

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

Part 1	General information
Manufacturers details	
Company information	
Name of manufacturer	Beximco Pharmaceutical Limited
Corporate address of manufacturer	19, Dhanmondi R/A, Road No: 7, Dhaka-1205, Bangladesh
Inspected site	
Address of inspected manufacturing site if different from that given above	Track-II, 126, Kathaldia, Auchpara, Tongi-1711, Gazipur, Bangladesh GPS coordinates: 23.9030049, 90.3912181 DUNS No: 73-157-9053
Unit / block / workshop number	OSD Unit (Track-II, in short TII)
Manufacturing license number, (delete if not applicable)	379 and 119 The Directorate of Drugs Administration, Bangladesh
Inspection details	
Dates of inspection	7-10 February 2017
Type of inspection	Initial GMP inspection
Introduction	
Brief summary of the manufacturing activities	Beximco Pharmaceutical Limited (in short BPL) is located in Tongi Industrial Area, Gazipur, about 25KM north of Dhaka city. The site has several facilities such as oral solid dosage, ophthalmic, metered dose inhaler, dry powder inhaler, liquid, cream, ointment, suppository, small volume parenteral, nebulizer, intravenous fluids, and lyophilized and prefilled syringe injectable. The site also has a small facility to produce Paracetamol as active ingredient.
General information about the company and site	The site was incorporate in Beximco Group in 1976, and launched its own formulation brand in 1983. The company has been exporting the finished formulation to several countries since 1993.

History	This was the first WHO-PQT inspection of BPL. The manufacturing site was inspected by several regulatory authorities in that: - US FDA January, 19-22, 2015, Carvedilol, TII Oral Solid Dose - TGA, Australia, November 24- 28, 2014, Facility inspection, TII Oral Solid Dose - AGES, Austria, March 24-27, 2014, Facility inspection, TII Oral Solid Dose - Health Canada, November 5, 2014, Approval based on AGES GMP documents submitted in 2014
Brief report of inspection activities undertaken	
Scope and limitations	
Areas inspected	The inspection was limited to oral solid dosage facility, in particular manufacturing of Lamivudine 300mg coated tablets.
Restrictions	None
Out of scope	None
WHO product numbers covered by the inspection	HA668 (Lamivudine 300mg tablets)

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**

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 procedures related to product quality review, quality risk management, deviations, change controls and corrective actions and preventive actions were 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

In general, good manufacturing practices were implemented. The necessary resources were generally provided. The procedures and manufacturing instruction were established. Qualifications and validations were performed, adequate premises and equipment were available for production, in-process controls and storage, and operators were trained.

At the time of the inspection, Lamivudine 300mg tablet (under assessment) was not produced by the manufacturer. The manufacturing facility is a multi-product / non-dedicated facility which produces several of the products using common equipment. Most of the production was performed in closed equipment and materials from different stages were transferred through vacuum transfer and pneumatic systems using hoses dedicated for the active substances.

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

This area was generally considered acceptable, from what was seen during the inspection of production. The wash room and toilet facility was provided for the staff before entering to the production area. The gowning instructions were available and appropriate primary and secondary gowning were provided for the staff and visitors.

4. Qualification and validation

Validation master plan (VMP) described qualification of facility, requalification, process validation, analytical method validation, periodic revalidation, computer system validation, cleaning validation and others.

Process validation protocol (PVP) for Lamivudine 300mg tablets described the objective, scope, responsibility, process flow diagram, equipment and utilities etc. Process validation report of Lamivudine 300mg tablets was reviewed which included details of three batches. It was noted that critical process parameters were challenged during validation, in particular extensive sampling and testing was done.

Cleaning validation protocol for granulation Unit-III and Blister III was available which provided justification for the selection of sampling locations.

5. Complaints

The procedure for handling market complaints was reviewed. A separate procedure was available for handling adverse drug reactions. The complaints were received by the marketing department through email and phone calls. The complaints were categorized as minor, major and critical.

6. Product recalls

Procedure for product recall described classification of recalls into Class I, II and III. The procedure defined withdrawal of a product from the market as well as recall of a specific batch. The procedure described recall simulation which is done once every year for the domestic market. For export markets, recall simulation was done once every three years.

7. Contract production, analysis and other activities

The WHO product, Lamivudine 300mg tablet will be manufactured at Beximco, Track-II, OSD facility, and shall not be contracted out as claimed by the company. It was noted that the manufacturer uses four different contract laboratories in order to carry out some tests. This section was not inspected in detail.

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

This section was not covered due to time constraints.

9. Personnel

In general, there were sufficient qualified personnel to carry out the tasks for which the manufacturer was responsible. The site employs 277 professionals and 576 operators.

10. Training

The procedure on training was reviewed which applied to all the personnel working in the facility. A training calendar for a year was prepared which included on the job training, SOP training and also included training on GMP, sanitization, safety etc. After imparting training, training was evaluated through oral and written test. The minimum qualifying criteria for the staff was set above 80%.

11. Personal hygiene

This area was generally considered acceptable.

12. Premises

Exposed surfaces were smooth, impervious and unbroken. Changing rooms were designed as airlocks and used to provide physical separation of the different stages of changing. Changing rooms were flushed with filtered air. Airlock doors were interlocked. Premises were cleaned and disinfected according to written procedures.

Rest and refreshment rooms were separate from manufacturing and control areas.

Storage areas were of sufficient capacity. Receiving and dispatch bays protected materials and products from the weather. Segregation was provided for the storage of rejected, recalled, or returned materials or products.

Separate sampling areas were provided for sampling of APIs, inactive materials, primary and secondary packaging materials. APIs, inactive materials and primary materials were sampled under laminar airflow (LAF).

Dispensing for APIs/inactive materials and primary packaging materials was carried out in dispensing rooms under LAF. Dispensing was carried out by warehouse officer and checked by the production officer. Materials were dispensed in poly bags and stored in stainless steel containers / cages.

Sufficient space was given to avoid mix ups and cross-contamination. Adequate storage space was provided for samples, reference standards, solvents, reagents and records.

The issues related to this section have been adequately addressed by the manufacturer, and the same shall 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 and were shared with other products.

Calibration and preventive maintenance (PM) master plan for laboratory and IPQA equipment for 2017 was available. It was noted that HPLC, GC, FTIR, AAS, UV, Potentiometer, moisture analyzer etc. were calibrated and maintained by respective vendors. Most of the equipment were calibrated once every 6 month whereas some of other equipment such as analytical balances were calibrated once every three month by in-house personnel. It

was noted that some of the equipment were calibrated using specific SOPs and protocols. The suppliers sent protocols before performing calibration activities.

The SOP on the management of instrument calibration (GE017-01 dated 1/8/2016) was in place. A yearly schedule was prepared before the start of a year for production and engineering equipment. Another procedure on the management of breakdown maintenance (GE002-01 dated 30/10/2016) was in place which described that trend analysis of breakdown should be done once in a year.

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

14. Materials

Warehouse has two sampling booths equipped with LAF, separate entrance for personnel and materials was provided. The APIs were sampled 100% for identification test whereas excipients initially sampled 100% for first three supplies and thereafter $n \frac{1}{2} + 1$. The HDPE bottles were sampled based AQL criteria. Retesting was performed once every year for APIs and once every two years for excipients.

The finished goods (FG) store equipped with two sensors for temperature and RH and claimed it was temperature mapped. There were separated areas for rejected material and returned goods.

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

15. Documentation

In general documents were designed, prepared, reviewed, approved, signed, dated and distributed with care by the appropriate responsible persons. Reproduced documents were clear and legible.

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

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 the production operator which was not verified by another production or QA operator.

Precautions were taken to prevent the generation and dissemination of dust by provided airlocks, pressure differentials, and air supply and extraction systems. In general contamination and cross-contamination of starting material or of a product by another materials or product were avoided. As a common corridor was serving several processing cubicles, it would be useful to conduct a risk assessment and propose additional procedural controls where required.

Before processing operations were started, steps were taken to ensure that the work area and equipment are clean and free from any starting materials, products, product residues, labels or documents not required for the current operation. Time limits for storage of equipment after cleaning and before use were stated and based on validation data.

Before packaging operations begun, steps were taken to ensure that the work area, packaging line, printing machine and other equipment were clean and free from any products, materials or documents used previously. The line clearance was performed and recorded in the BPRs.

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

17. Good practices in quality control

The QC function was independent of other departments. Adequate resources were available to ensure that all the QC arrangements were effectively and reliably carried out. The QC personnel had access to production areas for sampling and investigation as appropriate.

The quality control laboratory was consisted of various sections such as physico-chemical, instrumentation, microbiology, stability and retention sample area. The laboratory was spread over two floors.

The microbiological laboratory was not inspected due to time constraints. The microbiological results on purified water monitoring were reviewed and they were below the limit.

Inspection of chemical-physical quality control laboratory covered sample store room which housed raw materials, finished products, stability samples, validation samples, and packaging materials. The laboratory maintained analysts' competency matrix.

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, Beximco Pharmaceutical Limited located at Tongi, Track-II, Dhaka, Bangladesh 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-eighth 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-sixth 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. Fiftieth 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. Fiftieth 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. Fiftieth 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. Fiftieth 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