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

Part 1	**General information**
Manufacturers details - Company information	
Name of manufacturer	Micro Labs Ltd.
Corporate address of manufacturer	Micro Labs Ltd, 27 Race Course Road, Bangalore, Karnataka, 560 001, India
Inspected site	
Address of inspected manufacturing site if different from that given above	Micro Labs Ltd, Phase III & IV, Plot No S-155 to S-159 & N1 Verna Industrial Estate, Verna, Goa, 403 722, India GPS coordinates: N15^0 21'49.464", E 73^0 56'55.3776" DUNS number: 91-579-3658
Unit / block / workshop number	ML06
Manufacturing license number, (delete if not applicable)	Insp. GMP 22481/30300-0005 issued by UK MHRA 651 and 652 Issued by Directorate of Food and Drugs Administration, Bambolim Goa.
Inspection details	
Dates of inspection	15-18 June 2016
Type of inspection	Routine Inspection
Introduction	
Brief summary of the manufacturing activities	Manufacture of finished pharmaceutical products, intermediate or bulk, packaging, laboratory testing, batch certification and batch release, storage.
General information about the company and site	According to the opening meeting presentation: -Micro Labs Limited has been manufacturing medicinal products since 1973. The company is engaged in manufacturing of various therapeutic segments and has a total of 14 manufacturing facilities in India for the manufacture of products for domestic and export markets. The company is exporting to over 60 countries worldwide. -The manufacturing facility, Micro Labs Limited (ML06) was located in Verna Industrial Estate, Verna-Goa, India which is 25km away from main capital city Panaji.. -The site was engaged in the manufacturing of oral solid dosage forms of medicinal products -There were 215 staff in QC, 5 in IT, 347 in production and packaging, 67 in engineering. -The last FDA inspection was in 2014 and CAPAs were submitted to US FDA but

	were not yet accepted.
History	The last WHO inspection was a joint inspection with UK MHRA on 13-17 October 2014. Prior to this, the last routine WHO inspection was 15-18 January 2013
Brief report of inspection activities undertaken	**Scope and limitations**
Areas inspected	All block were inspected.
Restrictions	n/a
Out of scope	n/a
WHO product numbers covered by the inspection	**Prequalified:** HA483 Zidovudine 300mg tablets HA485 Lamivudine/Zidovudine (150/300) tablets HA536 Lamivudine 30 mg film coated tablets HA537 Zidovudine 60 mg film coated tablets HA555 Lamivudine/Zidovudine (30/60mg) tablets HA567 Nevirapine 20 mg tablets HA568 Nevirapine 50 mg tablets HA569 Nevirapine 100 mg tablets HA570 Nevirapine 200 mg tablets HA620 Lamivudine/Tenofovir disoproxil (fumarate) Tablet, Film-coated 300mg/300mg HA631 Emtricitabine/Tenofovir disoproxil fumarate 200 mg/300 mg tablets HA644 Lamivudine Tablet, Film-coated 150mg HA651 Efavirenz/Lamivudine/Tenofovir disoproxil (fumarate) Tablet, Film-coated 600mg/300mg/300mg **Under assessment:** HA629 Lamivudine/Nevirapine/Zidovudine Tablet, Film-coated 150 mg/200 mg/ 300 mg HA633 Efavirenz Tablet, Film-coated 600mg TB275 Cycloserine Capsules, hard 250mg MA132 Amodiaquine /Artesunate Tablets 67.5/25 mg MA133 Amodiaquine /Artesunate Tablets 135/50 mg MA134 Amodiaquine /Artesunate Tablets 270/100 mg MA674 Abacavir Dispersible Tablets 60 mg

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
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
QA	quality assurance
QC	quality control
QCL	quality control laboratory
QRM	quality risk management
RA	risk assessment
RCA	root cause analysis
SOP	standard operating procedure
TAMC	total aerobic microbial count
TFC	total fungi count
TLC	thin layer chromatography
URS	user requirements specifications
UV	ultraviolet-visible spectrophotometer

Part 2	Brief summary of the findings and comments (where applicable)

Brief summary of the findings and comments

1. Pharmaceutical quality system

The overall objective and direction of the company related to quality matters was formally described in the Quality Policy document that had been authorized by the Chairman & Managing Director of the company. Documents requested by the inspectors were available at short notice. 118 people were employed in QA.

Deviations

There were 2 SOPs in place:
-Handling of deviations (03/March/2016), valid for deviations during manufacturing, packing, storage and internal distribution,
-Handling of laboratory deviations (20/Jan/2015): this SOP was valid for any unusual / unexpected occurrence in the course of testing samples not leading to OOS results.
Differentiation in planned and unplanned deviations was done.
Deviation listing for 2015 and 2016 was available. Some examples were checked (see section about PQR).

Handling of OOS test results (05/Feb/2015)

The SOP was reviewed. Trending of OOS results for 2015 was available. 250 OOS were recorded. 230 investigations were closed at the end of the year. 46 were concluded as valid OOSs. In 119 cases, analyst errors were identified as the reason for the OOS result.
CAPA was initiated on 12 March 2016. Re-evaluation of all OOS results was done. Measures were implemented to reduce the number of analytical errors. The CAPA was still open at the time of the inspection, to monitor the effectiveness of the training for 6 months.

The logs for 2015 and 2016 were reviewed. In 2016, the following OOSs were noted:

- For zidovudine USP raw material OOS, assay results led to the rejection of a batch.
- Efavirenz tablets 600 mg, , assay, IP standard had OOS results for assay but was finally passed by Nilesh Jadhav (analyst).
- EET tablets (Efavirenz, emtricitaine and tenofovir) had an OOS at 40^{o}C 75% RH 3 M in blister packs of 10's, batch. The conclusion was "it is stability sample" for related substances. It was a confirmed OOS as of 28/04/2016.
- Lamivudine, zidovudine and nevirapine tablets for oral suspension (no dosage information seen in the log), in stability, 30^{o}C, 75%RH, 36 months, PVC, PVDC blister packaging dissolution problem was confirmed. The action taken was to further monitor stability in the submission batch.. Information was given that it was withdrawn. The company later on stated that this was for HA619, LNZ tablets dispersible 30/50/60 mg. As per a letter sent by WHO on 15 June 2016, the product had to be reformulated due to BE failure (Semler issue) and due to stability problems.

A copy of the entire log for 2016 was made by the company and retained by the inspector.

In the 2015 register logbook, the following OOSs were found:

- Amitriptyline tablets 50 mg,: there was a stability OOS for 25^{o}C, 60%RH (no timepoint given) in blister packs of 10, the assay results were found OOS, but were not confirmed and therefore the OOS was passed. This was not the first time, as issues were noted on the API RM amitriptyline HCL, , on 21/11/2015 (AR number illegible) and the batch was also passed.

- Lamivudine 150 mg and zidovudine 300 mg tablets: there was an OOS reported on 06/11/2015, in stability, for batches, 30°C 75%RH, 36 months, related substances. HDPE bottles 100's and 30's were OOS for the related substances test. The OOS was confirmed but the final conclusion was "long term to be performed". No final conclusion was available.

Handling of Non-conforming products (10/Aug/2015)

The procedure was in place to prevent the unintended use of any product manufactured at the site which is not conforming to its approved specification. According to the procedure, a NCR form was to be issued and non-conforming product should be quarantined. The review of the non-conformity and the recommendation of action to be taken were recorded in the NCR form.

Reworking was defined in the procedure. However, according to the information provided by ML, reworking of products was not permitted (this was also written in the SMF, point 6.3.5). The register of NCR investigations was available and was reviewed.

Handling of OOT test results

The SOP (23/Sep/2015) was reviewed. For APIs, in-process and finished product testing, the PQR data of the previous year was used as a standard for computing the limits for identifying OOT results.

Handling of corrective and preventive action (18/Feb/2016)

CAPA was to be initiated based on the investigation of the discrepancies reported related to processes, procedures and systems listed in the SOP. All relevant topics were listed.

Product quality review (PQR)

The QA procedure "Product quality review", effective from 03 March 2016, was reviewed. It included a detailed description of the whole PQR generation process and enclosures: e.g. PQR Plan, Report formats.

There were PQR plans for every year and for different markets. Preparation and completion time was defined for every market: e.g. PQRs for EU products should be done by end of the the calendar year and finished in the first quarter of the next year.

PQRs for WHO products / ROW (rest of the world) / domestic market should be done annually, starting from the month of product commercialization and should be finished within the next two months from the identified review period (new products) and in the 2nd quarter for existing products.

There were 95 products (tablets and capsules) produced at the site. Production was only done for export. A product list was part of the SMF (annex 2).

Plans for the PQRs for WHO (5 products) and EU (74 products) for 2016 were available. Approval of the plans was done on 04/Jan/2016.

Additional plans for the US/Canadian market (including Efavirenz tablets 600 mg) and other markets were also available.

PQRs for WHO products were available as planned. The Product Quality Reviews for the current WHO products for the year 2015 were sent before the inspection and reviewed in detail.

Examples:

- LAMIVUDINE 30MG AND ZIDOVUDINE 60MG TABLETS (film coated tablets): No batches were manufactured for the product during the year 2015. The master formula record and batch manufacturing record were changed together with CCR:03:002/15:098 to include the validated process parameters. Details of this change were evaluated. The change was proposed on 3 March 2015 to implement the results of the process

validation study and to add an additional supplier for Magnesium stearate. Closeout was documented on 5 June 2015. The validation report was approved on 4 March 2015.

A new supplier for magnesium stearate was added. A supplier audit was done on 9 February 2013 and specifications were added (REND407/R1, 19/June/2015). Details of the current specifications were checked and found in accordance with USP 39. An audit report from 8 April 2013 was available (15 pages, 2 major and 6 minor deficiencies were documented). An audit compliance report was provided on 27 May 2013 by supplier. Evaluation of the corrective actions and closeout of the audit was not documented by ML.
A statement from supplier, confirming that the magnesium stearate was produced from non-animal sources (free from any risk of TSE and BSE) was available. This was also checked during the site audit done by Micro Labs.
For the European market, raw material specifications RMS REND085 were used (same supplier). The specifications (REND085/R1, 10/July/2012) were checked and found in compliance with the EP.
According to the information given by ML, all batches were being analyzed according to the complete specification. Reduced testing was defined for the retesting procedure.

Finished product specifications were revised in accordance with change control CCR:11:017/15:667 (new MPR/BPR to provide the product to a new customer). Documentation was checked in detail. New master packing records, batch packing record and packing material specifications were generated.
Close-out of the change was documented on 23 December 2015. Detailed documentation for the change was available as an annex.

-Deviation: DR:03:009/15:068: It was opened because the hold time study sample of coating solution and lubricated blend of the batches mentioned in Annexure 1 and Annexure 1 (A) respectively, were not analyzed. It stated that the hold time study sample of coating solution and lubricated blend of the batches mentioned in the Annexure 1 and Annexure 1 (A) in the deviation report should be analyzed on the next commercial batches.
Status: according to the list of batches mentioned in the annexure, only Metformin 500mg coating solution hold time analysis was completed and others were pending due to unavailability of production plan and import alert of US product.
The deviation could be closed together with the initiation of the CAPA on 11 July 2015.

- LAMIVUDINE 150MG AND ZIDOVUDINE 300MG TABLETS
As PL Holder and Contract giver, “ROW” (rest of the world) was given.
5 batches were produced and released in 2015. Batch size was 1,000,000 tablets.
3 batches were under process at the end of review period.

One OOS together with raw material quality was confirmed (magnesium stearate, see below).

Changes in the production process: CCR:11:060/14:622 (BMR, BPR and AWR should be provided electronically through SAP) and CCR:05:060/15:299 (additional suppliers for magnesium stearate were included).

-CAPA CP:15:053 (11/07/15): Lamivudine 150 mg and zidovudine 300 mg tablets coating solution hold time analysis was completed and others were pending due to unavailability of production plan and import alert of US product. This CAPA was still open, because some of the products were not produced since the time as the deviation occurred.
The hold time study for lubricated blend lamivudine 150 mg and zidovudine 300 mg tablets had been done.

Five deviations were raised during the review period. For further details, refer to DR:03:009/15:068, DR:10:025/14:278, DR:03:023/15:082, DR:08:016/15:238 & DR:09:012/15:260.

- (24/02/2015): According to the OOS listing: the test for specified microorganisms was found OOS. According to the results observed, E. coli was present (Batches were rejected).

Documentation for this OOS investigation and the communication with the supplier were available. Risk assessment was documented. Status of the supplier was maintained after the evaluation because of a long history of delivering of product according to the specification.
Documentation of the data from the microbiological laboratory: The first microbiological testing (09/Feb/2015) gave the result of 120 cfu/g (Batch 1) and 100 cfu/g (Batch 2). Both results were OOT (normal results for the batches before were below 10 cfu/g). E. coli was absent during this first testing.
Because of the OOT investigation, microbiological testing was repeated (17/Feb/2015). Results for TAMC were confirmed. E. coli was found present in the samples.
The OOT investigation report (16/Feb/2015) and laboratory investigation report for the OOS results (presence of E. coli, 24/Feb/2015) were available. After the investigation it was decided that the OOS stood valid and the material should be rejected. The investigation was closed out on 11 March 2015.

From the details of the PQR it could be seen that the problem was with 2 deliveries of magnesium stearate (RMS:REND407-DF, supplier, 2 consignments were rejected out of 8).
This vendor was missing in the summary provided under point 5.3.4 (Details of Excipients Used) and 5.3.5 (Review of vendor audit details). Explanation was given by ML (in this section only information for the excipients and vendors would be included if the excipient was part of the product released in the PQR period).

Review of Qualification status of critical equipment and utilities was part of the PQR. The date for last qualification and next qualification was given for production equipment starting with dispensing booth up to coating machines and Tablet /capsule counters & fillers, and air handling units for all production stages.
The requalification period for production equipment was 3 years (5 years for Metal detectors) and 6 months for AHUs.

Environmental monitoring was carried out by using the following methods:
-Settle Plate Method-Processing area manufacturing & stores: monthly,
-Non processing area manufacturing & stores: monthly
-Volumetric Air Sampling- Processing area manufacturing & stores: Quarterly
-Non Processing area manufacturing & stores: Quarterly
-Contact plate Method: Processing area manufacturing & stores: Quarterly
Results of microbiological environmental monitoring for all the areas used for manufacturing and packing of Lamivudine 150mg and Zidovudine 300mg tablets during the review period were reviewed retrospectively and found satisfactory. The trend analysis for volumetric air sampling and settle plates were also reviewed and found within the acceptance limits.

The review of dossier variations submitted, granted or refused; and post-marketing commitments for new dossiers and variations to the dossiers was part of the document. In this case there were no changes.

Raw material specification:
There were eight different specifications for magnesium stearate (MS:REND407 / 407-DF, REND319 / 319-DF, REND755 / 755-DF, REND336 / 336-DF).)

Zidovudine USP:
For Zidovudine, 2 suppliers were given in the PQR (API Supplier 1, last audit 13/08/13 and API Supplier 2, last audit 11-12/09/13). There were 10 different specifications.

According to the explanation given by ML, specifications were written for every production site of the starting material. In addition, there were specifications for external markets with the code “DF” (duty free) at the end of the RMS number because of financial reasons.

Details of vendor qualification were checked. Detailed audit reports together with the compliance report from API Supplier 2 and the audit close-out report were available.
The audit at API Supplier 1was done for Unit A. Additional audits were documented for Unit B (RADM217), Unit C (RADM095) and Unit D (RADM216). All of them were qualified for Zidovudine. In 2015, material was only received from Unit A (specification RMS:RADM218).
Information in the approved vendor list gave only Unit 9. The other suppliers were deleted because of not supplying in the last 3 years.

Lamivudine USP: One supplier (last audit 11+12/02/16) and four specifications were given in the PQR.

Review of critical process parameters: Drying time for granules, inlet and outlet temperature, LOD, blending speed and blending time, machine speed (compression, coating), and spray rate were evaluated.
Everything was found within the limits.

Some important points were missing in the PQR. This was resolved in the company CAPAs.

NEVIRAPINE TABLETS USP 50 MG
2 batches were rejected during the review period due to failure in comparative dissolution profile (CDP). Problems were found during commercialization of this product after WHO approval. Changes in the production process (granulation) led to compliance with the requirements.

In addition, the PQR for EFAVIRENZ TABLETS 600 MG was reviewed. This product was under assessment at the time of the inspection.
38 batches were produced in 2015.
There was 1 complaint (customer).
The customer was not satisfied by the kind and quality of packing. CAPA was done by Micro Labs (shipper dimension, shipper weight and packaging configuration was changed).

API specifications: There were 2 specifications (RMS RADM172 and RADM229).
All consignments in the year 2015 were ordered according to RADM229.
Specifications were changed in the year 2015 (CCR:02:001/15:053).
Vendor's name was given with (last audit: 01/Dec/2012).
The PQR was finalized on 11 May 2016.

Change control (CC) system
All steps of the change control process were described in the SOP dated 19 October 2015 (initiation, evaluation, approval, implementation, monitoring of the effectiveness of the change, closeout, trending).
Changes were classified as minor, major or critical in relation with their impact to product quality and safety.
Major and critical changes and changes to corporate documents are approved by Corporate QA.
Change control requests should be closed within 30 working days or within the approved extended time period.
Review of open change controls should be done on a monthly basis by the CC coordinator together with Head of site QA / Corporate QA.
Trending of CCs for 2015 was reviewed. It stated that 766 numbers of CCs were initiated. Trending was done based on classification, department wise and category wise. 742 changes were approved (13 not approved, 11 still under evaluation at the end of 2015). 613 CC could be closed in the same year.

The hard copy change logs for 2016 and 2015 were reviewed. In 2016, the following was noted:

- A proposed change to reduce the incubation time for bacterial count (pour plate method) from 5 days to 3-5 days, with a target closure date of 12/18/2016. This may not be acceptable.
- The assay test specification limits for product AQAHG:CH01/R3 and AQCHG: CH01/ was to be revised according to the change control logbook (artesumate + amodiqauine 25/67.5, 30/135 and 100/270 mg).
- A change control for changing software from Chromeleon 6.8 to Empower 3 was seen but for laboratory B only. It was not listed as completed.
- The change control for emtricitabine was requested.

CAPA from USFDA:
The CAPA were declared to be completed by the company and the last update was sent on February 2015 to the US FDA. Letters were sent to them twice afterwards, the last one being in February 2016, requesting an inspection. They were being assessed by a consultant. No information has been received from FDA on the acceptability of their CAPAs, as stated by the Corporate site person.

Quality risk management
A corporate procedure dated 09/09/2015 on Quality Risk Management was available and reviewed.
The need for an annual risk assessment planner was defined. An overview for 2016 was available.
With regards to the air compressor (planned for July), the comment by the inspectors was given that the whole compressed air generation system should be included (compressors, dryers, filters, distribution system, valves).

The risk assessment team shall be selected by the originating department head in coordination with the head QA.

Brain storming sessions, methods of risk assessment, documentation and review of the results were described.

The topic “Cleaning of manufacturing area” was chosen.
Risk identification and quantitative evaluation record was available. Additional risk control measures were not necessary from the point of this evaluation because of all RPN were found below 20.
The final QA statement was done on 25 April 2016. Inspectors recommended to involve microbiologists in the evaluation of such topics.

Overall, the company had adequate systems in place to ensure the quality of products manufactured. There was an appropriately designed and implemented system of quality assurance incorporating GMP and quality control. It was documented and its effectiveness was monitored through audits and self-inspections. All parts of the quality assurance system were adequately staffed with competent personnel, and there were suitable and sufficient premises, equipment, and facilities.

2. Good manufacturing practices for pharmaceutical products

In general, products were consistently produced and controlled according to the quality standards appropriate to their intended use and as required by the product specification. However, some “major” and “other” deviations from GMP principles were observed and these were resolved in the company CAPAs.

3. Sanitation and hygiene

A satisfactory level of sanitation and hygiene was practiced on site. The scope of sanitation and hygiene covered personnel, premises, equipment and apparatus, production materials and containers, products for cleaning and disinfection, and anything that could become a source of contamination to the product.

4. Qualification and validation

Micro Labs identified what qualification and validation work was required to prove that the critical aspects of their operations were controlled.

Qualification

Qualification was described in the VMP (02/June/2016).
Qualification / Requalification status was given in annex 3A (existing building), 4A (new building), 5A (engineering and utility equipment). The requalification schedule for 2016 was available.

Examples for equipment qualification were checked for the following items:
-Compressed Air:
Compressed air was generated in-house and used for various manufacturing operations. According to the description in the SMF, oil free compressors were used for the generation of compressed air. 6 compressors were installed (4 for the existing building and 2 for the new production area).
Compressed air was supplied to a receiver, then passed through refrigerant type air drier for removing moisture content and filtered through a set of filters of porosity 5 µ, 1 µ and 0.2 µ / 0.01 µ before supplying for usage.
Complete drawing of the distribution system was available. The pipeline system was made from stainless steel.
Line pressure was around 7.5 bar.
Point of use filters were installed at the production area and were changed on an annual basis.

Additional pre-filters and activated carbon filter were only installed at the existing facility. An explanation for this different design was not available.

SOPs and log sheets for air compressors and driers were available. However, dew-point reading was not available at every drier used (e.g. no reading at the old air drier from Ingersoll Rand).

One air drier (Atlas Copco FX15) showed P1 failure at the display. Explanations were not available at the time of the inspection but this issue was resolved in CAPAs.

According to the information given by the company, acceptance criteria were specified in the requalification protocol. But only the limit for the bioburden was specified (NMT 100 cfu/ 1000 L). Explanation for this high limit after point of use filtration was not available. Further reduction should have been possible.
For particle and water content, reference to ISO 8573 was given but the specification of limits was missing. This issue was resolved in the company CAPAs.

Monitoring of compressed air was done every 6 months. The last measurement was done on 14 May 2016 by the microbiological laboratory. The last measurement before was done in September 2015. The SOP for monitoring (QCMB:031/E, 22/July/2015) and operation of the RCS high flow touch microbial air sampler was available. Microbiological monitoring was done by sampling of 1000 L. Results were documented in the range of 10 cfu/m^3.

Measurement of the other parameters was done by an external provider. Limits for compressed air water content was given in the protocol used by the external provider with dewpoint at -20 C. All results were found within limits. The limit for the oil content was given with NMT 0,1 mg/m^3. Measurement was done by filter adsorption and IR analysis afterwards. All results were given with < 0,001 mg/m^3.
Results for particles were found at a maximum of 9007 particles in the range from 0.5 to 1.0 µm and 244 particles in the range from 1.0 to 5.0 µm at point of use CA-208 (granulation II). Explanation for the relatively high particle load and bioburden after 0.01 µm point of use filtration was not available.

Design qualification:
DQ for Oil free type air compressor from 2010 was available.
DQ for other parts of the system for the design phase of the new building was missing.

URS for refrigerant air dryer was done in November 2015. This gave only the information that dew point of 3 °C was accepted. The reason for this and the water content resulting from this was not evaluated
DQ for the air dryer resulting from 23/12/2015 did not gave additional information about the water and oil content necessary for the type of products and operations on site.
Continuous moisture monitoring was not implemented. This could be important to make sure that condensation of water in the system would not occur, also for the case of malfunction or overloading of the dryer.
Quality of ambient air should be checked, especially from the point of view of hydrocarbons.
Risk assessment procedure and design verification for the whole compressed air system is necessary was performed further to this inspection.

HVAC system (operation and qualification):
74 AHU's were installed in the existing facility. 82 AHU's were in place for the expanded facility.

According to the SOP (27/March/2015) about operation and monitoring of Air handling systems, ventilation systems and humidifiers, list of units to be operated continuously should be prepared. The list was available showing 30 units for the existing and 31 for the new building, including corridors and storage/staging areas, because of contamination prevention.

Appropriate design qualification of the HVAC system was missing with regards to the area for primary packaging. Massive airflow was observed through wall breakthroughs in between primary and secondary packaging during inspection of the production area in the expanded building. No risk assessment and no continuous monitoring or manual checks together with appropriate documentation were in place. In some cases, airflow went from unclassified secondary packing area to classified primary packaging area. Problem of area contamination was not evaluated during design qualification or risk assessment for correct planning of HVAC system/ correct design of the packaging lines for both production areas (existing and expanded building). Smoke studies were done in 2010 for the existing area. Tests for the new area were missing.

AHU's for production rooms were operated according to the need of the area. If the AHU is off for more than 48 hours, then it is to be started within 72 hours and to be kept operational for NLT 4 hours.

The hold time study report for AHU shutdown was available. A study was performed to demonstrate the impact of AHU shutdown on cleaned status of areas along with differential pressure. Evaluation was done with microbiological, particle and pressure monitoring. A hold time of 72 hours was confirmed. The study was only done for the existing facility. Also appropriate design verification for the area and risk analysis to show, that appropriate backflow prevention is in place if the AHU's are not working, was missing.

Qualification / Requalification of the AHU for granulation-II (M-15 existing building, HEPA filter labelling was A09/SAH/041 till A09/SAH/046) was reviewed. The schematic drawing of the AHU was available (AHS-09, granulation-II). The requalification document for requalification done on 18/May/2016 was available. The report was signed on 30/May/2016. The extent of the verification was found acceptable (HEPA filter integrity, pressure differences, Air volume, particle measurement). Additional testing for recovery time and air flow pattern (smoke studies) were planned at different intervals (12 month and 24 months respectively). The last documented recovery test was done on 22/Oct/2015. Recovery time was measured with 9.83 minutes.

The last smoke test was done on 01/Nov/2015. For the evaluation only 1 CD was available without any comment. Clear valuation of the smoke test results was missing. Documentation on the CD (video) was checked.

Additional evaluation of leakage problems at critical installation should be added (power connectors, drains).

All dampers were regulated manually. Changes of the damper position would require requalification. The system was shut down at the end of each work day. Backflow prevention was not fully implemented (no automatic exhaust dampers in the AHU's). Measures to control the contamination were implemented (see hold time study). Documentation for turning AHUs on and off was available (AHU Start/Stop Log).

During the check of the appropriate function and installation of the HVAC system during the inspection several problems were identified. These were resolved in the company CAPAs.

Dedicated production area:
The dedicated area for production of Misoprostol / Diclofenac tablets was situated in the lower ground floor of the existing building. The area was not under operation since 2013 (production was only done for Canada).
The HVAC system and service area was separated from other production areas. Returned air was first passed through H14 filters. Production rooms were held under negative pressure. An additional "sink type" airlock was added in between the change room and corridor to avoid contamination of the other areas.

Gas Control Unit for Nitrogen purging (MLG/WH/13.001):
The unit was not included in the listing of qualification status of equipment (annex of the VMP). Qualification documentation was not available.

Scales installed in the production area:
Not all relevant scales were included in the listing of qualification status of equipment (annex of the VMP). Balance verification records were available. Daily verification was documented (example Essae weighing scale ds-451 in staging II of existing building, MLG/PR/07.029, operation range 1.5 – 135.00 kg).
The SOP about balance calibration and verification was available (QACB:003/G, 09/May/2016).
An overall listing of production equipment was available. According to this, the scale MLG/PR/07.029 should be in Granulation-V. According to the explanation, installation of the scales can be changed without changing the information given in the listing of production equipment.

Logbooks were reviewed for scale MLG/PR/07.029: Older logbooks were available, but only for the verification and calibration of the scale in the staging-II area. Older logbooks for the other scales (before 2011 were not available (maximum retention time for documents was given with five years).

Production equipment used in the "existing area":
Equipment used for manufacturing of Lamivudine/Zidovudine (30/60mg) tablets, batch size 1500000 tablets, was inspected during the tour through the production of the "existing area" (old building).
Equipment was found in good state. Listing of relevant equipment in the annex to the VMP was checked.
Examples:
-equipment in granulation II (Room M-15), e.g. Fluid Bed Dryer MLG/PR/09.009 (qualification was done in 2009/2010; requalification in 2015), Rapid Mixer Granulator MLG/PR/03.006 (initial qualification in 2004, requalification in 2015).
-Coating Machine MLG/PR/03.040 (Coating-1, M-43, Neomachines, initial qualification in 2004, requalification in 2015).)
-Analytical equipment in the IPC laboratory, e.g. disintegration tester MLG/QA/11.008 (qualification in 2011/2012).

Process validation

The current state of process validation for WHO products was checked on the basis of the listing available with the Validation Master Plan:

Cleaning validation was conducted and found to be generally acceptable (09/June/2016).
The cleaning validation procedure was based on the:

- "Product Group Matrix" revised every time, when a new molecule (active substance) is used in the plant.
- "Equipment Group Matrix" identifying equipment chain used for the manufacture of the certain molecule (product). Finally, a matrix for determination of Maximum Allowable Carryover (MAC) was prepared for each equipment chain.

However, mistakes in the calculation of the new MAC on the base of PDE values (permitted daily exposure) were found. Namely, a new concept of consideration of PDE (permitted daily exposure) in the calculation of the MAC was implemented in June 2016. Guidelines on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities (EMA/CHMP/ CVMP/ SWP/169430/2012) had been followed for the calculation of Permitted Daily Exposure (PDE). However, factor F5 was fixed at 1 for all API's. But factor F5 should be a variable factor that may be applied if the no-effect level (NOEL=No observable effect level) was not established. When only an LOEL (Lowest Observed Effect Level) is available, a factor of up to 10 could be used depending on the severity of the toxicity. Micro Labs had neither used the NOEL nor the LOEL. Instead of this, LD_{50} was used to calculate the NOEL, which was not in accordance with the current EMA guideline and not science based. From the viewpoint of the inspectors, a factor F5 should be set at 10 in this case and the resulting PDE should be compared with PDE calculation on the base of real NOEL values, established for all identified critical effects according to EMA guideline.
The formula used for the calculation of the residuals per 100 cm^2 was incorrect because the minimum therapeutic dose of the previous product was additionally included. In addition, calculation presented for granulation II (M 214, 12/June/2016) could not be traced by the inspectors. Recalculation according to the values presented by Micro Labs on the basic of the worst case API Nevirapine (given PDE value 0.04 mg) and the next product Zidovudine Tablets 300 gave 4.187 mg per swab instead of 267.1485 given by Micro Labs.

<u>Example for the cleaning validation report:</u>
Nevirapine tablets were determined as a worst-case product for Granulation-II, Granulation-III, Quadro Sifter, Octogonal Blender (4500L), Fette3090i compression machine and bulk packing.
MAC (mg/100 cm^2) was calculated based on dose criteria, 10 ppm criteria, on ADI and PDE base. Furthermore, minimum requirement was given for visual criteria with 0.1 mg/100 cm^2.
Equivalence report for Granulation-II and Granulation-III, showing that both areas are using the same equipment, was done.
Sampling locations for critical manufacturing equipment were specified in Annex I.
Detailed cleaning procedures for cleaning of saizoner mixer granulator (1400 litres) and fluidised bed drier (400 Kg), including equipment cleaning record, identification of parts of equipment, identification of hard to clean parts of equipment together with photos showing dismantling and assembling procedures and critical parts for visual inspection, were available.

During the cleaning validation, rinse and swab sampling was used to test traces of active substance and the cleaning agents. The analytical test methods used for cleaning validation (HPLC, UV) were validated. For the completion of the cleaning validation at least three batches were required.
Other observations together with cleaning validation:
-0.1 mg / 100 cm^2 limit was used as a general limit for visual clean. According to the literature, also lower limits are discussed.

-Limits for the different rinse samples were not calculated in the validation report for Granulation-II (expanded building) from 21/12/2013. In addition, there were no recovery studies / no method validations for the rinse sampling.
Water was used for rinse sampling of the API Nevirapine, which was practically insoluble in water.
Limit of detection for Nevirapine was given with 0.0130 ppm (LOQ 0.0394 ppm).
All results were found negative (not detected). Acceptable limit was given with 0.1 mg/swab. Limits and spike recovery for the rinse samples was not clear from the report. Also the LOD/LOQ was not considered together with the final reporting.
- In point 5.4.14.1.4 of the current SOP it was written: "lf the recovery obtained during the method validation is less than 80%, a-recovery factor shall be calculated and the final result shall be multiplied by this factor." It was not clear, why the recovery was not taken into account in every case if it was below 100 %. This was clarified by the company after the inspection.

Overview with regard to the current state of cleaning validation was not part of the VMP. Overview was prepared during the inspection.
According to this, for the equipment chain used for Lamivudine/Zidovudine (30/60 mg) tablets (including Granulation-II), Risperidone tablets 4 mg were chosen as the worst case product.
For the equipment chain including Granulation-III the cleaning validation was not finalised. Spironolacton 100 was selected as the worst case product.

Cleaning agents:
Only one cleaning agent, 0.1 % Teepol solution, was used at the site. Retrospective evaluation of the usage of this product (Report for determination of suitability of cleaning agent concentration) was done after last WHO inspection (finished on 16/July/2014). Glimepiride was chosen as the worst case API.
After cleaning, all results were within the limits (Glimepiride could not be detected).
During analytical method validation (04/Dec/2014) limit of detection for Glimepiride was found with 0.05 ppm. Limit of quantification was 0.15 ppm.
In the Report for determination of suitability of cleaning agent concentration no limit for the residual of the API after the cleaning was given. For this reason, it was not clear, if the method used was suitable to detect the amount which was acceptable. This was clarified by the company after the inspection.

Cleaning verification
According to the SOP (11/Oct/2014), cleaning verification by rinse and swab sampling should be done for any new product which is not a worst case product. Further, when the product is commercialized and if the equipment chain is different from the one used for submission batches. It should be executed on three batches.

Analytical method validation
Analytical method validation was general described in the VMP.
Overview with regard of the current state of analytical method validation was not part of the VMP. This was resolved in the company CAPAs.

5. Complaints

There was an SOP for handling of market complaints (01/Oct/2015). Log of all complaints in the Market Complaint Register should be done All complaints and other information concerning potentially defective products were reviewed according to written procedures and the corrective action was taken.
Site QA Head should evaluate the complaint with production, quality control and other relevant department heads and prepare the investigation report (template was given as an annex to the current SOP).
Testing of complaint samples was described.

Link to procedures about product recall, CAPA, risk analysis and root cause analysis was given.

Market complaint MC:167002 (Metformin tablets) was checked as an example.
The following tests has been done on the complaint sample:
Description, Identification by IR, Uniformity of the Dosage units (By mass variation), Weight per tablet, Impurities and degradation products (By HPLC), Assay (By HPLC), Dissolution (By UV), Microbial purity test, Identification of colouring agent
Complaint was received on 06/Jan/2016. Complaint sample was obtained on 16/Feb/2016. Complete investigation report was available. All quality parameters were found in specification. QA approval was done on 9 March 2016.

6. Product recalls
Recall procedure (2/Feb/2016) was available.
There was a system to recall from the market, promptly and effectively, products known or suspected to be defective.
The head of corporate QA should inform the State Licensing Authority.
Mock recall procedure was part of the SOP. These should be done annually.
The responsibility to recall the product rests with the Executive Director, Technical and Operations. As Corporate QA is the authorized person for the Goa facility, the responsibility should be changed accordingly.

7. Contract production, analysis and other activities
There was no contract manufacturing for any WHO products. The list of contracted laboratories was part of the SMF.

8. Self-inspection, quality audits and suppliers' audits and approval This area was not inspected in detail, but in general, the system for self-inspection was acceptable although an even higher level of stringency would have been expected given the issues raised in the US FDA letter. The most third party audit draft report was requested but could not be provided despite at least three requests made during the inspection.

9. Personnel
This area was not inspected in detail, but in general, there were sufficient numbers of qualified and experienced personnel. Their job descriptions were adequate and no issues of significance were noted.

10. Training
The SOP (15/July/2015) on training of personnel was available.

Department training coordinators were in charge to prepare Training Need Matrix and to conduct the planned and unplanned training.
The effectiveness of training (On-the-Job / Planned / Unplanned) given shall be evaluated through questionnaires and practical evaluation.

11. Personal hygiene
An adequate level of personal hygiene was observed during the tour through the production areas. Personal hygiene procedures included the use of appropriate clothing for all persons entering production areas including employees and visitors.

Dressing procedures and measures of personal hygiene were presented in the changing rooms in detail with photos.

Clean body coverings appropriate to the duties performed, including appropriate hair covering was worn.

Arrangements for hand washing and disinfection before entering production area were implemented. Direct contact was avoided between the operator's hands and starting materials, primary packaging materials and intermediate or bulk product.

12. Premises

The facility was designed to manufacture non-sterile oral solid dosage forms. The unit dose forms were tablets (uncoated and coated tablets) and hard gelatine capsules.
Appropriately designed change rooms and airlocks were established to allow qualified entry of personnel to the production area and change in between different areas.

The existing building was expanded towards south side of the plot and expanded building is connected through a two storey connecting corridor.

Modern automated high rack warehouse with 5840 pallet places was implemented in the expanded building. Temperature (25 °C) and humidity (40-65 %) monitoring was installed. Pest control was ensured.

The production operations carried out in manufacturing areas are sifting, dry mixing, wet granulation (aqueous and non-aqueous), drying, blending/lubrication, roll compaction, compression, coating (for coated products), capsule filling, inspection and blister/bulk packing.

In the manufacturing areas including sampling and dispensing areas, self-levelling epoxy floor was provided.

In areas where dust was generated appropriate measures were taken to avoid cross-contamination (dust extraction system, low-level exhaust air grilles).

Purified water

Purified water was used for cleaning and manufacturing purposes. The quality of the purified water met the requirements of the EP/USP. The purified water system was properly installed, qualified and regularly monitored chemically and microbiologically.

The source of raw water was bore well. After the initial purification process of the raw water, demineralized water was filtered through an ultrafiltration membrane. In addition, UV sanitizers were installed at the beginning and end of each purified water loop to control the bioburden of the distribution system. Adequate control of the UV units (check of power and operating hours) was in place.
There were two purified water generation systems in the facility. One system consisted of two stainless steel tanks of capacity 2000 L and 1000 L provided with separate purified water distribution loop I and II respectively and another system consisting of a stainless steel tank of capacity 2000 L with a single distribution loop.
Conductivity and TOC testing was done online.

Drawing of the purified water generation, storage and distribution system was part of the SMF (annex 7) and reviewed and discussed during the inspection.
The following points should be clarified:

- A "SIP tank" was displayed in the drawing. This was needed for sanitization of the ultrafiltration (at 80 C)
- Testing of potable water used for washing of equipment: a test program was available.
- Heat exchanger was only shown in the old system: Heat exchanger is only needed it there is no jacketed tank, heated by plant steam, installed. For new installations, jacketed tanks were integrated.

- Potable water storage tanks and raw water storage tanks are cleaned on monthly basis and twice in a month respectively. This cleaning was done manually with sanitization and flushing process afterwards.
- Water monitoring of sampling points S14 / S33 (in between storage tanks and UV sanitizers of old facility) and SP12: in between storage tank and UV sanitizer of expanded facility: daily sampling of these critical points was done.

The specifications, valid since 15/03/2012, were available.
Tests for Total Organic Carbon (limit Not more than 500 ppb) and Conductivity (Not more than 1.3 µS·cm-1 at 25 °C) should be performed daily on storage tank and return loop sampling point.
For other parameters, weekly complete testing shall be performed on the storage tank and return loop sampling point.
Tests for absence of Escherichia coli, Salmonellae, Pseudomonas aeruginosa and Staphylococcus aureus were part of the microbiological specification. Total viable aerobic count was specified with Not More Than 100 CFU/ml.
For microbial limit test (done by membrane filtration using R2A Agar medium), reference to SOP:QCMB:018 was given in the specification. For testing of specified microorganisms, the reference was missing. This was resolved in the company CAPAs.

HVAC system
The environmental conditions were assured by air handling units supplying all the facilities in the controlled areas.
The AHU's were qualified, regularly maintained and monitored. The last qualification results of the AHU9 were discussed .

Design of the ventilation system was done to reach ISO class 8 air quality (Class "D").

Differential air pressure is set up between areas of different air classification to prevent cross contamination. The process area corridors are maintained at a higher pressure with respect to the adjacent manufacturing rooms. Pressure cascade of 15 Pascal are maintained to ensure that direction of airflow is from clean corridor to the cubicle and from classified areas to non-classified areas.

13. Equipment
Equipment was located, designed, constructed, adapted, qualified and maintained to suit the operations to be carried out. The layout and design of equipment also aimed to minimize the risk of errors and permitted effective cleaning and maintenance in order to avoid cross-contamination, build-up of dust or dirt, and, in general, any adverse effect on the quality of products.

However, some minor problems were identified together with the documentation and installation, which were resolved in the company CAPAs.

14. Materials
All incoming materials were quarantined immediately after receipt until they were released for use or distribution. All materials and products were stored under the appropriate conditions established by the manufacturer and in an orderly fashion to permit batch segregation.

Sampling and dispensing processes were done under well designed LAF areas including installation of controlled HEPA filters. Dispensed materials were found appropriated packed for transport to production areas.

Vendor approval

Materials were sourced from approved suppliers. Several examples were checked. Only one problem was identified (Nitrogen supply, see below).

Revised procedure (approved on 07/June/2016) was available.
Questionnaires, TSE/BSE risk assessment, test samples were part of the procedure.
Audits for API manufacturers should be done before commercialization and afterwards any 3 years. For WHO and US products, validity can be extended for 3 more years based on supplier risk assessment / annual re-evaluation report.
Also for "functional excipients" (which can influence the drug product performance, e.g. coating agents for controlled-release products, disintegrants, antioxidants, antimicrobial preservatives) site audit was part of the vendor approval process. Justification should be provided by R&D.

Audit report should be forwarded within 45 working days to the vendor. Compliance report should be provided by the vendor within 30 days. After evaluation, audit closeout memo shall be issued.
Minimum requirements for the auditors, including third party auditors, were defined.

Some cases for the vendor approval process and the correct addresses of the manufacturing sites (list of approved vendors, audit reports) were checked together with the evaluation of the PQR's (see above).
Additional examples:
Nitrogen:
Vendor approval for Nitrogen used for stability protection in the case of relevant APIs during dispensing process was not available.
According to the information by Micro Labs, the Nitrogen was not used for current products and not relevant for WHO products.

Lamivudine : one supplier (, last audit 11+12/02/16) and four specifications were given in the PQR. The Audit was done at Unit A. Address given in the approved vendor listing was identical with the address given in the audit report. Audit closeout report was done on 13/June/2016.

Nevirapine anhydrous was supplied by (former name of the manufacturing site was). Last audit was done on 20/Nov/2015. Closeout was documented on 19/Jan/2016.
Audit was done by Mr. Kumar, CQA Micro Labs. Auditor certification for Mr. Kumar was done in Aug 2015.

Efavirenz: the vendor's name was Hetero Labs Ltd. (last audit: 11+12/02/16).
The audit was done at Unit IX (Visakhapatnam). This site was manufacturing Lamivudine, Zidovudine, Efavirenz, Tenofovir Disoproxil Fumarate, Emtricitabine, Abacavir Sulfate, Neviparine, Stavudine and Levetiracetam. The audit closeout report was documented on 13/June/2016.

15. Documentation

Production operations followed clearly defined procedures. All handling of materials and products was done in accordance with written procedures and was found well recorded.

The Master Formula Record details the manufacturing instructions. The manufacturing activities performed were recorded in approved batch manufacturing records. Checks on yields and reconciliation of quantities were carried out.

Batch were released by QA after ensuring that the batch was manufactured in compliance with the authorized instructions and in accordance with the GMP requirements. Document QAP: ML06:029 ((28/April/2016) contained appropriate arrangements for the review of batch manufacturing and batch packing report including QC documentation.

After complete review of the batch documents and analytical documents, product name, batch No., manufacturing date, expiry date, the quantity released, AR. No and date of release shall be written on the "Batch Release Certificate" QAP: ML06: 029:F8 and batch shall be released through SAP as per SOP:SAPQM:010, Procedural Control For Sampling, Result Recording And Usage Decision. The batch release certificate and the cover page of the BMR/BPR shall be signed for release of the batch.
Batch release was documented in the second part of the BMR/BPR issue register.
Mr. Bishnu N. Das (Head of IPQA & Compliance) and Mr. Ajaykumar R. Jagtap (deputy) were authorized for batch release.

Only minor problems were identified and they were resolved in the company CAPAs.

The in-process control tests (friability, disintegration, hardness, loss on drying, leak test) were performed in the IPC laboratory. It was located in the territory of the Production (within the controlled area) but was belonging to the IPQA Department therefore independent of the Production by organization.
Test documentation for IPC analysis was checked in detail.
The traceability of the documentation was found deficient in that:
- 2 operators have signed for several compression machine setting checks. It was not clear, which operator did the testing.
- Several devices were available for disintegration testing and friability test. From the documentation it was not clear, which device was used for the test.
- The weighing for the calculation of the friability was documented. It was not clear, which scale was used.
- According to SOP:QAOP:007/A (02/June/2014), analytical weighing balance and printer should be attached to take weight prints of the initial tablets and the final tablets. However, there was no attachment of printer and no printouts of the test or weighing results.

16. Good practices in production

Production processes, equipment and documentation for the relevant products was reviewed in detail. Detailed process flow charts were available for all relevant products. Details of equipment used during the production were given in the batch record.

In general, Micro Labs was found capable to manufacture pharmaceutical products of the required quality in a constant manner.
Problems identified were resolved in the company CAPAs.

17. Good practices in quality control

FDA warning letter:

The report from the independent consultant had been requested on Day 1 but could not be shown.
An example was shown for levocetirizine dihydrochloride 5mg tablets dating from 16.10. 2013
If a result was found which was out of specification, then the batches were considered for recall or rejections, as stated by Mr. Rajesh Kshirsagar.
He also explained that the results got overwritten in Shimadzu so the trial injection could not be recalculated. The manual acquisitions could be done on the Shimadzu system without getting recorded. This could

nevertheless be seen in what is called the "Daily audit trail" for the equipment. There was a filter called "normal", it was for timebase MLG-QC-12-027.

In a different example was shown for etoricoxib tablets, for in process product testing (bulk tablets? Or blend?), the OOS investigation report was requested to batch, that had a result of 89.2% when the trial injections were used for recalculation. This was claimed to be close to the result obtained for the other strength and was therefore likely to have been due to a mix-up with another strength. The OOS was dismissing on the basis of this and of stability results (which were not presented). The peak area of Vial No. 10, composite sample as claimed as being close (peak area of 81843, vs peak areas of 801203 and 807873) and that therefore there was a likely mix-up with vial No. 9. This explanation is considered rather weak and not supportable by concrete data. by the inspector.

Only 15 batches were claimed to have been produced from that time period for WHO products. This explanation and identification of batches was requested to be further elaborated on. There were no findings for WHO

166 batches were reviewed for the FDA.

Example 1:
Ramipril Ph Eur related substances tests were repeated with the same sequence name "QC DATA\HPLC\SEQUENCES\RM\SEPTEMBER\0615R1052_RS_B.SEQ, which goes against the procedure which stipulates that they should be identified separately. Namely, it was acquired on 23.09.15 at 13:16, and also at 23:41. It was also acquired again on 24.09.15, at 21:13, and then again on 26.09.15 and 27.09.15 and 28.09.15. On 28.09.15, in a separate file with the same name, the batch numbers ACIH001846, ACHI001920 were identified as "Experiment". Integration of one of the unknown peaks eluting at approximately 22.9 minutes, was inadequate and may have underestimated peak area although this was seen to be a blank peak. This was found in a laboratory deviation report No. LDR 15 10/139. The report states that during the analysis test for related substances, the peaks are not integrated properly. During final review for OOS investigation data (OOS ML06 15194), it is observed that the integration parameter was not set properly for experimental study chromatogram and therefore the folder for Month SEP 15 was unlocked and the sequence was reintegrated. There was no explanation of why integration was unsatisfactory.
On 27.09.15, an unknown with a peak area of 0.34% was osbjected at 5.73 minutes.
Again on 29.09.15, another experiment was done at 19:42 using sample batch ACIH001846. In some cases the unknown impurity peak at 23.28 minutes was integrated, in others it was not (in the report that was linked to deviation number LDR15:10/139. In some cases, the peak appears to be relatively large (0.16%).

OOS report No. OOS:ML06:15194 was sreviewed and it stated that there was an OOS for any individual impurity for all of 6 batches at 1.38 minutes. The OOS was closed on 11 november and was originally found on test results from 23/09/2015 but reported on 26/09/2015.

It is not clear why retesting was done on 23.09.15 and 24.09.2015, prior to initiating the OOS! The conclusion to retest was made only on 30.10.15 by the head of QA that "it is recommended to retest same batches in duplicate in presence of section head and analytical QA by same analyst". The root cause was identified as being contamination by a volatile impurity that could have originated from the glassware cleaning, since the impurity later on disappeared. The plausibility of this root cause is questionable and the decision making process was unclear in its documentation / did not appear to follow the sequence.

Example No. 2: (ebastine 10 mg tablets) HPLC/SEQUENCES/IP_FP/March/ _RS_B occurrence was listed as having occurred 29.03.16 at 9:25 due to a communication error and was therefore restarted. This was signed off by QA on 31.03.2016 in laboratory deviation report No. 16:03/133.

Also, another laboratory deviation was raised on 29.03.2016, for QC/DATA/HPLC/SEQUENCES/IP_FPMARCH/ DS A.SEQ, because shape of a peak was found improper so the colunn was washed. (Note: peak shape of ebastine was indeed found to look unusual/unacceptable). Retests were named "A1". Inproper initial run according to report was started at 18:56 and the test was for bulk tablets – improper peak shape appeared at 19:50. In the official analytical report RS B.SEQ, dated 04.04.2016, 20:40, this was resolved it seems Batch was tested then.

Example No. 3:
(batch No. SOAG003) 40°C 75%RH, 30's:
The analytical reports for GSTA 160778 were reviewed in hard copy after having found a number of repeated sequences for GSTA 160778_DP_B . The first analysis (the official one) was done at 3/31/2016 starting at 6:16 pm and ending at 2:18 am the next day. Disso 1 had a peak area of only 777.053, while disso 2 at 20 minutes had 880.584. Disso 5 had 768.588.
There was only 1 run with the name ending with DP B in the report.
Under "Reference no of deviation OOT OOS (if any specify): "NA".

Example No. 4:
30°C/75%RH (3M), GSTA160411 DS B, seen at 3/1/2016 5:06 pm on the audit trails. This was for batch number ZEDG001. There was no reference to deviations, OOTs, or OOS on the cover sheet form which had a section dedicated to this. The checklist verification did not raise any issues. Only 1 set of dissolution results was reported event though it could be seen that there were 4 sets in the sequence created 3/1/2016 at 2:32 pm. The sequence first injection (blank) was at 17:08 pm on 1.03.2016. Raw electronic data restored from Archives was looked at in Chromeleon. It was found in the March folder and only included runs DS A and DS B.
Note: typical chromatograms were included as part of the standard test procedure and they are found to include many impurities of simvastatin.

Example No. 5:
AR No. GSTA152154, , 9M (30°C/75%RH) 30's. Again, no deviation, OOS or OOT reported in the final sheet, although the report was signed as completed on 12/10/15 and it had been seen to have undergone many repeats according to the audit trail. "STABILITY/OCTOBER/GSTA/152154_DS_B.SEQ" which listed one of the batches to have been started on 7:05 pm on 10/7/2015 and finished at 1:32 am on 10/8/2015. This was the only run included.
According to the instrument history audit trail in Chromeleon, it was started again on 19:05 on 7 10 2015 until 1:32 am. It was started at 15:57 and changed several times (around 10 times) while running.
Run A was finished at 18:23 on 7.10.2015 (started at 16:49).

Example No. 6:
(bulk) GIBP160761. Again, No OOS, OOT or deviation in the cover page for the report signed and dated 28/03/2016. No issues seen in the audit trail.

Example No. 7: Ramipril OOS.

On the afternoon of Day 3, Chromeleon data was reviewed with a focus on stability tests. The following examples were selected for review by the inspector:

-GSTA160110 DP test was reviewed. There was a laboratory deviation for sequence A, because …the root cause was determined to be due to the usage of 1 1 decane sulfonic acid instead of 1 octane sulfonic acid. Sequence A was completed on 29.01.2016 at 14:41. A sequence called "GSTA160110 Hypo" was started on 20.01.2016 at 15:58. Hypo 2 was done on 20.01 at 18:12 until 20:15. The method run time was 10 minutes. Lamivudine was seen to be carried over into the next injection.

-GSTA160140 was reviewed. There was a dissolution failure for accelerated stability but intermediate stability passed (30/75).

GSTA160123 OI B was reviewed. This was for metformin organic volatile impurities. It was noted that there were 2 different types of system suitability samples. One was made by mixing metformin related compound B and C with metformin standard to a concentration of 0.00125% for resolution. The inspector verified whether or not the system suitability injections resembled sample in any way, whether there were any interruptions that could have allowed sample switching and none were found. Concentrations of the 2 impurities were also different in the official samples.

Administrator password was tested for changing time and date and this was not possible, but this was done only for Nayan 94585, not for the General Administrator who had broader user rights.

The stability protocol for Lamivudine 30 mg was also requested. Senior corporate management was asked whether there were issues with stability backlogs and the answer was no, that this had been resolved.

For product: The 24 month time point and 18 month, as well as 12 months were tested prior to the FDA warning letter.

Stability plans were requested to be reviewed against the testing declared to have been performed for the following products:

-Zidovudine 300 mg tablets USP: 3 commercial validation batches were fixed. It specified tests to be done at 1, 2, 3, 6, 9, 12, 18, 24, 36, 48 months.

-Nevirapine 200 mg tablets, 3 commercial batches.

Other products requested from list of PQd products were stated not to be commercialized.

The OOS logbook (2016) was not always accurate: in one instance, it only mentioned water failing the test limit, and not related substances, dissolution and assay (these were nevertheless declared in the stability report and in the OOS report although not shown to the inspector first hand) for at 48 month 30/75% RH time point on HDPBE bottles 30's. The failure was significant, for HDPE bottles of 100's, with a total impurity value of 27.97% and 14.76% 5 fluoracil analog and 7.87% Mono PC PMPA, against 68.9% assay. Similar results were obtained for the 30's bottle. Since these results were obtained in 18/04/2016 or before, it was surprising to notice that the company has asked for a 48 month shelf-life (date to be confirmed by the assessment team). The assessment team had rejected this request on the basis of MLT results only. This issue should be communicated to the assessors to verify whether information was conveyed in an honest manner.

The results at 36 months, tested on 14/04/2015 shall be verified because it is a very large change in 12 months. (results of 97.8% assay, 0.49% 5 fluoracil analog and 1.84% Mono POC PMPA were found then). GSTA is 150490 dating from 14/04/2015 for the 30's count. It was searched on Chromeleon system audit trails and electronic data for 2015 and could not be found but was seen on empower.

On day 4, before lunch, Mr. Rajesh, was requested to provide information on whether manual injections were still found to be occurring after the FDA warning letter and he stated that this could not have been happening, since each and every analytical report was being reviewed.

After lunch, key staff members were questioned: regarding the manual injection issue.
Rajesh stated that the old injections may have been taken for review and that that this could have been linked to the issue.

One of the examples was later on explained to be due to the installation of new software by the external service engineer. Entry and exit records into the facilities were requested at approximately 15:45 pm. Two sheets of paper printed with a table of names were shown – the company was told that this was not considered satisfactory evidence of his presence at the time where the audit trials were created. The service engineer came in within 20 minutes of the request. A card was shown to confirm his identity. He provided a partial explanation regarding the automatic appearance of manual in the daily audit trail.

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 Limited, ML-06, Plot No. S-155 to S-159 & N1, Phase III & IV, Verna Industrial Estate, Verna-Goa, 403722, 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 GMP guidelines referenced in the inspection

1. WHO good manufacturing practices for pharmaceutical products: main principles. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-eight Report Geneva, World Health Organization, 2014 (WHO Technical Report Series, No. 986), Annex 2.
   http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_986/en/

2. WHO good manufacturing practices for active pharmaceutical ingredients. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth Report. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957), Annex 2.
   http://www.who.int/medicines/publications/44threport/en/

3. WHO Good Manufacturing Practices: water for pharmaceutical use. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fourth-six Report. Geneva, World Health Organization, 2012 (WHO Technical Report Series, No. 970), Annex 2
   http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_970/en/

4. WHO guidelines for sampling of pharmaceutical products and related materials. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-ninth Report. Geneva, World Health Organization, 2005 (WHO Technical Report Series, No. 929), Annex 4
http://whqlibdoc.who.int/trs/WHO_TRS_929_eng.pdf?ua=1

5. WHO guidelines on good manufacturing practices for heating, ventilation and air-conditioning systems for non-sterile pharmaceutical dosage forms. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 5
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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
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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
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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/

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http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_981/en/

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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

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http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf

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22. Guidance on good data and record management practices. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifties Report Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 5 http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex05.pdf

23. WHO general guidance on variations to multisource pharmaceutical products. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifties Report* Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 10 http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex10.pdf

24. WHO good manufacturing practices for biological products. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifties Report* Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 3 http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex03.pdf