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Prequalification Team Inspection services
WHO PUBLIC INSPECTION REPORT
(WHOPIR)
Desk Assessment of Finished Pharmaceutical Product (FPP) Manufacturer

Part 1	**General information**	
Company information		
Name of Manufacturer	Mylan Laboratories Limited	
Corporate address of manufacturer	Mylan Laboratories Limited Plot No. 564/A/22, Road No. 92, Jubilee Hills, Hyderabad - 500 034, Telangana, India Telephone Number: +91-40-30866666, 23550543 Fax Number: +91-40-30866699 *Site: www.mylanlabs.in*	
Inspected site		
Name & address of manufacturing site	Mylan Laboratories Limited, Ahmedabad Sarkhej- Bavla NH No- 8A, Plot No 20/21 Pharmaceutical Special Economic Zone, Nr Village Matoda, Ahmedabad, Gujarat, 382213, India D-U-N-S 677604150, latitude 22.874 N, longitude 72.402 E	
Production Block/Unit	Injectables (by terminal autoclave sterilization) and OSDs (Oral Solid Dosage forms)	
Desk assessment details		
Date of review	5 March 2019	
Products covered by this desk assessment	Oral and injectable contraceptives. Specific products assessed: 1. Levonorgestrel Tablet 1.5mg 2. Levonorgestrel Tablet 750 mcg 3. Desogestrel/Ethinylestradiol Tablet 0.150mg/0.030mg 4. Ethinylestradiol/Levonorgestrel + Ferrous Fumarate Ethinylestradiol/Levonorgestrel Tablet + Placebo (Ferrous Fumarate Tablet) 30mcg/150mcg + 75mg 5. Desogestrel/Ethinylestradiol + Placebo Desogestrel/Ethinylestradiol Tablet + Placebo Tablet 150mcg/30mcg + 0mcg 6. Levonorgestrel Tablet, Film-coated 0.03mg 7. Medroxyprogesterone acetate Suspension for injection 150mg/ml	
Part 2	**Summary of SRA/NRA inspection evidence considered (from most recent to last)**	
US FDA	Dates of inspection:	23-29 August 2017
	Type of inspection:	Pre-approval inspection
	Block/Unit:	Main production block section for injectable products
	Type of products/Dosage forms covered:	Small volume parenterals
US FDA	Dates of inspection:	20-24 November 2017

	Type of inspection:	Routine
	Block/Unit:	Not specified
	Type of products/Dosage forms covered:	OSDs
Part 3	**Summary of the last WHO inspection**	
Date and conclusion of most recent WHO inspection	18-21 April 2016 for the manufacturing of OSDs only. Compliant 3-6 September 2012 for the manufacturing of OSDs only. Compliant	
Brief description of manufacturing activities	Coated and Uncoated Tablets with focus on reproductive health products (Oral Contraceptives and support placebos).	
General information about the company and manufacturing site	According to the SMF, Mylan Laboratories Limited is the Indian Subsidiary of Mylan Inc., USA, which is World's 3rd largest generics and specialty Pharma Company. Mylan Inc., USA was founded in 1961 and has Corporate Headquarters at Pittsburgh, Pennsylvania, United States. Mylan Inc., USA has primary businesses in following areas - • Generic Pharmaceuticals and Branded Generic Formulations • Specialty and Brand Pharmaceuticals • Active Pharmaceutical Ingredients Mylan Inc. is one of the world's leading quality generic and highest quality product portfolios, product pipeline and a global commercial footprint through operations in North America, EMEA and APAC. Mylan Laboratories Limited, Ahmedabad is engaged in manufacturing of medicinal products solid orals [Hormonal and Non-Hormonal Tablets] and Injectable formulations (Terminally sterilized suspensions). The facility was commissioned in 2009 as part of Famy Care Ltd. In the month of May 2015, Famy Care has demerged its female contraceptive business into "Jai Pharma Limited". Mylan acquired the Famy Care's female contraceptive business in November 2015. On 20th November 2015, Jai Pharma Limited became part of "Mylan Laboratories Limited". Presently, Mylan Laboratories Limited, Ahmedabad is supplying medicines to the Government of India, for its National Family Welfare program and is exporting its products to countries in North America, South America, Europe, Africa, Asia and Australia. The Ahmedabad site is accessible by road, railway & Air and is about 450 km towards north of Mumbai, on Ahmedabad-Rajkot highway and is approximately 42 km far from the Ahmedabad airport. The site is located in Pharmez, (The Pharmaceutical Special Economic Zone) with surrounding units engaged in manufacturing of only Pharmaceuticals Formulations Units. Access to the plot is through a security gate, which is manned 24 hours by trained security personnel. The plant is designed to manufacture hormonal tablets, nonhormonal tablets and small volume parenteral.	
Focus of the last WHO inspection	OSDs (with a focus on reproductive health products)	

Areas inspected	The inspection focused on the production and control of finished pharmaceutical products as listed under Part 1. 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.
Out of scope and restrictions (last WHO inspection)	Products that are not under PQ, including injectables
WHO products covered by the last WHO inspection	Coated and Uncoated Tablets : 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 at the time of the inspection)
Additional products covered by this desk assessment:	RH074
Abbreviations	**Meaning**
API	Active pharmaceutical ingredient
BMR	Batch manufacturing record
BPR	Batch production record
CAPA	Corrective and preventive action
CC	Change control
GMP	Good manufacturing practices
NC	Non conformity
NRA	National regulatory agency
PQR	Product quality review
PQS	Pharmaceutical quality system
QA	Quality assurance
QC	Quality control
QCL	Quality control laboratory
QMS	Quality management system
QRM	Quality risk management
RA	Risk assessment
RCA	Root cause analysis
SOP	Standard operating procedure
SMF	Site master file

Part 4	Summary of the assessment of supporting documentation

a) Manufacturing authorization and GMP certificate granted by the local authority:
Reviewed and considered acceptable.

b) Site master file (SMF):
The SMF dated 13 February 2019, was reviewed and is considered acceptable.

c) List of regulatory inspections performed in the last 5 years and their outcome:
The company declared that the site was inspected by the following authorities:
1. Health Authority Agency – Sudan. July 2018. In compliance
2. USFDA (OSD) – Jan 2018. In compliance
3. USFDA (Injectable) – June 2018. In compliance
4. Health care Inspectorate, Netherlands – April 2018. In compliance
5. Taiwan FDA – June 2017. In compliance
6. Berlin Authority, Germany – February 2016. In compliance
7. USFDA (OSD) – October 2014. In compliance
8. Health care Inspectorate, Netherlands – April 2014. In compliance

d) List of all the products and dosage forms manufactured on-site:
The list of products manufactured on site is acceptable and does not raise particular concerns with regards to potential cross-contamination. In the injectable facility, only medroxyprogesterone acetate injectable suspension is manufactured. In the OSD division, only tablets containing female generic hormones for human use are being produced at the site. It did not include any veterinary products.

e) Most recent product quality review(s) (PQR)(s) of the concerned WHO product(s):
No PQR is available as of yet for the RH074 product as only regulatory batches were manufactured. PQRs were submitted for the prequalified OSD products, namely: RH031, RH032, RH037, RH038, RH049 and RH057. The following PQRs were reviewed:
-For RH057: individual PQRs were submitted for the bulk product and for different finished product codes of the Product Levonorgestrel Tablets 0.03 mg. The PQR for the product destined to the Rwanda and Papua New Guinea market was reviewed. It was for the review period of January 2017-December 2017. It included a review of OOS, OOT, CPPs, in-process controls and finished product results, stability data, change controls, validation, returns, complaints, recalls, regulatory, review of open items for the previous PQR. It did not include a review of the utilities. The PQR for the bulk product was also reviewed and include supplementary sections (review of starting materials and packaging materials, review of the qualification status of relevant equipment and facility/utility, quality/technical agreements). This was considered acceptable overall.

f) Batch manufacturing and packaging record(s), including the analytical part, for the most recently released batch of relevant product(s):
An executed batch record was provided for the medroxyprogesterone acetate batch, manufactured 08 2018. It was released on 21/09/2018 and the quantity manufactured was 1,489 packages of 25 vials each (37,225 vials in total). It covered manufacturing by autoclave sterilization in a 250 L CIP vessel using sterile API (gamma irradiated by the supplier). This is close to the final commercial batch size of 50L/41,666 vials that is proposed for the commercial manufacturing process for WHO (same size as used for the biostudy/stability and process validation studies).

g) Recalls in the past three years related to products with quality defects:
The company provided a declaration on the absence of recalls in the last 3 years for PQ products. There were 2 class III (voluntary) recalls on the US market. Adequate corrective and preventive actions were made further to those recalls.

i) Confirmation by the senior quality assurance representative that a full self-inspection or external audit dedicated to the product(s) has been performed and all matters dealt with:
The declarations were provided for all WHO prequalified products. It stated that self-inspections are conducted every 6 months and all issues reported to senior management were handled through the QMS and closed. This is considered acceptable.

j) copy of any warning letter, or equivalent regulatory action, issued by any authority to which the site provides or has applied to provide the product:
A declaration was provided that no warning letter or equivalent regulatory action was taken by any regulatory authority for products supplied by Mylan.

k) Out-of-stock situations:
The company submitted a declaration that out-of-stock events for medroxyprogesterone acetate injectable suspension USP 150 mg/mL shall not be more than 0.1%. It also briefly described measures taken to avoid out of stock situations.
This declaration was also submitted for the OSDs RH031, RH032, RH037, RH038, RH049 and RH057 and considered acceptable.

l) Additional documents submitted:
Not applicable.

Part 5	**Conclusion – Desk assessment outcome**

Based on the previous WHO inspections and on the GMP evidence received and reviewed, it is considered that a desk assessment is acceptable in lieu of a WHO onsite inspection. The site ***Mylan Laboratories Limited, Sarkhej*** is considered to be operating at an acceptable level of compliance with WHO GMP guidelines.

This WHOPIR will remain valid for 3 years, provided that the outcome of any inspection conducted during this period is positive.

Part 6	List of guidelines referenced in this inspection report

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. ***Short name: WHO GMP Guidelines*** or ***TRS 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. ***Short name: WHO GMP for APIs*** or ***WHO TRS No. 957, Annex 2***
   http://apps.who.int/medicinedocs/documents/s20119en/s20119en.pdf

3. WHO guidance on good practices for desk assessment of compliance with good manufacturing practices, good laboratory practices and good clinical practices for medical products regulatory decisions. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-second Report. Geneva, World Health Organization, 2018 (WHO Technical Report Series, No. 1010), Annex 9. ***Short name: WHO TRS 1010, Annex 9***
   https://www.who.int/medicines/areas/quality_safety/quality_assurance/TRS1010annex9.pdf?ua=1

4. WHO Good Manufacturing Practices: water for pharmaceutical use. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fourth-sixth Report. Geneva, World Health Organization, 2012 (WHO Technical Report Series, No. 970), Annex 2.
   Short name: WHO TRS No. 970, Annex 2
   http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_970/en/

5. 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.
   Short name: WHO TRS No. 929, Annex 4
   http://whqlibdoc.who.int/trs/WHO_TRS_929_eng.pdf?ua=1

6. Guidelines on heating, ventilation and air-conditioning systems for non-sterile pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty Second Report Geneva, World Health Organization, 2018 (WHO Technical Report Series, No. 1010), Annex 8. ***Short name: WHO HVAC Guidelines*** *or* ***WHO TRS No. 1010, Annex 8***
   http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_1010/en/

7. 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.
   Short name: WHO TRS No. 937, Annex 4
   http://whqlibdoc.who.int/trs/WHO_TRS_937_eng.pdf?ua=1

8. 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.
   Short name: WHO GPPQCL guidelines* or *WHO TRS No. 957), Annex 1
   http://www.who.int/medicines/publications/44threport/en/

9. 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.
   Short name: WHO TRS No. 957, Annex 2
   http://www.who.int/medicines/publications/44threport/en/

10. 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.
    Short name: WHO TRS No. 961, Annex 6
    http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

11. 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.
    Short name: WHO TRS No. 961, Annex 7
    http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

12. 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.
    Short name: WHO TRS No. 961, Annex 9
    http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

13. 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.
    Short name: WHO TRS No. 943, Annex 3
    http://whqlibdoc.who.int/trs/WHO_TRS_943_eng.pdf?ua=1

14. 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.
    Short name: WHO TRS No. 961, Annex 2
    http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

15. 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.
Short name: WHO TRS No. 981, Annex 2
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_981/en/

16. 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. ***Short name: WHO TRS No. 981, Annex 3***
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_981/en/

17. 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. ***Short name: WHO TRS No. 961, Annex 14***
http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

18. 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.
Short name: WHO TRS No. 992, Annex 3
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf

19. 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.
Short name: WHO TRS No. 992, Annex 4
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf

20. 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. ***Short name: WHO TRS No. 992, Annex 5***
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf

21. Guidance on good data and record management practices. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fiftieth Report Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 5.
Short name: WHO GDRMP guidelines or ***WHO TRS No. 996, Annex 5***
http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex05.pdf

22. WHO general guidance on variations to multisource pharmaceutical products. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fiftieth Report* Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 10.
Short name: WHO TRS No. 996, Annex 10
http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex10.pdf