

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

Part 1		General information
Manufacturers details		
Name of manufacturer	Milan Laboratories (India) Pvt Ltd.	
Corporate address of manufacturer	<u>Head Office:</u> 303, 304, Odyssey IT Park, Opposite MIDC Office, Road No. 9, Wagle Estate, Thane (W) – 400604, Mumbai, India	
Inspected site		
Name & address of inspected manufacturing site if different from that given above	Plot No 35/36/63/64/65/67, Jawahar Coop Industrial Estate Ltd, Kamothe, Panvel, Navi Mumbai, Maharashtra, 410209, India <i>GPS: 19°01'18''N73°05'56''E</i>	
Unit / block / workshop number	General Plant 2 (GP-2)	
Inspection details		
Dates of inspection	4 - 8 February 2019	
Type of inspection	Routine GMP inspection	
Introduction		
Brief description of the manufacturing activities	<p>Milan Laboratories (India) Pvt Ltd has two manufacturing facilities:</p> <ol style="list-style-type: none"> 1) Panvel, Navi Mumbai, 2) Dahej SEZ, Gujarat. <p>The Panvel Plant was started in 1976 with liquid orals. Subsequently, the plant added other dosage forms/sections such as ointments/creams, tablets, capsules, dry syrups for general products and a separate Penicillin plant for tablets, capsules and dry syrups. The Panvel plant consists of three sub-plants:</p> <ul style="list-style-type: none"> – General Plant 1 (internal code: ML): Liquid Orals, Creams & Ointments, – General Plant 2 (internal code: GL): Tablets, Capsules & Dry Syrups (General Section) – Penicillin Plant (internal code: PP): Tablets, Capsules & Dry Syrups (Penicillin Group) <p>The QC, QA, Regulatory Affairs and R&D, serving the entire site are</p>	

	situated in the General Plant 1 building. The facilities of General Plant 2 are multi-product, without dedication and manufacturing 133 products using 56 APIs.
General information about the company and site	Milan Laboratories (India) Pvt Ltd was established in the year 1976 for pharmaceutical formulations manufacturing (export only) and managed by a family of Technocrats. The products of the company are registered and distributed in more than 30 countries.
History	<p>This was the second WHO Prequalification Inspection of Milan’ Panvel site. The initial PQ inspection was conducted in March 2018. The site was inspected amongst the following agencies:</p> <ul style="list-style-type: none"> – 2013 – MCC, South Africa – 2015 - FDA Maharashtra, India – 2016 - UK MHRA – 2016 - FDA Maharashtra, India – 2016 - UNICEF – 2017 - US FDA – 2017 - CDSCO and Maharashtra FDA – 2018 - WHO Geneva (non-compliant) <p>Based on the information provided according to the company’ site master file, the Panvel plants of general products (Tablets, Capsules, and Dry Syrups) and Penicillin products (Tablets, Capsules, Dry syrups) are approved by UK MHRA, MCC (South Africa), US FDA</p> <p>Substantial changes since the last WHO Geneva inspection were as follows:</p> <p><u>General infrastructure</u></p> <ul style="list-style-type: none"> – Renovation and relocation of R&D Lab, increasing space – Initiated 2D Barcode printing systems for EU-FMD compliance – Enclosed HVAC service floors by paneling for Penicillin Containment – Renovation of QC Department – New energy efficient Electric Transformer installed <p><u>Quality Control Department</u></p> <ul style="list-style-type: none"> – Increased space due to the relocation of QA – Expansion of Microbiology Department – Additional equipment procured in Microbiology (LAF 1 Nos, BOD incubators 1 No. Oven 1 Nos) – Implemented Caliber LIMS <p><u>General Plant - 2</u></p> <ul style="list-style-type: none"> – New Ductable Split AC with Heater banks for material stores – Modification in Pallet design to prevent obstruction of risers – Installation of Elevating devices on Blister Pack machines <p><u>IT upgradation</u></p> <ul style="list-style-type: none"> – Dedicated Server for Lab Solutions Software for key lab instruments

	<p>switch over from physical to virtual. The new one is SQL server</p> <ul style="list-style-type: none"> – Implementation of Caliber Document Management Systems – Implementation of Caliber LIMS in QC – Implementation of E-Scheduler software for maintaining all schedules – Implementation of Microsoft Dynamics ERP – Training: <ul style="list-style-type: none"> ○ Exhaustive internal & external Training sessions being conducted ○ Services of external consultants being employed for training and system improvisation ○ Initiation of Caliber Training module (Nichelon) <p><u>Penicillin plant</u></p> <ul style="list-style-type: none"> – Air Showers provided at: <ul style="list-style-type: none"> ○ Exit from Penicillin plant ○ Exit from Penicillin Utility – Ground Floor ○ Exit from Penicillin Utility – Terrace – Utilities of Penicillin plant enclosed with modular Panels. – Both Emergency Exit doors replaced with sealed emergency glass window
--	---

Brief report of inspection activities undertaken – Scope and limitations

<p>Areas inspected</p>	<p>Document Review included but was not limited to:</p> <ul style="list-style-type: none"> ○ Annual Product Quality Reviews (APQRs) ○ Change control management ○ Self-inspections ○ Product complaints ○ Product recalls ○ Training system ○ Supplier qualification, ○ Documentation system ○ Out of specifications (OOS) and Out of trends (OOT), ○ Deviation management ○ Corrective and preventive actions ○ Stability program ○ Software validations ○ Deviations ○ Personal hygiene ○ Contract laboratories ○ Cleaning validation ○ Changing and gowning <p>Site areas visited:</p> <ul style="list-style-type: none"> ○ Warehousing ○ Production ○ Quality control laboratory ○ HVAC system ○ Water system ○ Microbiology laboratory
------------------------	---

Restrictions	None
Out of scope	Other than GP-2
WHO products covered by the inspection	HA691: Sulfamethoxazole/Trimethoprim Tablet 800mg/160mg (under assessment) HA690: Sulfamethoxazole/Trimethoprim Tablet 400mg/80mg (under assessment)
Abbreviations	Meaning
AHU	Air handling unit
ALCOA	Attributable, legible, contemporaneous, original and accurate
API	Active pharmaceutical ingredient
APR	Annual product review
APS	Aseptic process simulation
BMR	Batch manufacturing record
BPR	Batch production record
CC	Change control
CFU	Colony-forming unit
CIP	Cleaning in place
CoA	Certificate of analysis
CpK	Process capability
DQ	Design qualification
EDI	Electronic deionization
EM	Environmental monitoring
FMEA	Failure modes and effects analysis
FPP	Finished pharmaceutical product
FTA	Fault tree analysis
GMP	Good manufacturing practices
GPT	Growth promotion test
HEPA	High efficiency particulate air
HPLC	High performance liquid chromatography (or high-performance liquid chromatography equipment)
HVAC	Heating, ventilation and air conditioning
IQ	Installation qualification
LAF	Laminar air flow
LIMS	Laboratory information management system
MB	Microbiology
MBL	Microbiology laboratory
MF	Master formulae
MFT	Media fill Test
MR	Management review
NC	Non-conformity
NRA	National regulatory agency
OQ	Operational qualification
PHA	Process hazard analysis
PLC	Programmable logic controller

PM	Preventive maintenance
PQ	Performance qualification
PQR	Product quality review
PQS	Pharmaceutical quality system
PW	Purified water
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
RO	Reverse osmosis
SIP	Sterilization in place
SMF	Site master file
SOP	Standard operating procedure
URS	User requirements specifications
UV	Ultraviolet-visible spectrophotometer
WFI	Water for injection

Part 2	Summary of the findings and comments
---------------	---

1. Pharmaceutical quality system

The quality assurance department was independent of the production and other departments.

The quality management and quality control functions were supported by IT software, including the following:

Name of Software	Applicability	Status of implementation	Comment
Lab Solutions	Lab Instrument connectivity	Validated, in use	NA
e-Schedule	Scheduling of calibration, qualification, maintenance activities	Validated, in use	NA
Microsoft Dynamics	ERP, material management and batch release, linked with Mint Matrix	Validated, in use	Integration with LIMS proposed date September 2019
Mint Matrix	Dispensing and charging of material, linked with MS Dynamix ERP	Completed also integrated with Microsoft Dynamics ERP	NA
Nichelon 5 cms	training program management	Under Implementation	Integration with DMS & QAMS proposed

			date September 2019
Caliber QAMS	Event management, including change management, deviation management, complaints handling, CAPA management, internal audit management	Validated, in use	Integration with Nichelon, proposed date September 2019
Caliber BRM	Handling of BMR masters, BMRs (paper-based) and e-BMRs	Partially completed	Integration with Microsoft Dynamics proposed date September 2019
Caliber LIMS	LIMS system for QC	Validated, in use	Integration with Microsoft Dynamics proposed date September 2019
Caliber DMS	Document management	Validated, in use	Integration with Nichelon, proposed date September 2019
e-Complaint	Complaint handling, E-Ticketing	Validated, in use	NA
Vendor Evaluation	Vendor Evaluation	Under Implementation	NA

The critical software components were identified and validated. Caliber software is commercial-off-the-shelf (COTS) customized to the user. As of now, various Caliber software was standalone and proposed to be integrated by March 2019. The user roles and belonging user rights were defined and software functions e.g. audit trail tested.

The protocol for electronic batch manufacturing record was reviewed which specified user requirement specification (URS). The company is planning to use e-BMR from Jan 2020. Batch Record Management (BRM) and other software are web-based portal (internet-based application). It is a license-based software (currently 25 concurrent licenses for BRM obtained for the entire site).

The user requirement specification (URS) was part of the qualification of the BRM system. However, these were not described in detail, especially for security configuration. It was also noted that screenshots did not capture the date/time when the challenge test was performed.

User requirement specifications of Quality Assurance Management System (QAMS) was discussed. It was noted that various quality system elements were implemented onto the QAMS in phased manner approach. Following QS elements were live as follows:

1. Change control: October 2016
2. Deviation: March 2017
3. CAPA: January 2017
4. Complaints: April 2017
5. Audit management: January 2018

The SOP on annual product quality review together with an APQR were discussed. As WHO products were not manufactured since the last inspection, a product containing the same API's as the inspected products (the manufacturing process was different) was discussed in detail. The APQRs schedules were prepared plant-wise. The review was done annually for all products manufactured between January and December. APQRs contained amongst others, the following information: general product information, review of the previous APQR, formula, RP/PM vendors, batch trends, specifications, list of batches, API/excipient trends, process flowchart, critical process parameters, process results, FP test results, yield, process validation status, cleaning validation status, investigation of events, stability testing, control samples, analytical trends, repacking, returns, equipment qualification status, technical agreements, registration status, evaluation and summary.

Though there were no WHO products manufactured since the last inspection, the APQRs were available for review of the stability program:

- Betrim forte tablet, APQR/M449/19/000, approved on 27/01/19
- Betrim 480 tablet, APQR/M464/19/000, approved on 30/01/19

Deviation management procedure was discussed. The deviations were handled through QAMS and any initiator can raise a deviation from any respective department. The deviations were classified into major and minor however these were not supported with any examples. The classification of deviations was done by QA and risk assessment was performed for major deviations. Deviations were trended on a quarterly basis. Trend analysis for July-Sept and Oct-Dec 2018 was available however it did not provide a useful analysis as for the increase in the number of deviations and effectiveness of CAPA. Total of 140 deviations was raised in 2018.

The SOP on change control management was reviewed. The number of changes recorded in the Caliber QMS since March 2018 (last WHO inspection) was 512, including 107 in Production.

Corrective action and preventive action (CAPA) were reviewed. The QAMS electronic system was used for the management of CAPA. The procedure was supported by a process flow chart. CAPAs are raised for deviation, regulatory inspections, audits, complaints, recalls, incidents, non-conformance, OOS, OOT etc and closed within 90 days based on a system generation. A total of 203 CAPA were raised in 2018.

Quality risk management /QRM procedure was discussed which provided a systematic approach on QRM of critical equipment, utilities, instruments, systems, processes and product throughout the lifecycle. The procedure was based on ICH Q9 and WHO QRM guidelines. The FMEA (using RPN) was used to perform a risk assessment. There was no consideration given to using tools other than the FMEA method.

Management review meeting /MRM was discussed. MRM was performed quarterly. An action plan was part of the discussion document. In general, this section found satisfactory.

Materials were purchased from vendors qualified by the QA according to SOP. The SOP covered suppliers of RMs (including APIs and excipients), packaging materials and process aids. The qualification process was based on a questionnaire, material sample test, supplier CoA, technical agreement and audit (if applicable). The decision on the necessity of the audit was decided by QA executive. The selection and approval of a new supplier are supported by change control investigation. The approved vendor list was available and contained the following information: item description, grade, ERP item, Item no, supplier name, supplier address, manufacturer name, manufacturer address.

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

Basic principles of good manufacturing practices were generally described and implemented. Manufacturing processes were adequately defined and documented in BMRs and BPRs. Required resources were available, including adequate premises, equipment, and utilities. Appropriately qualified personnel were employed. Similarly, to the previous WHO inspection all areas visited were generally clean, tidy and well-maintained.

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

Premises and equipment were generally cleaned according to established procedures. Change rooms were well maintained and authorized instructions displayed the steps and dress code. Cleaning records of manufacturing rooms and equipment were in place.

Environmental microbiology monitoring was due once / month in the GP-2 controlled areas.

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

4. Qualification and validation

The qualification, calibration, maintenance, and validation policy did not change since the last WHO inspection. The most substantial change was the implementation of new software (e-Scheduling) for managing qualification, calibration, maintenance schedules. The following documents and records were discussed:

- The SOP on the calibrations by external agency
- The SOP on maintenance of production equipment
- The SOP on internal calibrations (balances)
- Calibration schedule of balance
- Maintenance protocol and schedule of FBD

- Re-qualification protocols and reports of FBD
- Installation protocol, report, certificate and calibration of differential pressure gauge

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

5. Complaints

Quality complaints were received by e-mail. The initiator(QA) records the complaints into the Caliber software according to SOP. The Head of Quality operations finally reviews, approves and closes the complaint. There were 21 complaints received since the last inspection.

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

There was no product recall happened in the history of the Company. The related SOP covered potential recall procedures (initiated in a form of a self-recall or originated by a regulatory body) of the concerned markets, e.g. EU, US, PIC/S, ROW (rest of the world).

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

7. Contract production, analysis and other activities

The contract partners were indicated on the “Approved service provider list” v.00. The recent technical agreements of two quality testing laboratories (Chemotest and Manisha) were discussed.

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

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

The SOP described the internal audit procedure. The general format for an annual internal audit schedule was defined in the SOP. The audit schedule for 2018 together with the audit details of the Plant 2 were available. The qualified auditors were listed. The audits were managed and performed by at least two persons: 1 QA person and one expert of the relevant area.

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 manpower of the company was as follow:

Departments	Staff strength
Admin	6
Warehouse	26
Production	45
Engineering	16
IT	5
Quality Assurance	53
Quality Control	65
Regulatory Affairs	5
Temporary staff working in the production and warehousing areas	101

The hygiene, training, changing, medical check-up rules was applicable to both temporary and permanent staff.

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

10. Training

The training program consisted of induction, on-the-job, classroom and external training according to SOP. The training program was discussed:

- training calendar,
- common training matrix,
- individual training matrix,
- training file of a production officer who joined the company in 01/07/18 included:
 - induction training record
 - evaluation of training needs
 - completion of training needs

There is new software (Nichelon Training Software) under validation managing the training program and expected to be operational in March/April 2019.

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 SOP detailed the general personal hygiene and discipline. Ornaments were not allowed inside the warehouse area. A pictorial presentation was provided. The gowning procedure was found adequate (two-piece suit, hairnet and shoe cover). Biometric access was provided to GP-2 and separate change rooms were provided for the gents, ladies, and visitors. Before entering the change rooms, the staff was required to use the toilets for the washing of their hands. Gents change room was visited and was found clean and tidy. Separate change rooms were provided for both men and women also at the quality control facilities. The SOPs for the use of change rooms as well as for dress code were in available in English and Marathi.

Medical check-ups consisted of a review of health statement provided by the medical health professional of the applicant, followed by a regular (annual) health check performed by the factory medical health professional. Medical health checks (including induction and annual) of a Helper (production 2) were available.

The changing and gowning rules were detailed in different SOPs, e.g. at the main entrance Entry and Exit for Plant 2 core areas and use of changing room were available. Dress coding was defined for Plant 5 process areas e.g. boiler suite with a different color: dark buff for housekeeping, white for QA, management, and visitors, green for maintenance, light grey for operators. Boiler suits were also used for the personnel performing sampling and dispensing activities.

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

12. Premises

Before the site tour, the site layouts were discussed. The GP-2 was divided into three floors, basement for the storage of incoming materials (warehouse), ground floor for the production and first floor for primary packaging. The premises were multiproduct and multipurpose. The production area was equipped with the following sub-areas:

- Granulation area (two areas equipped with RMG, FBD / FBE, sifter, and co-mill)
- Two blending areas
- Tableting (three machines of the same make, Cadmach)
- Two coating areas

For WHO product amongst other areas, Granulation area I, blending area I and Compression 1, 2, 3 areas were used.

Penicillin containment study protocol cum report was reviewed. It was noted that protocol was prepared on the same day, sampling was performed on the same day and tested by an outside laboratory the next day using LC-MS/MS. The results were reported “not detected” for all samples taken from General Plant-2. Air samples were also taken from the Penicillin block and traces of Penicillin were found. In general, the study appeared satisfactory. It is recommended to perform testing of both non-penicillin and penicillin samples together.

In addition, risk assessment study for penicillin containment study for all plants (penicillin, GP-1, and GP-2) was performed in January 2019. There was no residue of penicillin found in any of the plants. The testing was performed in an external laboratory using LC-MS/MS and appeared satisfactory.

Validation of air handling units was done once every six months by an external party (Cool Tech Enterprises, Mumbai), in-house SME (Ketan from engineering & maintenance). Total number of AHUs in GP-2 is 35 and 5 AHUs (1 to 5) were used in the warehouse. Following tests were performed as part of the requalification of AHUs:

- ACPH/ once every six months
- PAO (filter integrity once in six months)
- Particle count (once in six months)
- Recovery (once in six months)
- Smoke study (once every year)
- Temperature & relative humidity (monitored on a routine basis)
- Core processing area negatively pressurized to adjacent areas
- For core processing areas, digital display/ monitoring of differential pressure
- For fine filters, the differential pressure across the filter is monitored using magnehelic gauges

“e-Schedule” system was used for scheduling purposes (calibration, requalification).

Differential pressures were monitored using a digital system whereas no recording was performed except area clearance. Although the digital system was connected to alarms there was no recording done for these alarms. Alarms were not challenged. The AHUs were equipped with 10um, 3um (fine filter) and HEPA. Terminal HEPA filters were used across the entire facility. Differential pressure was monitored only for the fine filter. The schematic diagram of AHU-23 (supplying to tablet compression 1) was reviewed.

- AHU-021 supplied to granulation area II
- AHU-019 supplied to blending area I
- AHU-023 supplied to compression room I
- AHU-025 supplied to compression room III
- AHU-020 supplied to granulation area I
- AHU-024 supplied to compression room II

AHU-020 supplied to granulation I was discussed. The tests were performed by Cool Tech Enterprises (1-2 October 2019). The tests (recovery, particle count, leak test and air changes per hour) were reported within the limit. The instrument used for requalification were calibrated and were within the calibration date.

AHU-019 supplied to the blending area I was reviewed. The tests were performed by Cool Tech Enterprises on 1-2 October 2019. The tests (recovery, particle count, leak test and air changes per hour) were reported within the limit. The instrument used for requalification were calibrated and were within calibration date.

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

13. Equipment

The production equipment was not dedicated and did not change since the last inspection.

The maintenance program was scheduled using e-complaint software and breakdowns were handled according to the SOP.

The qualification, monitoring and maintenance records together with the corresponding SOPs, protocols, and specifications of the purified water system supplying Plant 2 were discussed, amongst:

The system was constructed and qualified in the year 2011, appended with a loop in 2014 and did not change since the last WHO inspection. The system cleaning, maintenance, and sanitization were performed regularly, the records were available. Operation and cleaning of the purified water system of Plant 2 was reviewed.

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

14. Materials

Material handling and management were well designed. Incoming materials were deducted using a vacuum cleaner. Received materials were kept in quarantine until sampling by the IPQA personnel, QC tested and released, before transferring to the approved material area.

The material inspection report (checklist) was prepared for every consignment of material received on site. For Active substances, 100% sampling was performed for identification. The portable humidifier was removed and replaced with duct air-conditioners.

At the time of the inspection, Sulfamethoxazole BP from Virchow Labs Ltd was available in stock. Thermo-hygrometers were used for temperature and relative humidity.

Raw materials were dispensed under RLAF and using Mint matrix software. Separate airlocks (material and personnel) were provided for dispensing. At the time of the inspection, there was 4 personnel (2 store operator, 1 store officer and 1 from IPQA) inside the dispensing area. The packaging material store housed the printed packaging materials as well as the PVC/PVDC and HDPE bottles. Status labels on containers were barcoded.

The sampling of the primary packaging material was performed in a dedicated sampling / dispensing area equipped with separate material and personnel airlocks.

Differential pressure was monitored using a digital system for the production, sampling and dispensing activities whereas Magnehelic gauges were used to measure pressure across air handling filters.

In-process control was the responsibility of IPQA staff. The IPC laboratories were in the production areas. From the tour of the IPQA laboratory, it was noted that “Automatic weight and thickness measurement system” (AWT) was used for the recording of individual and average weights of the tablets. AWT software was initially qualified in February 2015 and requalified in March 2018. However, at the time of the inspection, the AWT system was out of order, operators recorded the weight of the tablets manually on the batch records. E-complaint had been issued on 27th January 2019, however, there was no action taken yet. It was claimed that AWT was not used for the thickness parameter.

Products were tested in “semi-finished” stage against the quality specification before released for packing.

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

15. Documentation

The activities, procedures were described in standard operating procedures (SOPs).

The document management system (DMS) was used for the management of SOPs, process validation protocols, cleaning validation protocols, analytical validation, air handling unit qualification.

Department codes used in the quality documents:

- P2 Production 2
- S2 Storage for Production 2
- M2 Maintenance for Production 2
- QC Quality control, for the whole site
- A2 Administration for Production 2
- QA Quality assurance for the whole site

For batch manufacturing records Caliber-BMR was used since September 2018. It was noted from the DMS that print request is given through print type “controlled copy, uncontrolled copy, training copy, display copy, reference copy, and master copy”. Users are given access to these print type.

The QA senior executive was responsible for reviewing of documents including BMR and BPRs. The system provided for selection of a specific plant (Dahej, GP1, GP2, Penicillin) for initiation, review, and approval of batch records. Currently, no master or working batch manufacturing record are available on this system for the WHO product as the product is under PQ review. BMR’s were issued based on production planning.

Batch requests are being receipted from the ERP by QA and are manually processed using Caliber BRM. There was no interfacing between ERP and Caliber BRM. Requests for Batch issuance was handled through Dynamics software which was not interfaced with Caliber BRM. Caliber BRM did not capture details on the number of copies printed.

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 production activities were displayed on a whiteboard. In the material quarantine room, batch-wise dispensed materials were stored and segregated with the use of nylon net and rope. The granulation, blender and compressed area were equipped with separate material and personnel airlocks. For the blending area, lifting & positioning device was used to load milled granules.

PLCs (granulation and blender) and SCADA (compression machines) were used for operating production equipment. The SOP for PLC password and operation & cleaning of tablet compression machine was reviewed. During the inspection, inspectors looked at the recipes stored in the compression machine. Different recipes had different operating parameters some of them fixed whereas rest of them were variable. SCADA was used for the compression machines and software provided was Zenon Supervision (version 7.00 SPO Build 2). The lifting & positioning device was used for bin loading on the compression machine. There were some issues noted on the privileges given to the operator, supervisor, and manager (QA or production or maintenance). From the discussion with the maintenance personnel, it appeared that maintenance work being done using the production supervisor's account. Although three access levels (operators, supervisor, and admin) were provided, common username and password were used for all the production equipment operated using PLC. For equipment operated through SCADA, three access levels (operators, supervisor, and admin) were provided and it was claimed that unique username and password were given to all users.

The qualification of PLC was found inadequate as it did not provide confirmation if PLC operated equipment were challenged at all three user levels and confirmed that level 1 (operator) has limited privileges (claimed to download recipes) and same applies to rest of the levels.

Upon review of the qualification document of the SCADA, it was noted that the PLC qualification template was used for the SCADA. Although three user levels (operators, supervisor, and admin) were identified, there was no information available to confirm what privileges were given to these three user levels, they were challenged and supported with screenshots.

The SOP for the PLC password was briefly reviewed and noted that the procedure did not confirm there were appropriate controls in place at all three user levels. There was no procedure available to confirm what privileges were given to these three user levels. There was no user-level provided for the maintenance, QA and administrator.

The primary packaging area was located on the ground floor of the GP-2. The area was equipped with 6 packaging lines (3 blister lines, 1 bulk pack, 1 strip pack and 1 dry syrup). The blister lines (1 & 2) were equipped with lifting & positioning (L&P) device for the transfer of tablets to the hopper. For line 3, the dedusting elevator was used for the transfer of tablets whereas, for line 4, the company is planning to implement the L&P system. Line 6 for bulk packing is a manual operated line wherein physical balances were used for the weighing of the tablets.

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 facilities, instrumentation and organizational structure of the quality control laboratories did not change since the last inspection. The same floor housed wet chemistry, instrumentation, microbiology and QA/QC offices.

All quality control equipment (including the ones operated by LabSolutions, analytical balances, pH meters, etc) were connected to LIMS. The Shimadzu equipment HPLC, GC, UV-VIS, AAS, and IR were integrated and operated by Lab Solutions (Shimadzu) software. The assess control of LabSolutions was described in the procedure. The laboratory was equipped with 12 HPLC, 1 GC, 1 IR, 1 UV-Vis, 1 AAS, and other equipment.

The company' data integrity policy, as well as the SOP on data integrity, was discussed. In general, the company's data integrity policy was adequate. Consideration should be given to creating a culture of quality giving confidence to the staff to come forward and report errors and mistakes. Audit trails were reviewed as per the procedure.

The inspection team spent time with the laboratory personnel for the workflow of LIMS. This is the new system implemented since the last WHO PQ inspection. Various user roles were defined in the LIMS such as four IT administrators, three laboratory QA, QA officer, QA executives, QA reviewers, assistance manager QA and QC and QA manager. The batch release was performed by QA Manager using ERP. QA reviewers were responsible for the review of QC records and approval of a product by way of certificate of analysis. It was noted that LIMS was being used for various laboratory related activities such as column management, reference standard management, weighing management etc. The following documents and records were discussed:

- Caliber LIMS qualification
- Computer system validation
- Performance qualification of LIMS software

The Laboratory Software Settings and list of the operator, reviewer, approver & IT administrator (dated 29/1/2019) were reviewed. System administrator (superuser) privileges were given to QA Manager (QAM) and Assistance QAM in addition to IT administrator.

The SOP for out of specification (OOS) was reviewed. Currently, all the OOS are handled manually and not integrated into LIMS. The process flow was part of the procedure. The investigation was performed phased wise and a hypothesis was performed. Retesting was performed 5 times with RSD NMT 2.0%.

Handling of out of trend results was reviewed. In general, the procedure was found adequate.

The quality specification of Betrim Forte was reviewed and noted that dissolution specification was revised to 80%(Q). The specification of Betrim Forte was revised based on the comments received from WHO for updating related substance specification. The specification of Betrim Forte was revised due to change in document control system (manual to electronic) as well as amendment to dissolution specification (NLT 75%(Q) of Sulphamethoxazole in 30 minutes and NLT 80%(Q) of Trimethoprim in 30 minutes. The specification stated that the dissolution test is only performed for validation samples (this was for the semi-finished stage).

Process validation protocol & record of Betrim Forte was reviewed. This was superseded by earlier protocol number due to changes proposed by WHO PQ assessors. The reason for revision/change history was part of the protocol. The protocol was revised from 000 to 001, 001 to 002, 002 to 003 and 003 to 004. The current process validation protocol & record was updated and to be submitted to the WHO PQ assessment team in due course.

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 – Inspection outcome
---------------	--

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, **Milan Laboratories (India) Pvt Ltd**, located at **Plot No 35/36/63/64/65/67, Jawahar Coop Industrial Estate Ltd, Kamothe, Panvel, Navi Mumbai, Maharashtra, 410209, India** was considered to be operating at an acceptable level of compliance with WHO GMP Guidelines.

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 WHO Guidelines referenced in the inspection report
---------------	---

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. **Short name: WHO 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 TRS 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
Short name: WHO TRS 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
Short name: WHO TRS No. 929, Annex 4
http://whqlibdoc.who.int/trs/WHO_TRS_929_eng.pdf?ua=1
5. 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 TRS No. 1010, Annex 8**
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_1010/en/
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
Short name: WHO TRS 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
Short name: WHO GPPQCL Guidelines or TRS 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
Short name: WHO TRS 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
Short name: WHO TRS 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
Short name: WHO TRS 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.
Short name: WHO TRS 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
Short name: WHO TRS 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
Short name: WHO TRS 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. **Short name: WHO TRS 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. **Short name: WHO TRS 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. **Short name: WHO TRS 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. **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
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. **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
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. **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
20. WHO Recommendations for quality requirements when plant – derived artemisin is used as a starting material in the production 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
Short name: WHO TRS No. 992, Annex 6
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 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