be implemented have been reviewed by the inspectors, and these were found to be acceptable. Their satisfactory implementation will be verified during future inspections.

2. Good manufacturing practices for pharmaceutical products

Good manufacturing practices generally were implemented. The necessary resources were provided. Materials were received following written procedures and controls. Materials were sampled and approved by the Quality Unit before being used in Production. The Quality Unit was separate from the Production Department. Overall, warehousing facilities were adequate. Manufacturing and packaging operations were conducted according to written procedures. Manufacturing and packing processes were clearly defined and systematically reviewed. QC laboratories were suitably equipped with the required instrumentation. Instruments and manufacturing equipment were qualified and validated. Operators were trained to carry out procedures correctly, and records of training were kept.

The actions taken or proposed to be implemented have been reviewed by the inspectors, and these were found to be acceptable. Their satisfactory implementation will be verified during future inspections.

3. Sanitation and hygiene

While inspecting production areas, it was noted that there was no hand washing facility provided for the visitors and staff after exiting from the production area except air shower.

The actions taken or proposed to be implemented have been reviewed by the inspectors, and these were found to be acceptable. There satisfactory implementation will be verified during future inspections.

4. Qualification and validation

The key elements of a qualification and validation programme were defined and documented in a validation master plan. The Validation Master Plan was available which described company's philosophy for the qualification and validation of process. Currently, the company uses prospective and concurrent validation approach taking three batches.

The actions taken or proposed to be implemented have been reviewed by the inspectors, and these were found to be acceptable. Their satisfactory implementation will be verified during future inspections.

5. Complaints

There were no changes made to complaint procedure since the last WHO inspection. It was also noted that the company did not receive any complaint for any of the WHO prequalified products since the last WHO inspection.

6. Product recalls

The SOP for product recall was briefly reviewed and noted that there were some changes made in the procedure related to recall committee, objective/scope redefined, flow chart of recall incorporated and mock recall

procedure was included. It was noted that there was no recall conducted from this site, whereas mock recall was conducted for European market (Netherland) in December 2015. No mock recall was undertaken from any of the African markets despite the product was marketed there. The protocol for mock recall (Myanmar market) dated 6/4/2016 was available.

7. Contract production, analysis and other activities

The GMP agreement between Stada Germany and Mylan was briefly sighted dated 20/8/2011, which specified responsibility of market complaints and recall rested with Stada whereas evaluation of complaints was the responsibility of Mylan. There was no validity established for the contact. Technical agreement between Teva Netherland dated 6 Feb 2013 was available which specified the responsibility of market complaint and recall with Teva whereas Jai Pharma provided a supporting role. It was noted that there was no technical contract available between Jai Pharma and clients of African countries (any of the African markets) as Jai Pharma was the MAH. Therefore, responsibility to recall product rested with Jai Pharma.

8. Self-inspection, quality audits and suppliers' audits and approval

This was not reviewed during this inspection.

9. Personnel

It appeared from the review of several documents and inspection of several areas, there were insufficient qualified personnel to carry out the tasks for which the manufacturer was responsible. The training records of these two staff were also reviewed for compression training and were trained in January 2016. Job descriptions/duty statements of QC Head/QA Head/Production Head/Senior Manager QC and Section Head of Finished Products testing area were reviewed. The documents were satisfactory. However, the responsibility of OOS investigations was missing from the Production Head job description and responsibility of managing contract testing was missing from the QC Head job description.

The actions taken or proposed to be implemented have been reviewed by the inspectors, and these were found to be acceptable. Their satisfactory implementation will be verified during future inspections.

10. Training

Training procedure was reviewed and found to be satisfactory. After induction, training of staff became the responsibility of individual areas, where recruited staff ended up working. On-job training started with questionnaire. If the score was less than 80%, retraining was imparted. This was followed by hands –on training. cGMP training was run at twice a year or as needs basis. For contractors, cGMP was provided in Hindi then further training became the responsibility of specific areas to which staff were assigned.

The actions taken or proposed to be implemented have been reviewed by the inspectors, and these were found to be acceptable. Their satisfactory implementation will be verified during future inspections.

11. Personal hygiene

Appropriate gowning was provided for the staff and visitors, and air shower was provided for the personnel before leaving the production area. This area was generally considered acceptable with some minor issues observed during inspection.

12. Premises

In general the buildings and facilities used for manufacture and quality control were located, designed, and constructed to facilitate proper cleaning, maintenance and production operations. It is a dedicated facility for hormone tablet manufacturing, and a separate facility for inert & Ferrous Fumarate tablet manufacturing was part of the same site. Quality control laboratories were separated from production areas.

The Unit-II was comprised of first and second floor wherein QC, manufacturing and store was located on the first floor and QA and store was located on the second floor.

The actions taken or proposed to be implemented have been reviewed by the inspectors, and these were found to be acceptable. Their satisfactory implementation will be verified during future inspections.

13. Equipment

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. Equipment in production area were non-dedicated.

The actions taken or proposed to be implemented have been reviewed by the inspectors, and these were found to be acceptable. Their satisfactory implementation will be verified during future inspections.

14. Materials

In production, dispensed starting material and intermediate products were identified during the different production stages using proper labels that include the identity and status of each material or product. Materials were obtained from approved suppliers.

Vendor audit report was reviewed and noted that it was audited on 22-23 September 2014 for Levonorgestrel and Norgestrel. While inspecting APIs approved storage area, it was noted that Levonorgestrel from API manufacturer was being used by the site for non-WHO products. This API manufacturer was declared non-compliant after the WHO-PQT inspection.

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 laid out in an orderly fashion and were easy to check. Reproduced documents were clear and legible.

Most of the SOPs and other documents reviewed during the inspection had 3 years review period in comparison to the usual industry practice of 2 years.

The actions taken or proposed to be implemented have been reviewed by the inspectors, and these were found to be acceptable. Their satisfactory implementation will be verified during future inspections.

16. Good practices in production

In general, raw materials for manufacturing of tablet were dispensed, processed, packaged and distributed under appropriate conditions. Actual yields were compared with expected yields at designated steps in the production process. Processing status of operation room was labelled with product names and batch numbers. In-process controls were performed by QC analysts. Manufacturing areas were accessed through secondary change rooms.

Separate areas for staging, sifting, binder preparation, granulation, washing, blending, compression, coating and inspection. IPQC area was equipped with all essential equipment /instruments for in process checks. Separate storage area for blend and bulk tablets was available, also separate areas was provided for primary packing and secondary packing. All core manufacturing, sampling and dispensing areas were as per ISO 8 classification and with dedicated air handling units to maintain temperature, relative humidity, pressure differential with plenum HEPA filter and terminal HEPA filter.

The temperature/relative humidity of the processing area was set to 21±4°C / NMT 55% whereas 22±5°C / NMT 60% was set for the non-processing areas such as corridors, quarantine store and secondary packaging areas. The corridor was set to positive with respect to atmosphere and differential pressure limit of 10-40pa was set for the processing and primary packaging areas including alert and action limit.

During inspection of OCP production area, it was noted that operators were provided with bunny suits and compressed air was used for pressing suits. These pressing suits were cleaned once every 5 days and face masks were replaced weekly and or change in person. Excipients were received from a separate pass-box to day store whereas a separate pass-box was provided for lactose granules. Lactose granules were produced on site in an inert manufacturing area and transferred to production through pass-box. Wet granulation was not used for any of the products produced on site. The production area was equipped with double cone blender, sifter, compression, and coaters. The area had three blister packaging lines.

The actions taken or proposed to be implemented have been reviewed by the inspectors, and these were found to be acceptable. Their satisfactory implementation will be verified during future inspections.

17. Good practices in quality control

The quality control lab consists of a chemistry section and a microbiology section, and was fully equipped with HPLC, FTIR, UV-VIS, analytical balances. The HPLC systems were operated using Empower-3 through network system. Since the last WHO inspection, the site had purchased two HPLC (Make: Waters), new autoclave in microbiology and new bio-safety cabinet installed in microbiology.

The actions taken or proposed to be implemented have been reviewed by the inspectors, and these were found to be acceptable. Their satisfactory implementation 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, *Jai Pharma, Sarigram, Unit II, Plot No. 1606 to 1609, G.I.D.C, Sarigam, 396155 Valsad, Gujarat, India* was considered to be operating at an acceptable level of compliance with WHO good manufacturing Practices for pharmaceutical products.

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.

PART 4
List of GMP guidelines referenced in the inspection

1. WHO good manufacturing practices for pharmaceutical products: main principles. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-eight Report Geneva, World Health Organization, 2014 (WHO Technical Report Series, No. 986), Annex 2. http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_986/en/
2. WHO good manufacturing practices for active pharmaceutical ingredients. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth Report. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957), Annex 2. http://www.who.int/medicines/publications/44threport/en/
3. WHO Good Manufacturing Practices: water for pharmaceutical use. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fourth-six Report. Geneva, World Health Organization, 2012 (WHO Technical Report Series, No. 970), Annex 2 http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_970/en/
4. WHO guidelines for sampling of pharmaceutical products and related materials. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-ninth Report. Geneva, World Health Organization, 2005 (WHO Technical Report Series, No. 929), Annex 4 http://whqlibdoc.who.int/trs/WHO_TRS_929_eng.pdf?ua=1
5. WHO guidelines on good manufacturing practices for heating, ventilation and air-conditioning systems for non-sterile pharmaceutical dosage forms. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 5 http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1
6. Supplementary guidelines on good manufacturing practices: validation. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fortieth Report. Geneva, World Health Organization, 2006 (WHO Technical Report Series, No. 937), Annex 4 http://whqlibdoc.who.int/trs/WHO_TRS_937_eng.pdf?ua=1
7. WHO Good Practices for Pharmaceutical Quality Control Laboratories. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth Report. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957, Annex 1 http://www.who.int/medicines/publications/44threport/en/

8. WHO Good Practices for Pharmaceutical Products Containing Hazardous Substances. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth Report. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957), Annex 2 http://www.who.int/medicines/publications/44threport/en/
9. WHO good manufacturing practices for sterile pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 6 http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1
10. WHO guidelines on transfer of technology in pharmaceutical manufacturing WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 7 http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1
11. Model guidance for the storage and transport of time-and temperature-sensitive pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 9 http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1
12. General guidelines for the establishment maintenance and distribution of chemical reference substances. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-First Report Geneva, World Health Organization 2007 (WHO Technical Report Series, No.943) Annex 3 http://whqlibdoc.who.int/trs/WHO_TRS_943_eng.pdf?ua=1
13. WHO good practices for pharmaceutical microbiology laboratories. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 2 http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1
14. WHO guidelines on quality risk management. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Seventh Report Geneva, World Health Organization, 2013 (WHO Technical Report Series, No. 981), Annex 2 http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_981/en/
15. WHO guidelines on variation to a prequalified product. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Seventh Report Geneva, World Health Organization, 2013 (WHO Technical Report Series, No. 981), Annex 3 http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_981/en/
16. WHO guidelines for drafting a site master file. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 14 http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1
17. WHO Guidelines on good manufacturing practices: validation, Appendix 7: non-sterile process validation. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Ninth Report Geneva, World Health Organization, 2015 (WHO Technical Report Series, No. 992), Annex 3 http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf
18. WHO General guidance on hold-time studies WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Ninth Report Geneva, World Health Organization, 2015 (WHO Technical Report Series, No. 992), Annex 4

http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf

19. WHO Technical supplements to Model Guidance for storage and transport of time – and temperature – sensitive pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Ninth Report Geneva, World Health Organization, 2015 (WHO Technical Report Series, No. 992), Annex 5 http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf
20. WHO Recommendations for quality requirements when plant – derived artemisin is used as a starting material in the prosecution of antimalarial active pharmaceutical ingredients. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Ninth Report Geneva, World Health Organization, 2015 (WHO Technical Report Series, No. 992), Annex 6 http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf
21. WHO good manufacturing practices for biological products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifties Report Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 3 http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex03.pdf
22. Guidance on good data and record management practices. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifties Report Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 5 http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex05.pdf
23. WHO general guidance on variations to multisource pharmaceutical products. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifties Report* Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 10 http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex10.pdf
24. WHO good manufacturing practices for biological products. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifties Report* Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 3 http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex03.pdf