

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

Part 1	General information
Manufacturers details	
Company information	
Name of manufacturer	Sun Pharmaceutical Industries Limited
Corporate address of manufacturer	
Inspected site	
Address of inspected manufacturing site if different from that given above	Village-Ganguwala Paonta Sahib District Sirmour Himachal Pradesh, 173025 INDIA
Unit / block / workshop number	Manufacturing blocks of Tablets and Capsules (Block- A, B, C, D, E, F, G and H)
Manufacturing license number, (delete if not applicable)	MNB/95/2 and MB/95/2
Inspection details	
Dates of inspection	10 – 12 October 2017
Type of inspection	Routine GMP inspection
Introduction	
Brief summary of the manufacturing activities	Production and quality control of FPPs including tablets, hard gelatin capsules and soft Gelatin Capsules.
General information about the company and site	Sun Pharmaceutical Industries Limited (hereafter named “Sun”), located in Paonta Sahib, Himachal Pradesh, India, is a large multiproduct manufacturing site for pharmaceutical finished dosage forms. Sun manufactures a wide range of generic medicinal products for worldwide markets including the EU market. Dosage forms are tablets, hard capsules and soft capsules. The annual capacity is over 6000 million tablets and capsules.
History	The site was last inspected in December 2013 by WHO, Irish Medicines Board, UK MHRA, Health Canada and Health Sciences Authority, Singapore in 2013.

Brief report of inspection activities undertaken	
Scope and limitations	
Areas inspected	All products for the EU market and WHO programs (refer to the list above) including all activities and areas involved including manufacturing, QC testing and warehousing. Manufacturing plants within scope are A, B, C, D, E, F, G and H.
Restrictions	None
Out of scope	All areas, activities and products that are not relevant for EU and WHO products.
WHO product numbers covered by the inspection	Lamivudine/Zidovudine tablets, Film-coated 150mg/300mg Nevirapine tablets 200mg Efavirenz tablets, Film-coated 600mg Lamivudine/Nevirapine/Zidovudine tablets, Film-coated 150mg/200mg/300mg

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

1. Pharmaceutical quality system

A system for quality assurance was established, with procedures covering key quality elements in place. The procedures were reviewed and discussed during the inspection. Operations were specified in written form and GMP requirements were essentially being met. Managerial responsibilities were appropriately specified in written job-descriptions. Product and processes were monitored and the results taken into account during batch release; regular monitoring and reviews of the quality of pharmaceutical products were being conducted according to documented schedules and procedures.

Annual product quality review was performed according to a documented procedure.

The company had SOPs in place for change and deviation management. The procedures as described were generally of a good standard.

The company's procedures on "Quality risk management" QRM were reviewed. This SOP discussed various risk assessment tools.

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

Good manufacturing practices were implemented and followed. Required staff and system resources were provided. Manufacturing processes were clearly defined and documented. Qualification and validation were performed. Operators were trained to carry out procedures correctly, and comprehensive records were made during manufacture.

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

In general, premises and equipment were maintained at a satisfactory level of cleanliness. The company had a standard operating procedure as the basis for its approach to personal hygiene and sanitation in its production facility, with appropriate hand washing facilities.

Clean areas were cleaned frequently in accordance with approved written procedures. Environmental monitoring of viable particles was regularly undertaken.

4. Qualification and validation

The company approach to validation was documented and explained in the Validation Mater Plan (VMP) and the VMP was briefly reviewed by the inspectors. The key elements of a qualification and validation programme were defined.

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

5. Complaints

Complaints were handled according to a documented procedure and were classified as minor, major or critical, depending on the nature of the complaint. The SOP Management of product quality complaints was reviewed and the following complaints were selected for review from the 2017 list.

- 276184 possible mix-up Pantorazole 40mg.
- 276891 black discoloration on tablet Simvastatin 40mg.
- 278703 one partial tablet.
- 280204: missing variables and data matrix on one carton Ofloxacin 200mg.

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

6. Product recalls

The product recall was described as a policy rather than procedure.

Recalls are also managed in Trackwise using SOP OP013057 Management of product recalls. The list of recalls 2015-2017 contains 8 recalls. Recall 197563 for incorrect carton artwork for Ranitidine 10mg tablets (UK) was reviewed which did not lead to any observations.

7. Contract production, analysis and other activities

There are no manufacturing operations outsourced to CMO's and Sun uses two CLO's in India, namely SGS India (Chennai, Tamilnadu) and Choksi Laboratories (Manorama Ganj, Indore).

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

The procedure OP013066 v2 Internal Quality Audits, the planning for 2017 and the internal audit checklist and report (incl. the response) performed in 2017 is seen. The qualification of SD as QMS auditor from the Learning Management System (LMS) was seen.

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 manufacturer had an adequate number of personnel with the necessary qualifications and practical experience. Responsibilities of staff, and their specific duties were recorded in written job descriptions. Personnel interviewed during the inspection were aware of the principles of GMP in general. An organization charts and job descriptions were available and considered acceptable.

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

10. Training

Procedure OP013044 v1.0 Training management is seen. Yearly a master training Needs Matrix is made per department for different job roles. Which is entered in the training system per person for the applicable job role. New employees get induction training which includes a current GMP training. The GMP training is repeated yearly. Gowning procedures are identical for all blocks except for block H that has additional requirements. Gowning and de-gowning is prescribed by SOP OP001333 (primary gowning) and SOP OP014874 (secondary gowning).

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

Changing and washing before entry to production areas followed a written procedure. Direct contact was avoided between the operator's hands and starting materials, primary packaging materials and intermediate or bulk product. No concerns of note were identified during the inspection. The approach to sanitation and hygiene was in general acceptable.

12. Premises

Generally premises were located, designed, constructed and maintained to suit the operations to be carried out. The layout and design of premises minimize the risk of errors and permit effective cleaning and maintenance in order to avoid cross-contamination.

Manufacturing areas were generally of a good standard and suitable for the activities conducted therein. Exposed surfaces were smooth, impervious and unbroken to minimize the shedding or accumulation of particles or microorganisms and permitted the repeated application of cleaning.

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

QC laboratories were separated from production areas. Adequate space was provided for samples, reference standards, solvents, reagents and records.

The plant is divided into multiple manufacturing blocks, of which the following are in scope of this inspection:

- Block A: manufacturing of tablets and hard capsules; packaging.
- Block B: manufacturing of soft capsules; packaging. Dedicated to Isotretinoin.
- Block C: manufacturing of tablets and hard capsules; packaging.
- Block D: manufacturing of tablets and hard capsules; packaging. Small batch size.
- Block E: manufacturing of tablets and hard capsules; packaging. Small batch size.
- Block F: manufacturing of tablets and hard capsules; packaging.
- Block G: manufacturing of tablets; packaging. Dedicated to Esomeprazole.
- Block H: manufacturing of tablets; packaging. Imatinib and Letrozole.
- Furthermore, there are two (main) laboratories, namely the QA/QC Laboratory and the Stability Laboratory. Warehouses 1 and 2 are located adjacent to manufacturing blocks.

All above mentioned facilities were visited during the inspection.

13. Equipment

The equipment installed for tablet manufacturing was of a good standard. The facility and equipment appeared to be running well with no significant stoppages on either line noted during the inspection. The detailed procedures for the operation of key equipment were generally well documented. Laboratory equipment and instruments were suited to the testing procedures undertaken in general.

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

14. Materials

Starting materials and packaging materials were purchased from approved suppliers. Printed packaging materials were stored in secure areas.

Finished products were held in quarantine in production area until their final release, after which they were transferred to and stored under appropriate and monitored conditions in a separate store, in a different building across the road.

Rejected materials and products were marked as such and stored in designated secure areas.

SOP OP012986 Vendor management prescribes the qualification requirements per type of material. A site audit is required for API's and printed and primary packaging materials. Frequencies are based on corporate quality audit SOP GQA/009/10. The approved manufacturer list can be extracted from the SAP system. The list of 12 Oct 2017 was shown as well as the audit planning. Audits are planned by the vendor qualification office, a corporate department. There is no backlog in audits.

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, documentation was designed, prepared, reviewed and distributed according to a documented procedure. Documents were regularly reviewed and kept up to date.

Approved, signed and dated testing procedures and specifications were available for starting and packaging materials and for finished products

Batch Records

The following batch manufacturing records were reviewed:

- BR for Imatinib Mesylate tablets 400 mg; no comments were made.

In addition to the documents mentioned in other parts of this report, the following document were reviewed as well:

- Temperature mapping of block G of raw material store-PGS-01, PEN AHU13, performed May 2017. Re-evaluation is performed every 3 years.
- Mapping data warehouse 1 PENAHU05 performed Jun 2017.
- OP001598 Pest control, rodent control, fly control & insect v 11.0. Pest control agency, layout and procedure.
- In process holding time study report of Levetiracetam tablets 1000mg (14 July 2010).
- SOP OP001377 Measurement of pressure differential in process area and maintenance of manometer.
- SOP OP001523 Sampling of intermediates, finished products and stability samples.

Sun uses a number of electronic systems such as SAP, Trackwise, Documentum, SumTotal LMS, and Novatek Stability Software system.

Pressure differential record for raw material staging area PDS010, block D, 3 July 2017 to 30 September 2017.

Pressure differential record for Fabrication II PDF02, granulation area, block D, 3 July 2017 to 30 September 2017.

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

Production processes were presented and discussed. For more information refer to the Site Master File.

Process validation of isotretinoin cold formulation capsules USP 20mg included three full scale batches. The same applies for the 10mg strength.

PPQ protocol and report C/PPQ/17/043/00 of Imatinib Mesylate tablets 100mg, block H, completed 28 August 2017. The product was transferred from the Sun Batamandi site. PPQ protocol and report C/PPQ/17/044/00 of Imatinib Mesylate tablets 400mg, block H, completed 12 Sept 2017. The product was transferred from block A.

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 the QC arrangements are effectively and reliably carried out in general.

Handling of out of trend procedure (OP013051) was discussed. An example of OOT 277689 was selected as OOT result was observed for related substance test of Isotretinoin capsule. An investigation was conducted and reanalysis on fresh sample was performed. The result was reported within normal trend. It was concluded that due to sample analysis, OOT was triggered.

The stability quality control was inspected and noted that laboratory performed stability studies for exhibit and commercial batches. Laboratory was equipped with sophisticated equipment and instrument (34 HPLC, 15 dissolution and 9 stability chambers including room for controlled temperature and 30°C/75%) and 46 manpower. The stability chambers were equipped with Newtronic whereas stability rooms were equipped with Eurotherm. Monthly planner for commercial batches as well as for exhibit batches. The stability study of two batches of Isotretinoin capsule supplied to the UK. The stability study was commenced in April 2017, and 6 month stability analysis was completed. The balance sample quantity was verified and found satisfactory. Another example of Etoricoxib tablet marketed to Germany was reviewed. The samples were withdrawn from the stability chambers were stored in controlled temperature room before taken up for analysis. The stability samples were withdrawn within 3 days from respective chambers and analysed within 30 days for real time and 14 days for accelerated.

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, Sun Pharmaceutical Industries Limited, located at Village-Ganguwala Paonta Sahib District Sirmour Himachal Pradesh, 173025, 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-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