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

Part 1	**General information**
Manufacturers – Company information details	
Name of manufacturer	Micro Labs Unit-3 (previously named ML-03)
Corporate address of manufacturer	No.27, Race Course Road, Bangalore-560001
Inspected site	
Address of inspected manufacturing site	92, SIPCOT Industrial Area, Hosur, Tamil Nadu, India
Unit / block / workshop number	ML01 location 1, ML01 location 2, Unit-3 (previously named ML-03)
Inspection details	
Dates of inspection	7-10 December 2015
Type of inspection	Special
Introduction	
Brief summary of the manufacturing activities	Manufacturing, Quality Control, Storage, Distribution
General information about the company and site	Micro Labs had 4 manufacturing sites: • Hosur (inspected on days 1 to 4 – object of the present report) • Verna Goa (not covered –inspected by US FDA in May 5-13 2014 with a large number of data integrity findings, a special joint inspection with MHRA on 13 – 17 October 2014 focusing on issues identified by USFDA was closed with a compliance outcome) • Kumbalgodu (inspected on day 2, 3, and 4 – covered in a separate report) • Bommasandra API Division (inspected on day 2, 3, and 4 – covered in a separate report). There was also a pilot, pharmaceutical development plant in Bangalore, called Micro Advanced Research Centre. This was not covered in the scope of the inspection.
History	This was the 8th WHO inspection of this site. In total, there had been 16 WHO inspections, 16 MHRA inspections and 6 USFDA inspections, for a total of 38 inspections of Micro Labs sites in the last 5 years. It was also inspected by UNICEF on 10-12 March 2014.

Brief report of inspection activities undertaken- Scope and limitations

Areas inspected	• Implementation of CAPAs from inspections of February, July and December 2014. • Status of regulatory action taken by other agencies on all Micro Labs sites. • Production in Hosur (ML01 Location 1, ML01 Location 2, Unit-3) • Data integrity and quality control • Product quality reviews
Restrictions	None
Out of scope	N/A

WHO product numbers covered by the inspection

PQP Number	*Product*	*Strength*	*Dosage Form*
TB171	Pyrazinamide	400 mg	Tablet
TB172	Pyrazinamide	500 mg	Tablet
TB173	Isoniazid	100 mg	Tablet
TB174	Isoniazid	300 mg	Tablet
TB237	Levofloxacin	250 mg	Tablet
TB238	Levofloxacin	500 mg	Tablet
TB239	Prothionamide	250 mg	Tablet
TB240	Ofloxacin	200 mg	Tablet
TB241	Ofloxacin	400 mg	Tablet
TB242	Ethionamide	250 mg	Tablet
TB263	Moxifloxacin	400 mg	Tablet
MA112	Artemether/Lumefantrine	20mg/120mg	Tablet, Dispersible
MA114	Artemether/Lumefantrine	20mg/120mg	Tablet

Abbreviations

AHU	air handling unit
ALCOA	attributable, legible, contemporaneous, original and accurate
API	active pharmaceutical ingredient
APQR	annual product quality review
BDL	below detection limit
BMR	batch manufacturing record
BPR	batch packaging record
CAPA	corrective actions and preventive actions
CC	change control
CFU	colony-forming unit
CoA	certificate of analysis
CpK	process capability index
DQ	design qualification
EM	environmental monitoring
FAT	factory acceptance test
FBD	fluid bed dryer
FG	finished goods
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
ID	identity
IR	infrared spectrophotometer
IPC	In process control
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
NIR	near-infrared spectroscopy
NMR	nuclear magnetic resonance spectroscopy
NRA	national regulatory agency
OQ	operational qualification
PHA	preliminary hazard analysis
PM	preventive maintenance
PpK	process performance index
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
RH	relative humidity
RM	raw materials
RS	reference standard
SAP	system applications products for data processing
SFG	semi-finished goods
SOP	standard operating procedure
STP	standard test procedure
T	temperature
TAMC	total aerobic microbial count
TFC	total fungal count
TLC	thin layer chromatography
TMC	total microbial count
URS	user requirements specifications

UV	ultraviolet-visible spectrophotometer
VMP	Validation Master Plan
WFI	water for injection
WS	working standard

Brief summary of the findings and comments

1. Implementation of CAPAs from inspections of February, July and December 2014

1.1 General CAPA plan

In response to the issues found by USFDA of trial injections being performed and of products being tested into compliance at Micro Labs Goa and Bommasandra, in response to the WHO and MHRA, as well as UNICEF inspection observations: Micro Labs main CAPAs were:

- Implementation of new corporate quality assurance procedures (QAP)s at all Micro Labs sites as of 25.12.2014 to harmonize the quality systems across sites.
- Implementation of a new data integrity policy (reported by the company to be done across sites).
- Increased internal audits.
- Performance of monthly quality system reviews.
- With regards to analytical tests and computerized systems:
    - Enabling of audit trails on all instruments.
    - Removal of most standalone HPLC and GC Systems. Installation and validation of CFR21 compliant software (Empower 3 at Hosur, Goa and Bommasandra, Empower® 2 at Kumbalgodu as well as Chromeleon® on some GC systems at all sites). Purchase of new software licenses to ensure the ability to create individual user ID's.
    - Removal of ability to change time and date on systems through installation of desktop security (only IT administrators capable of changing them).
    - Identification, challenge and documentation of user access privileges – implementation of desktop policies and privileges for 26 workstations in QC block for ML01 products, and 20 in QC block for Unit-3 products.
    - System of backing up data on HPLC instruments set in place.
    - New validation master plan created for computerized systems and validation performed on all software used on computerized systems.
    - Validation of compendial methods was undertaken because of issues noticed with the application of some of the compendial methods.
    - Strengthening of their laboratory control procedures to better control manual integration, system suitability and to remove the performance of trial injections. Runs were divided into Set I for system suitability and Set II for the run including samples. Failing system suitability was now being trended under deviations. Runs failing after system suitability tests were investigated as out-of-specification test results.
    - Retrospective review was being conducted for all batches within their expiry dates.
    - Revision of IT SOPs and implementation of a SOP on disaster recovery and management.
- Improvements in the training program:
    - Technical training coordinators identified from individual departments.
    - Behavior change training was implemented across the different sites.
    - Training on good documentation practices to personnel from production, packing, QA and QC.
    - Implementation of an electronic training system (Nichelon) for planning, execution, evaluation and tracking of trainings.

- Hiring of new staff (Note: stability of staff/high turnover was acknowledged to be a big issue at the company). This included:
    - An increase in quality assurance staff from 19 to 28 in Unit-3
    - An increase in quality assurance staff from 31 to 48 in ML01
    - An increase in quality control staff from 39 to 43 in Unit-3
    - An increase in quality control staff from 70 to 90 in ML01
    - An increase in analytical QA from 10 to 11 in Unit-3 and from 14 to 19 in ML01
- Improvement in the performance of complaint investigations (the previous procedure was raised as inadequate by UNICEF because it did not explain how to proceed when the complaint sample was not received).
- Implementation of software (Minitab) for statistical evaluation of critical quality attributes and process parameters for the product quality reviews.
- Improvement of procedure for inspection of tablets/capsules to provide instructions to record the details of rest timings and reason in the Machine Usage and Cleaning Log under the columns "machine down time" and "reason for down time".
- Sharing of learnings from one site to another was done through corporate management but was not done systematically through the use of a database. See "Part 6" for observations.
- Uniform implementation of quality system between ML01 Location 1, ML01 Location II and Unit-3 (note: ML01 and Unit-3 were defined as separate by the company, having fully independent manufacturing and QC facilities and separate heads of warehouse, production, quality control, engineering and quality assurance and also now with separate manufacturing licenses – ML01 was not manufacturing any prequalified products.)

To recapitulate, the following observations were raised previously for ML01 and Unit-3 by WHO. The review of whether or not the issues were resolved is included below each observation:

1.2 Electronic data

A previous inspection of the quality control laboratory of ML01 revealed that the company had failed to establish, implement, and maintain policies, systems, procedures and controls to ensure the reliability and integrity of data. Laboratory instruments were not appropriately used and controlled. For example:

a) At least five HPLCs with instrument identification numbers 70, 71, 55, 56, 57 were used even though the audit trail function had been disabled resulting in the fact that the sample sets shown could not be satisfactorily verified;

b) Although the audit trail function was enabled for some HPLCs, review of the sample set for Paracetamol 500mg tablets analyzed on 3 February 2014, showed that there was no audit trail of the manual integration of the peak for 4 aminophenol which was reflected on the electronic chromatograms as "bb";

c) The printouts of the chromatograms referred to in (b) above did not reflect the integration (e.g. BB, bb etc);

d) Even though the chromatograms showed manual integration (as referred to above), the checklist for the analysis was marked and signed for, indicating that there was no manual integration, and no justification for the manual integration;

e) There was no SOP to describe the policy, standard practice and circumstances under which manual integration would be allowed;

f) During the interview with the system administrator, he indicated that he had been newly appointed to the site and had been there for about three months. Reviewing the audit trail, it was established that he had been signed in since 27 July 2013. The system administrator had therefore provided misleading information to the inspection team. In addition, when asked to show the audit trail settings, he was unable to do so as he had been blocked from the system for the "last two weeks". He indicated that this had been reported and that he was still

waiting for a new password. On challenging this, he was "given" a new password within seconds (on 2014-02-11 at the time of the inspection) and was able to log in;

g) At least five HPLCs with instrument identification numbers 70, 71, 55, 56, 57 were used with the date and time function unlocked, which could be changed by any person as these HPLC were associated with computer systems that were not linked to the server (also referred to as "stand alone systems");

h) In reviewing the audit trail on HPLC 111 for sample analysis in February 2014, it was established that a common password had been used by laboratory personnel reflecting only "Lab-user/analyst" in the audit trail, hence unable to attribute the individual activities to the specific analyst;

i) Trial system suitability (which was performed in some cases before the start of a sample set analysis) was not included in the sample set. This trial was not mentioned in the analytical report and the chromatogram obtained was not filed as part of the analytical report (e.g. Paracetamol 500mg tablets). The SOP only stated that the trial injection could be performed "if necessary before starting a sample set". It was not clear when it will be necessary, or how this will be recorded or how the results will be filed.

j) It appeared that analysts were allowed to and were able to delete files without control and documented justification. A file was identified in the "recycle" bin on 2014-02-11 on HPLC 70 and there was no documented explanation in the audit trail or otherwise why it had been deleted

k) Electronic analysis data reviewed on several HPLC systems reflected that the responsible analyst could not be identified on the system as the user was logged in as "lab-user" and not identified by his/her unique username and password;

l) The company failed to appropriately secure the data obtained from stability testing, specifically as the SOP required that backups of data were to be done on the first day of every month for standalone HPLC systems. The company and IT administrator confirmed several times that the backup for December 2013 was made. However, when the inspectors went to the IT office to review the backup data, there was no backed up data for December 2013 or January 2014 for HPLC S 82;

m) Further to the lack of control over HPLCs and ensuring the reliability and integrity of data, the inspectors reviewed analysis of Captopril 25 mg tablets USP Batch No CPUH0034. On verifying the source data, the system audit trail showed that the system was last running at 05.07.28PM and again started at 10PM. The analysis was apparently performed between 5.07.28PM and 10.00.48PM according to the printed chromatograms;

n) While manual integration was performed to integrate impurity peaks, there was no procedure available on manual integration. In addition, although existing procedure (SOP QCGN: 050) on Empower Chromatography Data Management didn't provide privilege for an analyst to change integration parameters, analysts were able to perform manual integration. The procedure applies to ML01 and ML03.

Review of resolution of the issues on site: Audit trails were enabled on most systems in ML01, but at the time of the inspection, there were still some issues seen for 2 systems that were networked together but standalone from the others in ML01.

1.3 Product quality reviews

During a previous WHO inspection, the SOP and PQR for INH were reviewed and the following issues were noted:

a) There was no provision for review of post marketing commitments;

b) 39 batches were produced in the period January to December 2012. Quality attributes were reviewed and trended but there was no risk assessment for a product, and no risk assessment to determine the CQAs and CPPs for each product;

c) Results were presented in graphical form, and an OOT limit of 1% above lower specification limit and 1% below specification limit was set. There was no actual statistical calculation for trending of results obtained from batches manufactured over the specified period of time (e.g. no 3 sigma, CpK or PpK);
d) The PQR reflected results for Purified Water for two sampling points, and there was no reference to the separate water report. Water results were not trended by means of statistical calculation (e.g. 2 sigma or any other suitable method);
e) Despite the fact that no statistical methods were used for determining whether the process was capable, the company concluded that the process was validated and that there was no need for any change.

Review of resolution of the issues on site: although the timely writing of product quality reviews for all products was still an issue, most of the above observations were resolved.

1.4 Documentation – analytical worksheets

During a previous WHO inspection, Analytical Work Reports (AWRs) specifically in ML01 were not appropriately issued by the laboratory QA section; and different stages of preparation of samples, solutions, buffers and testing were not recorded at the time of analysis; and results were not processed in a timely manner.
Specifically:
a) Some AWR sheets were issued by the laboratory QA, but required information such as product or batch number or AWR numbers were not recorded when these were issued;
b) AWRs were not always completed at the time of sample preparation/ weighing of sample/standard, preparation of buffer solution, mobile phase, impurity solution, system suitability solution, test solution, standard solution (e.g. Gabapentin analysis of February 2014 for early and late eluting impurity);
c) No evidence was available in the AWR for the calculation of the concentration of the of the eluting compound;
d) The weighing slips for materials (standard and sample) for the Identification test had no entries for the AR or test name e.g. in Paracetamol tabs PCLH0935, 3 February, AR MBP140273.
e) There was no record for the preparation of 0.1 M Sodium Hydroxide used during the analysis of Paracetamol tabs PCLH0935, 3 February, AR MBP140273.
f) In several AWRs, results were recorded by analysts days before the inspection, but these results/calculations were not appropriately recorded as e.g. chromatograms had not been printed or other documented evidence existing to show that the results were within specification. These prepared samples were no longer available to allow for any investigation in case of an out of specification (OOS) result or re-testing where appropriate;
g) The AWR for MethylDOPA tablets 250mg BN MTYH0176 sampled on 4 February 2014 at 16:10, AR MBP1400295 showed that for the assay test, no record was available for the preparation of the standard. (The weighing slips showed that it was done on 6 February). In addition, there was no record or reference to the preparation of reference solution a or b and no record for the system suitability (number of theoretical plates and tailing factor) for the related substances test as required by the test method; The ratio of solvents in the mobile phase for the test for related substances for Paracetamol tablets was incorrectly stated as 50:375:375 on the approved AWR (related substances) since 2012 and not identified by the company or updated accordingly (e.g. Paracetamol tabs PCLH0935, 3 February, AR MBP140273

Review of resolution of the issues on site: significant improvements had been made in the above area and no observations were made in this regard during this inspection.

1.5 Laboratory controls – OOS

During a previous WHO inspection, it was found that the company had failed to appropriately manage OOS results:

OOS reports for Isoniazid 100mg uncoated tablets, blister and bulk: 13001, 9, 16, 23, 24, 25 were requested for review. It was noted that several batches of INH tablets were failing stability testing at different time points, under different conditions (accelerated and 30C/75%RH e.g. Batch IZBBH0006 (January 2013). There was some limited impact assessment of the failure, but not all batches, material, packaging material; and batches were included in the impact assessment. No risk assessment had been done up to the date of the inspection. No recall had been initiated. (It was noted that there was some explanation given as to the ongoing investigation by the company in relation to the interaction between lactose and INH).

Review of resolution of the issues on site: this issue was resolved in the company CAPAs.

1.6 Laboratory controls – Stability

During a previous WHO inspection, it was found that the company had failed to appropriately ensure the integrity and reliability of stability data produced by the Stability Section in ML01. Specifically:

a) The audit trails of several HPLC systems in the stability section were "disabled" even as these were standalone systems that were not linked to a server;

b) The stability report for Captopril 25 mg USP tablets for the 12 month time point for Batch 0037 could not be located on the day of the inspection.

Review of resolution of the issues on site: this item still appeared to be an issue but for a limited number of systems. This was stated to be corrected in the company CAPAs.

1.7 Laboratory controls – Traceability

There was lack of traceability of materials and standards used during the analysis of materials and products. For example:

i) Petri dishes with KBr were kept in a dry box in the laboratory for the preparation of pellets used in performing an identity test of materials/products. The petri dishes were inappropriately labelled and did not reflect information such as a batch number of the KBr and dates (expiry, loading to the dry box);

j) The KBr supposed to have been used in the identity test of Gabapentin in February 2014, was recorded as having been opened on 9 January 2014. This batch could not be located in the laboratory. An open bottle (with a different batch number) was kept in the cupboard but had no label to indicate the date of receipt or date of opening. Laboratory personnel also showed another bottle that was "in use" with a date of opening stated as mid-2013.

Review of resolution of the issues on site: this item was found to be resolved in the most part.

1.8 Laboratory controls – CoA

During a previous WHO inspection, it was found that the creation, preparation, saving of Certificate of Analysis (COAs) was not appropriately managed:

a) There was no electronic copy of the COA maintained, nor any printed copy on file in the laboratory. (One copy is kept with the analytical report (which is kept with the BMR),

b) There was a contradiction between raw data and CoA for certain batches. For example, for AR HPP120065 for Moxifloxacin Batch MXBHH0003, (Dec 2011, EXP Nov 2013), an initial printed COA submitted with the sample to the CRO stated "white" tablets but the raw data recorded by the analyst showed "pink" tablets.

Original COAs (or copies thereof) for e.g. HPP120065 was not kept on file as required – and no copy appeared to be available on site;

c) There was no deviation recorded for the issuing of a corrected COA. In addition, the new COA was dated as 14.02.2012 even though the company was informed of the incorrect information on the COA only on 17 April 2012;

d) There was an SOP for the creation and control of COAs which was effective from 11 June 2012. A register was to be maintained for the creation of COAs, however there was no register maintained for 2012;

e) The SOP did not specify what action should be taken in the event of a COA created with incorrect information.

Review of resolution of the issues on site: this item was found to be resolved in the most part.

2. Good manufacturing practices for pharmaceutical products

The practices in ML01 Location 1 (briefly inspected on Day 1) and ML01 Location 2 (briefly inspected on Day 4) were different from those at Unit-3 (briefly inspected on Day 1 and Day 3).

In Unit-3, in the granulation suite, a sifter was found unprotected by dust extraction but most equipment was using vacuum transfer and/or had dust extraction. All compression equipment had metal detectors.

In ML01 Location 1, operators were scooping powders from large blue plastic drums. Their gloves did not extend beyond approximately the first half part of the arm. Since gowning was only changed twice per week, this could have resulted in the transfer of powders from personnel gowns from one product to another.
The cleaning room that was used for cleaning of granulation equipment was found to contain stagnant water and apparent black mold growth visible on the walls and ceilings. These issues were resolved in the company CAPAs.

3. Status of regulatory action taken by other agencies on all Micro Labs sites

Recalls were performed for 11 batches further to re-analyses of 166 batches.
Canada ordered the reanalysis of market samples, including 150 samples in Canada and 400 samples in Europe by 3 independent laboratories, but the outcome of this was not presented by the company.

4. Data integrity and quality control

Unit-3 **laboratory**

The SOP on control of QCL equipment and software described 3 categories of equipment: those that are captured on the server, those that do not have audit trails but whose audit trails are captured by the class agent server, and standalone equipment supported by daily backups and where the data is pushed to the server.

The laboratory in ML02 (used for Unit-3) was equipped with 18 HPLCs and 1 GC.

The I094 system was disconnected on 02/11/2015 at 18:26 and reconnected only on 03/11/2015 at 17:44 only.

Months of June, July, August were checked for any apparent repeat testing.
Clarithromycin blank performed on 13 October, had an impurity peak eluting at the same time-point as Impurity E. No clear explanation could be provided for this, and the impurity E peak in the blank was higher than in the system suitability solution.

There were out-of-specification results OOSs for clarithromycin at the 36 month, time-point. An OOS was found for HSS150267 (CLABH0001) and 150269 (CLABH0002). The company stated that these OOSs were due to sonication at first. Then, when asked about the method, the explanation was modified. The hypothesis of sonication under heat, as the root cause, was eliminated. The peak at 14.803 minutes was failing with a peak area of 12907, corresponding to approximately 1% of the main peak. The company attempted to prove the hypothesis of contamination by adding 20 mg of resagiline and 20 mg tramadol to a sample. The peak area at that specific retention time did not appear to be higher than for un-spiked samples, and the sequence did not include an injection of un-spiked sample hence their conclusion on probable root cause was likely erroneous.

Furthermore, the repeat analysis on fresh sample done on 21/10/2015 led to an OOS result again with 0.77% for the single unknown impurity for HSS150277 (batch number CLABH0001 30°C/75%RH) and HSS150278 (CLABH0002). Impurity I was failing (single maximum impurity). The full scale investigation had yet to be done.

Placebo was injected but passed off as blank – one of the analysts confirmed it was actually placebo but then retracted his statement afterwards. It appeared that placebo was injected although this had not been documented in the reports shown, because the chromatograms contained a number of large peaks. This lack of traceability can compromise the system for investigation of OOSs. The conclusion had not been made and a full scale investigation was still due.

Another OOS for the same batches, was obtained at the 30°C/65%RH condition, 36 month time-point. Failing dissolution testing with results of 5.1% and 5.3% were observed.

Another OOS was opened on 25/06/205 and reviewed for isoniazid tablets. Since it was deemed valid, a variation was filed and approved by WHO, for a revised limit for single unknown impurity, including 1.5% for the impurity with a RRT of 1.62. The variation was applied for testing of batches IZBAH0005, 0006, 0007, 0004 and 0005. Blisters showed impurity levels of up to 2.1 % but since they are not prequalified, this was not raised to the WHO assessment team.

An OOS from 14/05/2015 was requested. It was on erythromycin EP, Batch No. CEPEB019015. It stated that a result of 0.5642% for sample I, and 0.6074% for sample D were observed against the specification limit of NMT 0.10%.

There were 36 different time-point samples of Clarithromycin tablets 250 mg and 500 mg samples at 25°C/60%RH and 30°C/75% RH. Dating from March 2015, that were not analyzed, for batches CLABH001, CLAB H002, CLBBH001, in packaging formats of 10 x 10's, 500's, 100's. Although this was claimed to be due to a lack of manpower, it also appeared to be related to the ongoing OOS investigations.

There were 7 tests for isoniazid 100 mg and 300 mg that were not complying with specification limits.

The deviation for artemether/lumefantrine DT 20/120 mg tablets not being tested on time (withdrawn on 30/05/2015), at 30°C/75%RH and 30°C/65%RH, was requested for review.

ML01 Laboratory

The ML01 laboratory was only briefly inspected on Day 4. In the ground floor, there was a laboratory described to be used for process validation, analytical method validation and cleaning validation. It contained a large number of HPLC systems distributed in 2 different rooms.

In the back room, there were 2 standalone systems found using Chromeleon, ML/AVL-078 and ML/AVL-079. These were turned on and the instrument audit trail was opened. It was found to contain only a limited number of entries and it was later on noted that it was fully turned on only on 13/11/2015 for these two instruments (ML/AVL-078 and ML/AVL-079). These systems had been in use since much earlier than 13/11/2015 and were sometimes used to test raw materials, as seen in the case of metformin API related substances test and in the case of AR Number MRM152059 (Instrument ML-AVL-079).

The instrument logbook for instrument ML-AVL-079 did not contain all of the analyses appearing in the instrument audit trail for the month of November. Namely:

-Saved as \NOV\RM\MRM152059_RM_AS_Set 2 01.seq, started on 24 November by Yuvaraj 98633, at 20:40 and ended at 00:26 on 25 November 2015.

-Saved under the same file name, the batch named MRM152059, started on 25 November 2015 by Yuvaraj 98633, at 13:25 and finished at 14:47, was not recorded in the logbook. Before it was started, the standard and samples for investigation were added, the vial number was updated, and the sample set was updated.

-Saved as Set 2 02 seq., it was started again on 26 November 2015, at 17:16, the vial number was updated at 18:23 and it was finished at 19:40. There were no records of instrument usage in the instrument audit trail between this date and December 1st, even if the instrument log stated that calibration was done on 27 November 2015 and 30 November 2015, which could lead inspectors to believe that calibration was not actually conducted on those dates.

The logbook for ML-AVL-079 only contained 3 entries in November:

-24 11 2015 preventive maintenance

-27 11 2015 calibration

-30 11 2015 calibration

The impurity limit was 15.30 to 18.70%. Upon retesting, at 100% filled vial, the result was 19.35%. Solutions were prepared on 26 November 2015. The 70% full vial gave results within limits of 15.81%. The OOS report did not document any of the 2 different investigations done. Other results obtained were of 13.08% sample 1, 14.89% sample 2, initially.

Another instrument, No. 021 was not on the network – it was stated that this was due to the fact that there was a problem with it.

The protocol for review and accountability of chromatographic data system and electronic raw data files in the QC laboratory, dated 21/11/2014, was reviewed.

Stability studies

As of 17/11/2015, the company stability status included 63 samples with one test pending, and 18 samples with 2 tests pending. An observation was raised in this regard. It was resolved in the company CAPAs.

5. Product quality reviews

Product quality reviews were managed in accordance with an SOP effective as of 11/05/2015. The period of review was January to December for products for the EU/UK markets (review completed by 31 March) while the commercialization anniversary was used for products for the US (review with 2 months) and WHO/ROW/Domestic (review within 3 months). The SOP identified methods to assess variation and trend, including my means of a variety of statistics. The issue noted includes:

- Whereas the SOP provided for reviewing of completed batches only, the template for the PQR included batches under process at the time of review.
- There was no schedule for products to be reviewed based on their anniversary of commercialization.
- The SOP provided for a separate PQR for products supplied to different customers and a summary PQR for similar products. The term "similar products" had not been defined and a list of such products was not available.

PQR of the following products were available and briefly reviewed:

- Pyrazinamide 500mg BP: Jan-Dec 2014, 1batch, approved 05/11/2015.
- Pyrazinamide 400mg USP: Jan-Dec 2014, no batch, completed 08/09/2015
- Isoniazid 100mg BP: Jan-Dec 2014, 4 batches, completed 24/08/2015
- Isoniazid 300 mg BP : Jan-Dec 2014, 7 batches, completed 21/08/2015
- Levofloxacin 250mg IHS: Jan-Dec 2014, 27 batches, completed 28/11/2015
- Levofloxacin 500mg IHS: Jan-Dec 2014, 4 batches, completed 10/07/2015
- Prothionamide 250mg: Jan-Dec 2014, 8 batches, completed 08/09/2015
- Ofloxacin 200mg, 4 batches
- Ofloxacin 400mg, 4 batches
- Ethionamide 250mg, 4 batches, completed 08/09/2015.

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, **Micro Labs Hosur Ltd**,located at **92, SIPCOT Industrial Area, Hosur,** Unit-3 (previously named ML-03)**, Tamil Nadu, 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

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