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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 Pharmaceutical 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 20 & 21, Pharmez Sarkhej-Bavla National Highway No. 8A, Near Village Matoda, Taluka: Sanad, Dist. Ahmedabad, 382 213, Gujarat, India
Unit / block / workshop number	Oral contraceptive and general blocks
Manufacturing license number, (delete if not applicable)	G/25/1842 (General Products) and G/28/1297 (Oral Contraceptive Products)
Inspection details	
Dates of inspection	18-21 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 manufacturing facility of Jai Pharma Limited, located at Plot No 20 & 21, in PHARMEZ, Pharmaceuticals Special Economic Zone, Sarkhej-Bavla, NH No 8A, Near Village Matoda, Tal. Sanand, District Ahmedabad – 382213, Gujarat, INDIA was

site	inspected by WHO under its Prequalification of Medicines Programme from 18 – 21 April 2016.
History	The manufacturing site was first inspected by WHO-PQT in September 2012, and this was the second WHO-PQT inspection.
Brief report of inspection activities undertaken	
Scope and limitations	
Areas inspected	Production and controls 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. **RH031** Levonorgestrel Tablet 1.5mg 2. **RH032** Levonorgestrel Tablet 750mcg 3. **RH037** Desogestrel/Ethinylestradiol Tablet 0.150mg/0.030mg 4. **RH038** Ethinylestradiol/Levonorgestrel + Ferrous Fumarate Ethinylestradiol/Levonorgestrel Tablet + Placebo (Ferrous Fumarate Tablet) 30mcg/150mcg + 75mg 5. **RH049** Desogestrel/Ethinylestradiol + Placebo Desogestrel/Ethinylestradiol Tablet + Placebo Tablet 150mcg/30mcg + 0mcg 6. **RH057** Levonorgestrel Tablet, Film-coated 0.03mg (under assessment)

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

There was a QA department responsible for the quality assurance system headed by the Sr. Vice President, CQA who was supported by the site QA Head and QA Manager. In general PQS was implemented. Production and control operations were specified in written form and GMP requirements were generally followed. Managerial responsibilities were specified in job-descriptions. Product and processes were monitored and the results taken into account in batch release and regular reviews of the quality of pharmaceutical products were conducted. Periodic management reviews were performed.

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.

2. Good manufacturing practices for pharmaceutical products

In general good manufacturing practices were implemented. The necessary resources were generally provided. Qualification and validation were performed. Significant deviations were recorded and investigated. Records covering manufacture and distribution, which enabled the complete history of a batch to be traced, were retained.

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

Premises and equipment were maintained at acceptable level of cleanliness. The scope of sanitation and hygiene covered personnel, premises, equipment and apparatus, production materials and containers, products for cleaning and disinfection.

4. Qualification and validation

The key elements of a qualification and validation program were defined and documented in the Validation Master Plan (VMP). The procedures for vendor Qualification, Validation Master Plan, Process validation protocol and the procedure Process Validation were reviewed. The Production Validation developed in Ahmedabad (R&D) was correctly transferred to the manufacture site and was used to support the validation of ~~three~~ different markets (Europe, WHO, R.O.W., US, Australia, Canada, India).

5. Complaints

A procedure for handling complaints was in place. It was noted that assessment of complaints related to counterfeits was included in the revised procedure. Trending of complaints for 2015 was reviewed. Majority of the complaints were for missing components. It was noted that some of the corrective actions had already been implemented as part of the complaint investigation; however risk assessment had not been initiated as yet.

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.

6. Product recalls

There was no product recall in year 2015 and 2016. It was noted that mock recall from Germany market was made (as noted during Sarigram inspection) but there was no mock recall conducted from African markets where product was primarily distributed.

7. Contract production, analysis and other activities

Not inspected

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

Procedure for self-inspection was reviewed and noted that self-inspections were carried out twice in a year by a cross functional team of experienced auditors (who had minimum of 5 year experience).

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.

9. Personnel

Individual responsibilities were clearly defined and recorded as written descriptions. Personnel were aware of the principles of GMP received initial and continuing training, including hygiene instructions. The Organogram presented was approved and dated, Site QA Head, QA Manager and Site QC Head reported to the Sr.Vice President CQA.

There were insufficient personnel with appropriate experience and skills in QC & QA areas, which led to ineffective review of documents, investigation and root cause as evident from several examples.

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 in accordance with written programmes was provided for all personnel involved in manufacturing areas and control laboratories as well as for technical, maintenance and cleaning personnel. Besides basic training on the theory and practice of GMP, newly recruited personnel received training appropriate to the duties assigned to them. Training was given continually and its practical effectiveness periodically assessed. Approved training programmes were available. Training records were kept.

11. Personal hygiene

This area was generally considered acceptable.

12. Premises

Premises were laid out in such a way as to allow the production to take place in areas connected in a logical order corresponding to the sequence of the operations and to the requisite cleanliness levels and allowed logical positioning of equipment and materials. In general where starting and primary packaging materials and intermediate or bulk products were exposed to the environment, interior surfaces were smooth and free from cracks and open joints, did not shed particulate matter, and permitted easy and effective cleaning. Production areas were effectively ventilated.

Rest and refreshment rooms were separate from manufacturing and control areas. Facilities for changing and storing clothes and for washing and toilet purposes were easily accessible and appropriate for the number of users.

The Quality Control laboratories (including physico-chemical and microbiology laboratory, stability chambers, retention sample room and the auxiliary areas) were situated away from production areas.

13. Equipment

Equipment was located, designed, constructed, adapted and maintained to suit the operations to be carried out. 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. Current drawings of critical equipment and support systems were maintained.

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

The material management records were paper based

The procedure for return of excess packing material to packing material store described procedure for return of primary and secondary packaging materials from the production area to warehouse.

The SOP for receipt and handling of excess returned packaging materials from production described procedure for handling of excess packing materials i.e. printed packaging materials such as cartons, leaflets, catch covers in intact packs. The left over loose quantity were destroyed by the production department.

15. Documentation

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

The procedure Document Control was in place and described the purpose, scope and responsibilities as well how to prepare, review, approve, distribute, control, revise, archive and destroy the quality documents.

16. Good practices in production

In general production operations followed defined procedures. Deviations from procedures were recorded and investigated. Checks on yields and reconciliation of quantities were carried out. Materials, bulk containers, major items of equipment, rooms and packaging lines being used, were labelled to identify the product or material being processed and the batch number. Access to production premises was restricted to authorized personnel. In-process controls were performed by operators and discussed by workshop QA within the production area. Friability test, hardness, weight variation and disintegration tests were carried out in IPC laboratory. To minimizing the risk of cross-contamination and mix- ups, only one product was manufactured in the OSD workshop at a time.

In general, the production facility was maintained clean and tidy.

17. Good practices in quality control

The QC function was independent from other departments. QC personnel had access to production areas for sampling and investigations if required.

The laboratory had sufficient staff for the microbiology, physical & chemical testing of finished product analysis. A monthly trend summary in graphical presentation was carried out taking pH, conductivity, TOC and total microbial counts. The alert and action limits were set for these parameters.

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 Limited, Plot No 20 & 21, Pharmez, Village: Matoda, Taluka: Sanad, District: Ahmedabad, 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