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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	**HLL Lifecare Limited**
Corporate address of manufacturer	HLL Lifecare Limited Thiruvananthapuram, Kerala, India
Inspected site	
Address of inspected manufacturing site if different from that given above	Kanagala 591 225, Dist. Belgaum, Karnataka, India GPS coordinates: 16.3164^0 N, 74.4262^0E. DUNS Number: 725552330
Unit / block / workshop number	UniPill block
Manufacturing license number, (delete if not applicable)	KTK/28/258/93
Inspection details	
Dates of inspection	16-19 January 2017
Type of inspection	Initial GMP inspection
Introduction	
Brief summary of the manufacturing activities	HLL Lifecare Limited, UniPill block Kanagala, is a tablets manufacturing unit at Belgaum district, Karnataka, India.
General information about the company and site	HLL Lifecare Limited (HLL) is a public sector enterprise under the Ministry of Health and Welfare. HLL has seven manufacturing units – Peroorkada Factory, Trivandrum (PFT), Akkulam Factory Trivandrum (AFT), Kanagala Factory Belgaum (KFB), Kakkanad Factory Cochin (KFC), Irapuram Factory Cochin (IFC), Manesar Factory Gurgaon (MFG) and Pharma Factory Indore (PFI). The management of the company belongs to the government of India (financial support

	whereas personnel are recruited by the Unit Head). The site consisted of two parts with separate production facilities, warehouses, personnel, material management and independent quality assurance systems. The "Old facility" (out of the inspection scope) was being used for the domestic markets. It was claimed that the formulation of Levonorgestrel (LNG) 1.5 mg tablets produced for domestic market is different in formula and manufacturing process from WHO submitted product. There were 2 production lines in the new plant: - Line-1: smaller capacity for LNG 1.5mg tablet, development products e.g. LNG 0.75mg and 0.03mg tablet, LNG 0.15mg and Ethinylestradiol (EE) 0.03mg combi tablet, - Line-2: larger capacity line planned mainly for commercial manufacturing of LNG/EE.
History	The company has commenced in 1966 to assist various family planning programmes implemented by Ministry of Health and Family welfare, Government of India (GOI). To begin with, HLL started first condom manufacturing Unit at Thiruvananthapuram, Kerala with installed capacity of 189 million pieces per annum. Currently the company has four condom, four pharmaceutical formulations, bulk drug, intra uterine device (IUD) manufacturing, medical device manufacturing and in vitro diagnostic (IVD) manufacturing units at eight locations.
Brief report of inspection activities undertaken	
Scope and limitations	
Areas inspected	Pharmaceutical quality system Warehouses Production (Line 1) Quality control Utilities (water system, HVAC)
Restrictions	No restriction
Out of scope	- The inspection partially covered Line 2 (only areas common with Line 1) in the new plant. - "Old plants" located on the same site were excluded from this inspection.
WHO product numbers covered by the inspection	WHO product number: RH065 Levonorgestrel 1.5mg 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 site had a quality assurance organization. The implementation of quality system was in general satisfactory and led by the Head QA. 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 issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

2. Good manufacturing practices for pharmaceutical products

Although, production in question was not running at the time of inspection, the site demonstrated the good manufacturing practices using placebo on the same Unit-1.

Good manufacturing practices generally were implemented. Necessary resources were generally provided, including qualified and trained personnel, adequate premises, suitable equipment and services, appropriate materials, containers and labels, approved procedures and instructions, laboratories and equipment for in-process and other controls.

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

3. Sanitation and hygiene

There were SOPs in place covering cleaning of auxiliary/external areas, usage of cleaning agents, dry and wet mops, cleaning of trolleys, cleaning of dust bins, cleaning of drain pits, change and wash rooms. The cleaning was done by contract personnel (based on long-term contract). The production officer/executive was responsible to ensure the execution of the cleaning procedures. The SOP contained a table indicating the usage of cleaning agents/disinfectants and the cleaning frequency.

4. Qualification and validation

The validation Master Plan (VMP) contained the general policy of the site on the qualification and validation. It was applicable to the new facility only. The VMP described qualification, revalidation, acceptance criteria, analytical method and cleaning validation and stated that process validation should be done prior to distribution (prospective validation).

Project validation plan described the validation requirement and plan of process validation of hormonal oral solid dosage forms manufactured at UniPill block. This document was cross referenced to VMP. The UniPill production block had two equipment lines for production of hormonal formulations i.e. Line 1 and Line 2.

The issues related to this section have been adequately addressed by the laboratory, and the same shall be verified during future inspections.

5. Complaints

The SOP described the procedure of market complaint handling. Complaints are to be indicated in a register together with a unique compliant number. The deadline for investigation depends on the classification of the complaint.

6. Product recalls

The product recalls initiated by adverse drug event, market complaint or regulatory activity were handled according to the procedure.

7. Contract production, analysis and other activities

Quality agreement with external laboratory for analysis was in place.

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

A procedure for internal audit was available which provided guidance for internal audit to determine effectiveness of quality management system. A list of qualified auditors was available; it was noted that auditors were selected from different departments such as QA, QC, production. The procedure requires that all areas should be covered once a year. The deficiencies were classified into critical, major and minor and were supported with examples. The deficiencies should be reported within 7 days and CAPA should be finalized within 15 days.

Approved vendor list was available. Vendor audit schedule for 2016 was available which identified the current status of the sites, previous audit and next audit schedule etc. The procedure for contractor and vendor management described the procedure for evaluation, approval and disqualification of vendors. After identification of vendors, sample was requested for testing and used in trial batches. This was followed by completion of questionnaire before an on-site audit was scheduled. Risk assessment was required for APIs, excipients and primary packaging materials, and decision to perform the on-site audit shall be taken based upon the control measures and risk assessment. The vendors were re-audited once every three years.

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

9. Personnel

The organizational chart of the site was available. The job descriptions were based on the functional responsibilities. The job description of Unit head, Head QA, QC head and an IT officer were discussed.

10. Training

The procedure for competency mapping and training & development of employees described the procedure of core competencies mapping and training and development of employees. Induction training was given upon joining of an employee wherein regular (once/year April-March) training was given once every year. The training on SOPs was covered by a separate QA procedure. The training calendar for 2016 was available.

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

11. Personal hygiene

The basic personnel hygiene rules were summarized in the procedure. Medical health check of the staff was managed by the HR manager with the contribution of a full-time physician.

12. Premises

The total project area is approximately 20000m^2. The complete facility is having the following blocks/ buildings:

- Formulation Block - 4040 m^2
- QA, QC, Admin. - 1600 m^2
- Warehouse - 2120 m^2
- Utility Block - 525 m^2

The manufacturing premises were facilitating unidirectional material and personnel flow. The construction was monolithic, crevices free finishes with epoxy flooring. Containment and HVAC System was in place to protect the product, operator and environment. There was a building maintenance plan for the facility, including contingency maintenance. Teams of executives from project, engineering, QA and production department were responsible for identification of areas and type of maintenance.

The common facilities of Line 1 and Line 2 were as follows: In-process Control (IPQA), Laboratory, Shifting room, API dispensing, Primary packaging, and secondary packaging.

The manufacturing processing area was operating under negative pressure with respect to adjacent corridor area. The differential pressure was monitored every 2 hour during production operation. The sampling and dispensing of LNG was performed in an isolator equipped with hand gloves. For dispensing, API was mixed with an excipient and dispersion was formed before it was transferred to the production area.

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

13. Equipment

Equipment used in the manufacture, processing and packing were appropriately designed, facilitating operations for their intended use, cleaning and maintenance. Processing equipment parts coming in product contact were made of SS 304/ SS 316 or other materials verified for not affecting product quality. The list of major production and quality control laboratory equipment were available. Processing equipment starting with dispensing of the API until coating had complete containment by means of rigid isolators, canopies and material movement by split butterfly valves and rapid transfer ports (RTPs). Equipment was identified for preventive maintenance and calibration as per the standard procedures.

Measuring instruments were calibrated periodically as per pre-defined schedule.

The layouts and engineering drawings showing the location and construction of the HVAC systems and AHUs were available.

The SOP for validation of HVAC systems served as basis for regular testing, e.g.: air flow pattern (every 2 years), non-viable (biannual), recovery (every 2 years), differential pressure (continuous), temperature/humidity (continuous), air velocity/air change (annual), filter integrity (annual).

Preventive maintenance (PM) schedule for formulation department was available which provided due month for preventive maintenance for a period Jan-Dec 2017.

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

14. Materials

The warehouse was common for raw materials (solvents and excipients), packaging materials, and finished products. The temperature and humidity was monitored and recorded in the warehouses electronically. The records were printed out then checked manually every day by the store executive. The SOP for temperature and humidity monitoring in stores provided procedure for monitoring of temperature using Testo software. The system was equipped with alarm and messaging.

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

15. Documentation

Documentation system was paper based with initiatives to implement SAP modules (e.g. for material management). The basic principles of the documentation were described in SOP for document and data control together with SOP for SOPs. The document archive was located near the QA offices. The department-wise Master list and review plan of documents covered SOPs and specifications.

Electronic data were handled in particular during the QC activities. The users of the computerized systems were controlled according, together with password management procedure.

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

16. Good practices in production

The submission batches were manufactured in September 2015, the process validation batches in June 2016. Inspectors visited the production block. At the time of inspection, a placebo batch was taken to demonstrate manufacturing capabilities to the inspectors. In general, the production area was found adequate for the type of product being produced.

17. Good practices in quality control

The Quality Control (QC) had physico-chemical and microbiology sections. The physico-chemical laboratory facilities consisted of instrumentation laboratory, wet chemistry laboratory, stability chamber room, washing-cleaning area.

The tour at the QC laboratories covered weighing room, HPLC lab, stability chambers and handling of reference and working standards. The laboratory was equipped with 4 HPLC, 1 GC with Head Space system, UV-VIS, FTIR, Auto-titrator, dissolution, disintegration and other equipment and instruments.

Both the reserve and control samples were stored in the room located at the QC laboratories. The reserve samples of APIs, excipients, packaging materials were taken by the QC. The QA was responsible to take control samples from finished products (including exhibit, validation and commercial samples).

Microbiology laboratory was divided into microbiological test 1 and 2 wherein microbiological test 1 was responsible for microbial limit test and environmental monitoring and micro test 2 was responsible for growth promotion test and culture handling. Both areas were equipped with biological safety cabinets, class-2. The gowning instructions were provided at the entrance and exit of the microbiology laboratory through the use of SOPs and pictorial instructions.

The issues related to this section have been adequately addressed by the manufacturer, and the same shall 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, **HLL Lifecare Limited**, UniPill Block, Kanagala, 591225, Belgaum, Karnataka, India, located at 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